BURN MANAGEMENT

CHI Formulary Indication Review

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Abbreviations

5-FU	5-Fluorouracil
ABA	American Burn Association
ADL	Activities of Daily Living
AGE	Arterial Gas Embolism
ARDS	Acute Respiratory Distress Syndrome
ASD	Acute Stress Disorder
ASR	Age-Standardized Ratio
ATB	Antibiotic
BAL	Bronchoalveolar Lavage
BBA	British Burn Association
CADTH	Canadian Agency for Drugs and Technologies in Health
CFU	Colony Forming Unit
CHI	Council of Health Insurance
CN	Cyanide
CNS	Central Nervous System
CO	Carbon Monoxide
CPR	Cardio-Pulmonary Resuscitation
DALY	Disability-Adjusted Life Years
DVT	Deep Venous Thrombosis
EAPC	Estimated Annual Prevalence of burn Cases
EBA	European Burn Association
ECG	Electrocardiogram
ECHM	European Committee of Hyperbaric Medicine
EMA	European Medicines Agency
FDA	Food and Drug Administration
FPHC	Faculty of Pre-Hospital Care
GDP	Gross Domestic Product
GoR	Grade of Recommendation

G-CSF	Granulocyte-Colony-Stimulating Factor
HAS	Haute Autorité de Santé
HBOT	Hyperbaric Oxygen Therapy
HSCT	Hematopoietic Stem Cell Transplantation
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IDF	Insurance Drug Formulary
IM	Intramuscular
IQWIG	Institute for Quality and Efficiency in Healthcare
ISBI	International Society of Burn Injuries
IV	Intravenous
KSA	Kingdom of Saudi Arabia
LA	Long-Acting
LMWH	Low-molecular weight heparin
LoE	Level of Evidence
MA	Mafenide Acid
MDRO	Multi-Drug Resistant Organisms
MHRA	Medicines and Healthcare products Regulatory Agency
MTBI	Mild Traumatic Brain Injury
NAI	Non-Accidental Injury
NICE	National Institute for Health and Care Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over the Counter
PBS	Pharmaceutical Benefits Scheme
PEEP	Positive End-Expiratory Pressure
PG	Practice Guidelines
PICU	Pediatric intensive care unit
PMDA	Pharmaceutical and Medical Devices Agency
PO	Per Os
PT	Pressure Therapy

PTSD	Post-Traumatic Stress Disorder
PVI	Povidone Iodine
QOL	Quality of Life
RITN	Radiation Injury Treatment Network
RLS	Resource-Limited Setting
RRT	Renal Replacement Therapy
RSI	Rapid Sequence Intubation
SDI	Sociodemographic Index
SFAR	Societé Francaise d'Anesthésie et de Réanimation
SFDA	Saudi Food and Drug Administration
SNS	Strategic National Stockpile
TAC	Triamcinolone Acetonide
TACO	Transfusion Associated Circulatory Overload
TBSA	Total Body Surface Area
TRALI	Transfusion Related Acute Lung Injury
TRAMI	Transfusion Related Immunomodulation
UHC	Universal Health Coverage
UTI	Urinary Tract Infection
VAP	Ventilator Associated Pneumonia
WBC	White Blood Cells
WHO	World Health Organization
YLD	Year of Healthy Life Lost to Disability
YLL	Year of Life Lost

Executive Summary

Burn injuries are a trauma that is often overlooked yet may happen to anybody, anywhere, at any time. Although friction, cold, heat, radiation, chemicals, and electric sources can all result in injuries, heat from hot liquids, solids, or flames is the main cause of burn injuries[1].

It's critical to define burn injuries based on their severity, including their size and depth, in addition to identifying their etiology. Burns that only impact the epidermis are classified as superficial (first-degree) burns; they cause the skin to turn red and have brief periods of discomfort. Second-degree, or superficial partial-thickness burns (formerly called 2A burns), are painful, weep, require wound care and dressing, and may leave scars but may not require surgery. Due to a partial loss of pain receptors, deep partial-thickness (second-degree) burns (previously known as 2B burns) are less painful, drier, necessitate surgery, and leave scars. Due to damage to the nerve endings, a full-thickness (third-degree) burn that penetrates the entire dermis usually does not hurt and must just be kept from getting infected (unless it is extremely tiny) and managed surgically. Lastly, a fourth-degree burn is characterized by damage to deeper tissues, such as muscle or bone, is usually blackened, and results in the loss of the burnt portion. More serious burns require meticulous therapy, which may involve topical antimicrobial dressings and/or surgery. Although superficial and superficial partial-thickness burns typically heal without surgical intervention, more severe burns seldom do. Crucially, burns can be categorized as severe or minor. In general, a minor burn is defined as one that covers less than 10% of the total body surface area (TBSA), with most burns being superficial. In contrast, the definition of a major burn is less clear; guidelines for classifying severe burn injuries are as follows: >10% TBSA in elderly patients, >20% TBSA in adults, and >30% TBSA in children. Burns can also result in physical trauma to other organs, such as smoke inhalation[1].

Following the determination of the extent of the burn injury, the patient must be appropriately referred to and triaged. Major burn patients require a lot of resources, their care is frequently provided in specialist facilities, and their treatment has a lasting effect on the patient's life as well as the lives of their family and caregivers.

While burn injuries are on the decline in high-income nations, they are still quite common in low- and middle-income areas, accounting for around 90% of all burns. According to World Health Organization (WHO) estimates, there are 11 million burn injuries globally each year, 180,000 of which are fatal. Burn injuries occur with a great deal of variety. For instance, the Ivory Coast in Africa has 14.53 burn-related fatalities per 100,000 people, but Malta has 0.02 deaths connected to burns. Children die from burns seven to eleven times more frequently in low-income nations than in high-income ones. All burn injuries in the United States have a bimodal age distribution,

with young children (1–15.9 years old) and people of working age (20–59 years old) accounting for the bulk of injuries[1].

When treating any kind of burn, the treatment is influenced by the country's healthcare setting, and special populations (pediatrics, elderly…)[1].

In 2019, 8,378,122 new cases (95% UI, 6,531,887–10,363,109 cases) of burns were reported worldwide. Men and women were represented roughly equally in these instances, with most new cases falling between the 10- to 19-year-old age range. In addition, 111,292 deaths (95% UI, 132,392–88,188) worldwide in 2019 were related to burns, with most of these deaths occurring in children 1-4 years old. In 2019, the number of burns assessed in disability-adjusted life years (DALYs) was 7,460,448.65 (95% UI, 5,794,505.89–9,478,717.81), with years of life lost (YLLs) accounting for 67% and years of healthy life lost to disability (YLDs) for 33% of the total burn burden. The age-standardized rates (ASR) of incidence, DALYs, and deaths were all negative, the estimated annual percentage changes (EAPCs) were negatively correlated with sociodemographic index (SDI) levels, gross domestic product (GDP), and universal health coverage (UHC), and the ASRs of incidence, DALYs, and deaths were thought to be declining in most of the regions[2].

The number of burn DALYs and death cases, as well as the age-standardized rates of burn incidence, DALYs, and mortality, will all continue to decline globally, while the number of new burn cases is trending upward. Furthermore, the EAPCs for incidence, DALYs, and mortality showed that, in most locations, the burden of burns was thought to be declining. Furthermore, the correlation between EAPCs and GDP, UHC index, and SDI shows that preventive burns depend not only on health spending per capita but also on per capita education level and the performance of the healthcare system. However, this does not imply that higher health spending translates into higher UHC index, as high efficiency in converting health spending into personal health gains is required[2].

Although comprehensive data on the burden of burns and its economic impact in the Kingdom of Saudi Arabia (KSA) are currently limited, future research and analysis are crucial to gaining a clearer understanding of the disease's prevalence, impact, and associated costs in the country.

This report compiles recent clinical guidelines and evidence related to burn management and its associated complications. The information presented in this report is derived from authoritative sources, such as the International Society for Burn Injuries (ISBI), the World Health Organization (WHO), the American Burn Association (ABA), the European Burn Association (EBA), the Société Française d'Anesthésie et de Réanimation (SFAR), the British Burn Association (BBA), the Faculty of Pre - Hospital Care & British Burn Association Expert Consensus Meeting and the Royal Manchester Children's Hospital. Also, main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current

medications in burn management were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Scheme (PBS).

The primary focus of this report is to narrow the recommendations outlined in these sources regarding the classification of burns, risk stratification, management strategies, and supportive care. **The aim is to ensure timely and safely access to drug therapies for patients with burns in Saudi Arabia.**

To manage burns effectively, risk stratification plays a crucial role. Major burns include >20% TBSA in adult, >10% TBSA in young or old, >5% full-thickness burn, high-voltage burn, known inhalation injury, any significant burn to face, eyes, ears, genitals, hands, feet or major joints, significant associated injuries (e.g., major trauma). These patients need to be referred immediately to a burn center[3,4].

The management objectives of burns are to detect patients in need of immediate hospitalization before it's too late, to limit damage in tissues by initiating appropriate therapy, to monitor wounds for any infection and healing improvement, to reduce risks of potential complications due to burns (burn shock…).

There are currently different recommended drug therapies for the management of burns, and KSA has access to all medication cited in initial and maintenance treatment; some sections suggest the use of one or another medication, and KSA has access to at least one of them. Some recommendations are well supported by reference guidelines, Grade of Recommendation (GoR) and Level of Evidence (LoE).

Treatment begins by assuring the patient's environment, by pulling him out in case of intoxication, stabilize vitals, cover wounds, and decide to transport to hospital / burn center or not depending on severity detected. In hospital / burn treatment center, patient my need IV fluid resuscitation in case of burn shock, administer enoxaparin in case of deep vein thrombosis (DVT) risk, and antidote in case of toxic exposure. After urgent treatment (if needed), the patient should receive wound care, beginning by cleaning the wound with chlorhexidine, then applying topical antimicrobials like silver sulfadiazine to limit infections. Topical petroleum derivates and dressings may also be used. The wound needs to be regularly checked and maintained in good condition. Other treatments post-burn may include physiotherapy, massages and other as rehabilitation tools[3–12].

Major recommendations for suggested drug therapies are summarized in tables 1 and 2. The report concludes with a key recommendation synthesis section that emphasizes the utilization of each drug class for specific patient groups. Additionally, the section highlights the need for additional evidence and improvements in cost-effectiveness to promote broader endorsement of therapies in patients with burns.

Table 1. SFDA-Registered Drugs for the Management of Burns

Medication	Indication	Line of therapy	Level of Evidence / recommendation	HTA recommendation
Norepinephrine	Vasoconstrictor - limiting blood loss agent	NM	NM	There are no recommendations issued by the HTA bodies for Norepinephrine
Atropine sulfate	Antidote to organophosphorus poisoning	Probably 1st	Strong evidence	CADTH: Regarding the clinical efficacy of atropine at different dosages for organophosphate poisoning in a pre-hospital context, no pertinent research could be found. There were no evidence-based recommendations found for treating organophosphate poisoning in a prehospital context[13].
Enoxaparin sodium	DVT prophylaxis	1st	Strong evidence	NICE: For medical, surgical, and trauma patients, ensuring that prophylaxis is begun as soon as feasible and within 14 hours of hospital admission will lower the risk of VTE[14,15]. HAS: can be used as a prophylaxis in surgeries and in moderate to high-risk patients[16]. CADTH: few biosimilars can be used as alternatives[17].

Chlorhexidine gluconate	Wound cleaning before invasive procedure, and wound cleaning	1st	Strong evidence	NICE: can be used for infection surgical prophylaxis[18]. HAS: can be used before invasive procedures on the skin to limit infections[17]. CADTH: for surgical infection and wound healing[19,20].
Propranolol	Hypermetabolism in children	NM	Strong evidence	There are no recommendations issued by the HTA bodies for Propranolol
Bleomycin	Resistant lesions and keloid diathesis	NM	Strong-evidence guideline	There are no recommendations issued by the HTA bodies for Bleomycin
Verapamil	Young hypertrophic and keloid scarring	NM	Strong-evidence guideline	There are no recommendations issued by the HTA bodies for Verapamil
Calcium gluconate	Hydrogen fluoride poisoning	1st	NM	There are no recommendations issued by the HTA bodies for Calcium gluconate
Dobutamine	Inotropic instability in sepsis prophylaxis	NM	Strong evidence	There are no recommendations issued by the HTA bodies for Dobutamine
Lactated Ringer	Fluid resuscitation	1st	Strong	NICE: If patients require IV fluid resuscitation, provide crystalloids with sodium concentrations between 130 and 154 mmol/l with a 500 ml bolus over less than 15

				minutes. Tetrastarch should not be used for fluid resuscitation[20].
Deferoxamine	Antioxidant deficiency during chlorine poisoning	NM (limited data)	NM	There are no recommendations issued by the HTA bodies for Deferoxamine
Human albumin	Hypovolemia	NM	Class II evidence	NICE: Consider human albumin solution 4% to 5% for fluid resuscitation only in patients with severe sepsis[20].
Silver sulfadiazine	Wound infection prophylaxis	1st	Strong evidence	NICE: insufficient data to conclude concerning its use in wound infection prevention[21]. HAS: FLAMMAZINE used as a prophylaxis agent[22]. CADTH: can be used to limit wound infection[19].
Tetanus vaccine	Tetanus infection prophylaxis	1st	Strong evidence guideline	There are no recommendations issued by the HTA bodies for tetanus vaccine
Paracetamol	Pain	NM	Level D	NICE: not for chronic use in 16yo and above[23]. CADTH: Limited data shows that IV acetaminophen may provide better pain relief within the first hour of delivery in individuals with moderate to severe pain in the ED, but equivalent pain reductions after 4 hours when

				compared to oral acetaminophen[24].
Buprenorphine	Analgesic (1:40 morphine equivalent)	NM	Level C	There are no recommendations issued by the HTA bodies for Buprenorphine.
Dexmedetomidine	Analgesic; and reduces opioid requirement; sedative	1st line sedative	Level D	HAS: With a marketing authorization approved in September 2011, its unique indication cites: "Sedation in ICU (Intensive Care Unit) in adults requiring state of sedation no deeper than that allowing a response to a verbal stimulus (corresponding to a score of 0 to -3 on the scale of Richmond Vigilance-Agitation (RASS)"[25].
Fentanyl	Spontaneous pain management and procedural pain	NM	Positive recommendation	CADTH: 2015 recommendations from the Italian Intersociety recommend IV paracetamol for pain management morphine and fentanyl for severe pain[26].
Gabapentin	Neuropathic pain; adjunct to opioids	1st	Level C	NICE: Gabapentin and pregabalin are a first choice and initial treatment in neuropathic pain (except trigeminal neuralgia) in non-specialized settings. Pregabalin and gabapentin are Class C controlled substances (under the Misuse of Drugs Act

				1971) and Schedule 3 under the Misuse of Drugs Regulations 2001[27]. CADTH: Recommended as non-opioid drugs for the treatment of neuropathic pain.
Pregabalin	Neuropathic pain; adjunct to opioids	1st	Level C	NICE: Gabapentin and pregabalin are a first choice and initial treatment in neuropathic pain (except trigeminal neuralgia) in non-specialized settings. Pregabalin and gabapentin are Class C controlled substances (under the Misuse of Drugs Act 1971) and Schedule 3 under the Misuse of Drugs Regulations 2001[27]. CADTH: Recommended as non-opioid drugs for the treatment of neuropathic pain.
Ketamine	Procedural sedation; post-operative analgesic	NM	Level B; Level D	CADTH: During the short-term period (between 48 hours and two weeks), IV ketamine infusions dramatically lowered pain ratings and had considerably greater positive response rates; however, these effects did not hold true for the longer follow-up period (four to twelve weeks). Ketamine's

				short-term effects were unaffected by dosage, the kind of persistent pain, or other medications[28].
Lidocaine	Local anesthesia	2nd, 3rd	Level D	CADTH: Lidocaine is indicated in loco-regional anesthesia and intravenously: to prevent pain linked to propofol injection; for the prevention of post-operative pain, particularly in order to speed up recovery intestinal transit after abdominal surgery[29].
Methadone	Used for long-duration treatment and small risk of addiction	NM	Level C	There are no recommendations issued by the HTA bodies for Methadone
Morphine	Severe pain	1st	Positive recommendation	HAS: Morphine has been indicated in "Intense pain and/or unresponsive to lower-level analgesics"[30]. CADTH: The 2015 recommendations from the Italian Intersociety recommend IV paracetamol for pain management morphine and fentanyl for severe pain[27].

Oxycodone	Morphine substitute	NM	Level C	HAS: with marketing authorization accorded in March 2005, its indication cites: "Severe pain that can only be properly treated by strong opioid painkillers; especially in pain of cancerous origin"[31].
Propofol	Procedural sedation and anesthesia	1st	Positive recommendation	HAS: With medication approved since 2002 for the 1% product, in 2007 for the 2% product and 2008 for the 0.5% product, indications of this drug include: Induction and maintenance of general anesthesia in adults and children more than 1 month (3yo and beyond), Sedation of ventilated patients aged over 16 in ICU, Sedation during diagnostic or surgical procedures, alone or in combination with local or regional anesthesia in adults and children[32]. CADTH: It is advised to use propofol-based sedation to enhance patient safety, comfort, procedural effectiveness, and favorable outcome. Pre-procedural Assessment and Preparation: Patients who take

				alcohol, barbiturates, benzodiazepines, or anticonvulsants on a regular basis may require higher doses of propofol. Monitoring During Rehab and Release: There must be at least 30 minutes of recovery time after propofol sedation[33].
Epinephrine	For preventing any heavy hemorrhage during burn wound excision	1st	Positive recommendation	There are no recommendations issued by the HTA bodies for Epinephrine
Granulocyte-colony-stimulating factor (G-CSF)	Lymphopenia during mustard agent intoxication	NM	Positive recommendation	There are no recommendations issued by the HTA bodies for G-CSF.

NM: not mentioned

Table 2. Non-SFDA Registered Drugs for the Management of Burns

Medication	Indication	Line of therapy	Level of evidence/ recommendation	HTA recommendation
Petroleum derivates	Emollient	1st	Strong evidence guideline	There are no recommendations issued by the HTA bodies for Petroleum derivates
Petroleum/petrolatum/paraffin derivatives are non-SFDA registered agents. They are widely commercially available as cosmetic products and are excluded from CHI coverage.				

Triamcinolone acetonide	Hypertrophic scars	NM	Strong-evidence guideline	There are no recommendations issued by the HTA bodies for Triamcinolone acetonide
Butorphanol	Analgesic (1:5 morphine equivalent)	NM	Level C	There are no recommendations issued by the HTA bodies for Butorphanol.
Hydrocodone	Pain management	NM	Positive recommendation	There are no recommendations issued by the HTA bodies for Hydrocodone.
Nalbuphine	Analgesic equivalent to 1:1 morphine		Level C	HAS: With a marketing authorization accorded in December 2001, nalbuphine use is insufficient in severe and/or intractable pain occurring in any other chronic non-cancer and non-neuropathic pain context, particularly chronic inflammatory rheumatic diseases, primarily consisting of rheumatoid arthritis and spondyloarthritis. [27]
Sodium nitrite	Hydrogen sulfide poisoning	NM	Positive recommendation	There are no recommendations issued by the HTA bodies for sodium nitrite.
Bacitracin	Topical antimicrobial	NM	Positive recommendation	CADTH: No statistical significance was shown between bacitracin irrigation and saline, and that an increased level of infections was

				observed with bacitracin compared to cefazolin[34].
Cerium nitrate	Topical antimicrobial for full thickness burns when early surgical excision and wound closure cannot be performed	1st	Positive recommendation	There are no recommendations issued by the HTA bodies for Cerium nitrate.
Honey	Homeopathic treatment with anti-infective properties, can be used as astringent to reduce discomfort associated with swelling; also for superficial partial thickness burns	NM	Positive recommendation	There are no recommendations issued by the HTA bodies for Honey.
Mafenide acetate	Topical antimicrobial used for deep or infected burns and deep burns of the ear	NM	Positive recommendation	There are no recommendations issued by the HTA bodies for Mafenide acetate.
Acetic acid	Antiseptic activity to prevent infection; used in wound cleaning	2ND	Positive recommendation	There are no recommendations issued by the HTA bodies for Acetic acid.
Dakin's solution	Antiseptic activity on wounds		Positive recommendation	There are no recommendations issued by the HTA bodies for Dakin's solution.

Cetrimide	Antiseptic solution used for wound cleaning	2nd	Positive recommendation	There are no recommendations issued by the HTA bodies for Cetrimide.
Iodine	Can be used for graft donor site with minimal to moderate exudate and for partial thickness burn with moderate to high exudate.	1ST	Positive recommendation	CADTH: the report shows that iodine can achieve complete wound healing in chronic wound care, and infections occur less in patients using povidone iodine (PVI). However, no effect on pain or length in hospital. As for cost-effectiveness, to avoid more than one wound complications, cost raises to USD99.94[19].
Lorazepam	Anxiolytic	1st	Positive recommendation	CADTH: Lorazepam is recommended as a rapid IM tranquilizer in hospital setting[35].
Vaseline	Treatment with fatty substance that can limit pain and act like an emollient	NM	Positive recommendation	There are no recommendations issued by the HTA bodies for Vaseline.

NM: not mentioned

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

To date, there are no clinical guidelines published by Saudi bodies for the management of burns.

1.2 International Guidelines

1.2.1 International Society for Burn Injuries (ISBI) Practice Guidelines for Burn Care (2016, 2018)

The ISBI practice guidelines (PGs) were developed by two subcommittees that conducted reviews on literature and expert opinions, with a focus on costs associated with the disease between limited and non-limited resource settings. These PGs divided between part 1 and 2 developed in 2016 and 2018, cover all aspects of burn injuries with part 2 evaluating the cost-effectiveness of the management methods used[11,12].

The PGs include the different techniques of burn management, balance of benefits and harms of these methods, values and preferences, and costs.

This section focuses on the recommendations outlined in the ISBI Guidelines for diagnosing burn types, management, and relative supportive care. All recommendations in this section are of strong evidence unless otherwise indicated.

Initial steps in a burn situation

In the setting of burns, several initial steps need to be done on site and in the hospital to save the patient's life:

- Responders or people on site should start the procedure by removing the patient from its potential burning environment, forbid him to run, and place him in an adequate position as lying or sitting down, "Stop, drop and roll" if enough space, cover with blankets if available and poor water to stop the fire.
- Responders should also take care of their own safety in all situations.
- Identification of Total Burn Surface Area (TBSA)
- In the case of thermally burned patients, wounds need to be refreshed using clean and supported temperature water for 15-20min (this can be applied to

electrically burned patients too). After that, the patient needs to be kept warm until taken in charge in a healthcare facility.

- In the case of chemically burned patients, an ultimate diagnosis of the chemical agent should be done, with the desi toxication of materials and clothes of the victim.
- In the case of electrical burns, the patient needs to be pushed out of the zone and if possible, find and strangle the initiating source and assess the need for cardio-pulmonary resuscitation (CPR).
- During the patient' transfer to a healthcare facility, ensure that his limbs are elevated to prevent an edema, and initiate the ABCDE pathway to assess any potential type of life threat[12].

Smoke inhalation management

Following a smoke inhalation accident, first aid steps require to:

- Assessment and monitoring of the respiratory function. Endotracheal intubation or tracheostomy may be prescribed and monitoring during these procedures is essential to maintain good lung function (weak evidence).
- Diagnose possible etiologies and diverse physiologic compounds like a decrease in consciousness, facial burns, and soot in the oral cavity. Others may include dyspnea, wheeze, and carbonaceous sputum (weak evidence).
- Inoculation of high-flow oxygen of 6h and more in suspected or confirmed carbon monoxide (CO) inhalation (insufficient evidence)[12].

Burn shock resuscitation

Burn shock can manifest as a massive hypovolemia putting the patient in danger; hence, intravenous (IV) fluid resuscitation is indispensable:

- With a TBSA surpassing 20% in adults and 10% in children, salt-containing fluid resuscitation should be immediately initiated, with a preference for lactated ringer (LR).
- Within the first 24h following injury, and when IV fluids are required, 2 to 4 ml/kg body weight/% of TBSA should be administered. If oral fluids are prescribed, then drinks in the equivalence of 15% of the body weight with 5g of a salt tablet (5g per ingested liter) should be taken for two days.
- Titration of salt-containing fluids can be initiated to create a urine output of 0.3 to 0.5mL/Kg/hour in adults and of 1mL/kg/hour in children (class 1 evidence lacking)[12].

Electrical burns

Electrical burns can sub-divided between low and high voltage electrical burns:

- In the case of low voltage burns, patients should be subjects to an electrocardiogram (ECG).
- In the case of high voltage burns (> 1000V) with or without myoglobinuria and/or neurologic deficits, patients should be transferred to burn care facilities.
- In both cases, rehabilitation after injury is a must to maximum recovery[11].

Chemical burns

In the incrimination of chemicals in the onset of burns:

- Immediate removal of chemical agents needs to be done to limit future absorption, followed by cool watering and dressing application. Evaluate the possible effect of pulmonary toxicity following chemical cutaneous removal.
- Apply the specific treatment protocol for each chemical[11].

Wound care

This section tackles dressing types for different burn categories:

- All burn thickness categories should receive dressing application, and the best is to leave them for long time as possible.
- Superficial burns and donor sites of split-thickness skin grafts can be at least covered for one week with humid and heat-preserving dressings, if not, moist dressings with possible application of antimicrobial creams (water-soluble base). Contaminated wounds with exudate need a daily refreshment of dressing with application of antimicrobial cream until infection extinction. Iodine and silver-based dressing can be used for graft donor site with minimal to moderate exudate and for partial thickness burn with moderate to high exudate.
- As for blisters, covering with modern dressings or biologic membranes is the first choice; if not available, de-roofing the blisters and application of classical dressings are the next step of wound care. Change the dressing after 3 to 5 days (no evidence).
- Cleansing with washing is essential in wound entertainment. Till now no significant difference have been made between tap water and saline. Therefore, method of application is more concerning than the agent's nature (the most important part is that it must be sterile or at least decontaminated): irrigating (mechanical cleansing) the wound might be the best way to clean it.

Several ways can be used to irrigate: gently to avoid abrasions on lower layers of the skin, or aggressive in the case of heavily contaminated wounds or biofilms. If the biofilm resists to irrigation, debridement (surgical cleansing) can help cleaning.

- Antimicrobials / antiseptics can be used to clean after mechanical or surgical cleansing.
- Raw areas should be covered with classical dressing until analysis of the wound, exudate, and infection status. If exudate is present, modern dressing is required. Wound profile and products availability condition the dressing type (no evidence).
- Usage of topical antimicrobials depends on the potential risks of delaying wound healing (because of several side-effects affecting this process) versus consequences of infection (sepsis etc.). Thus, this could guide the choice, concentration, and duration of application of the topic.
- Silver-based topics can be used for deeper burns and long-acting (LA) silver agents can be used on superficial wounds (cytotoxic). Little evidence suggests that silver topics prevent wound infection. Mafenide acetate (MA) is used for deep or infected burns and deep burns of the ear. Topical antiseptics like Dakin's solution and acetic acid have broad spectrum effect and rare resistance, effective against biofilm, useful for chronic, heavily colonized, and infected wounds. Topical ATB ointments have a restricted spectrum and thus used in small superficial burns including the face. Topical honey can be used in superficial partial thickness burns. Cerium nitrate used for full thickness burns when early surgical excision and wound closure cannot be performed[11]. (low-quality evidence to prevent burn wound infection)

Surgical intervention

Two major approaches are considered in burn surgeries: debridement and skin grafting.

- Debridement can be found in four different ways depending on timing and depth: early excision (within first week to 10 days after injury), delayed excision (after 10 days but before 3 weeks), tangential excision, fascial excision (down to deep fascia) and late grafting (undertaken after delayed primary burn excision or after conservative sloughing of the burn wound and grafting onto granulation tissue)
- Early excision and grafting were shown to be the best approach for patient survival. In a resources-limited setting, surgical cleansing with appropriate dressing followed by late grafting is aborded (conservative approach). In the

latter, surgical team may also respond to development of pain, nutritional intake, and prevent physical therapy and splinting.

- For preventing any heavy hemorrhage during burn wound excision, subcutaneous epinephrine (vasoconstrictor) in 1/200,000 to 1/1,000,000 of large volumes normal saline is used; in addition, it provides better visualization of the wound and increases surgery precision. When used as topical compounds on excised wounds or donor sites, it also prevents blood loss at concentrations of 1/33,333 to 1/100,000 in saline.
- For infiltration, a good all-purpose solution is 2 mL of 1 mg/mL of epinephrine in 1000 mL of normal saline, producing a concentration of 1 in 500,000. Stronger concentrations may be used for facial burn excision. The fluid should be warm. For topical application, 30 mL of 1 mg/mL of epinephrine in 1000 mL of normal saline produces a solution of 1 in 33,000, which is a potent topical hemostatic agent. The solutions should be carefully marked to avoid accidental injection of the potent topical application solution[12].

Non-surgical interventions

Concerning the scar management prophylaxis:

- Superficial burns may be covered with topical emollients (silicone, vegetable oils, butters, alcohols, and petroleum derivates) or humectants (glycerin, sugars, proteins, amino acids, elastin and collagen), sun protection (creams, clothes…) and massage after healing. It should be sufficient to apply simple emollients rather than silicone gels/sprays (supportive evidence).
- Pressure therapy (PT) with or without silicone therapy is used as a first-line modality to prevent hypertrophic scarring.

As for the scar management treatment of hypertrophic burn scars:

- Pressure therapy with silicone therapy is used as a first-line treatment for all extensive burn hypertrophic scars.
- Intralesional therapies are limited to hypertrophic burn scars:
  - Young hypertrophic and keloid scarring: Triamcinolone acetonide (TAC) improves inflammation and increases collagen degradation; as well as verapamil and 5-Fluorouracil (5-FU). The latter inhibits fibroblast proliferation. Combinations of TAC and 5-FU can be done.
  - Resistant lesions and keloid diathesis: bleomycin.
  - Old lesions: TAC + cryotherapy with microneedles[12]

Infection prevention and management

This section discusses the medical staff and people's behavior, antibiotic stewardship and infection control (sufficient evidence).

Behavioral prevention:

- Always keep a clean hospital environment by surfaces and hands cleaning, in addition to environmental monitoring, to limit infection transmission and of course the burden of the disease.
- Patients with high-degree burns should be isolated to prevent any form of contamination.
- The education of staff and families is as important as surfaces and hands cleaning, to ensure the most secure environment.

Antibiotic stewardship:

- The use of antibiotic prophylaxis in acute burns is not recommended because it enhances the development of multi-drug resistant organisms (MDRO), despite that it can be beneficial for the patient's health and may reduce pulmonary complications.
- Their use can be accorded in the case of resources-limited setting (RLS) where the lack of microbiology diagnosis can be fatal especially in sepsis.
- Implement an antibiotic stewardship program (ASP) to control the overuse of broad-spectrum antibiotics and thus limit the development of MDRO.

Infection management

This section can be subdivided between sepsis, pneumonia, UTI, and wound infection.

a. Sepsis management

- Considering burn sepsis patients as a new category will help determine the need of broad-spectrum antibiotics; a <15% TBSA patient may not be responding in an enlarged inflammation, so no sepsis and then no need for strong antibiotics to treat or prevent sepsis.
- In the case of TBSA >15-20%, all patients should be considered subjects to sepsis, and thus constantly monitored for any signs and symptoms. Diagnosis of sepsis may include higher or lower temperature, tachycardia, tachypnea, confusion, hemodynamic instability, vasopressor requirements, increased fluid requirements, thrombocytopenia, base deficit, hyperglycemia, and nutritional intolerance. In addition, detection of culture-positive infection, pathologic source of infection, or clinical response to antimicrobials is required to diagnose sepsis.

- In RLS, microbiological identification may not be available, and so sepsis diagnosis may rely on clinical symptoms.
- Empiric treatment of sepsis includes:
    - IV fluids to reach a mean arterial pressure of 65mmHg and to restabilize lactate levels (to be initiated with crystalloids)
    - Norepinephrine with vasopressin or epinephrine as vasopressors
    - In inotropic instability dobutamine might be given
    - Full body check to wounds and culture of fluids that might contain pathogens before initiating antibiotics. The latter needs to cover the bacteria identified and sensitive to the strain. Systemic antibiotic prophylaxis is not advised.
    - Infection control: remove or change catheters, clean wounds[11]

b. Pneumonia management

- Patients with major burn injuries (>15-20% TBSA) experience immunosuppression; inhalation injury impairs lung immunity and thus increases risks of pneumonia to 20%. Pneumonia associated to intubation increases needs in oxygen by more than 20%, increase in positive end-expiratory pressure (PEEP) > 3cm, body temperature > 38°C or <36°C or WBC > 12,000 or < 4000 and antimicrobial intake more than 4 days. Thus, intubated burn patients should be closely monitored for pneumonia.
- In intubated patients, bronchoalveolar lavage (BAL) or subglottic specimens should be used to identify the incriminated pneumonia pathogen.
- Risk factors of pneumonia in burn patients include inhalation injury at a scale of 3 to 4 identified on bronchoscopy, large burns (>20% TBSA), initial PaO_2/FiO_2 < 300mmHg, carboxyhemoglobin exceeding 10% on admission, smoking history.
- Clinical diagnosis of pneumonia includes: 1) persistence of infiltrate, consolidation, or cavitation on X-RAY, 2) sepsis, 3) recent change in sputum or exudate in the sputum.
- Pneumonia antibiotic prophylaxis is not advised for burn patients on admission even in the case of inhalation injury, it should be targeted on the pathogen identified.
- In a confirmed pneumonia status, antibiotic therapy suiting the pathogen detected should be installed, as covering the gram-stain identified and furthermore the antibiogram, drug availability and pathogen identified. The course duration depends on the bacteria and patient's case severity. For patients with ventilator-associated pneumonia (VAP) not due to gram-

negative bacilli, a fixed course (7–8 days) of antibiotics may be optimal, as it does not increase the risk of adverse clinical outcomes and may reduce the emergence of resistant organisms compared to a 10–14day course. For patients with VAP due to nonfermenting gram-negative bacilli, a 10–14-day course of antibiotics may reduce the incidence of recurrent pneumonia compared to a 7-day course, but little study of this has been conducted in burn patients.

- Patients with VAP may be exposed to stress ulcer and deep venous thrombosis (DVT) risks; to minimize these risks certain parameters may be modified, like elevation of the head of the bed to 30°, daily oral care with chlorhexidine, minimizing sedation, changing the ventilator circuit only if visibly soiled or malfunctioning, stress ulcer prophylaxis, and deep venous thrombosis (DVT) prophylaxis[11].

c. Urinary tract infections (UTIs) management

- Catheters should only be inserted in certain conditions: 1) when patients are expected to receive large volume infusions or diuretics; monitor urinary output during initial fluid resuscitation; 2) an expected prolonged duration of surgery with need for large-volume infusions and/or the need to monitor intraoperative urinary output (catheters inserted for this reason should be removed postoperatively); 3) measurements of urinary output in critically ill patients; and 4) when selected patients with urinary incontinence need assistance in healing of open skin grafts. It should be installed for the needed duration.
- Indwelling urethral catheters aren't recommended in urinary incontinence or in measurement of urinary volume. And so, external catheters and diapers remain a good choice in these situations for both adult and pediatric patients.
- Insertion of urinary catheter required skilled personnel that ensure an aseptic technique. Monitoring of the inserted system is essential to maintain a closed drainage system and action in the case of breakage of the latter (take back and replace with a new aseptic one accompanied with a new collecting system). Concerning indwelling catheters, they're not required to be changed regularly, but only in clinical indications like infection, obstruction, issues in the closed system.
- Bladder instillations using normal saline or antimicrobials in the catheter are not recommended as prevention of catheter-associated infections[11].

d. Wound infections management

- Invasive burn wound infection is characterized by the microbial evasion of normal non-burned cells by 10^5 CFU/g of tissue detected on biopsy surrounding the wound. Quantitative diagnosis is often recommended to

modify antimicrobial therapy. In RLS, clinical symptoms are crucial to put in place invasive wound infection management: early separation of the eschar, brown-black foci of discoloration, sub-eschar suppuration and ecthyma gangrenosum.

- Burn wound infections are initially treated with topical and systemic antimicrobial agents. Adequate early debridement of the infected burn wounds removes the infected tissue, improves the local perfusion, and reduces the risk of colonization with direct impact on outcomes. If the diagnosis of burn wound infection was established, and early debridement is not an option (patient status, resource availability), increased frequency of antimicrobial application should be performed along with a targeted systemic antibiotic therapy. The presence of invasive burn wound infection will lead to prolonged hospital stay.
- Certain factors could influence the decision to perform early burn wound excision. Some of these factors include patient status and comorbidities, extent and depth of the burn wounds, resources available (operating room, staffing, topical antimicrobial supplies, availability of temporary wound coverage) and the local burn management practice.
- Infection monitoring of the burn wound is essential to assess the pathogen involved and the evolution of the infection, and thus to decrease inappropriate use of systemic antimicrobials.
- Prophylactic antibiotics are not recommended to patients with non-severe or severe burn injuries in the first 5-10 days after injuries to reduce the burn wound infection rates, because studies showed it's not beneficial, and it raises MDRO rates.
- In large burn wounds, investigation of possible fungal infection is essential because they're associated with greater mortality. The diagnosis is made by culture and histologic examination of the biopsied tissue and immunofluorescence testing. If diagnosis is made, aggressive wide debridement of the infected areas and systemic antifungal therapy is required.
- The commitment to infection control practices towards burn patients, like physical isolation in a private room, use of gowns and gloves during patient contact, and hand washing before and after each patient visit, and the use of a laminar airflow isolation room reduces the risk and incidence of outbreaks in burn wound infection with nosocomial bacteria.
- As a regular monitoring, burn-care centers should investigate the wound colonization status of patients and staff, antimicrobial profile of these pathogens and possible trends of nosocomial spread[11].

Metabolic manipulation

The metabolic stable state maintenance of burn patients helps improve the patients' status. The dominant determinants of metabolic aberration remain nutrition, wound closure, and prevention/treatment of infection.

- Maintenance of body temperature during the acute phase for burns involving >20% of TBSA helps avoid heat loss, by applying dry dressings and cooling the environment with ventilation and air conditioning systems.
- The return to exercise and early mobilization should be initiated rapidly and progressively after the burn injury.
- For burns greater than 20% TBSA, caloric requirement should be provided predominantly with carbohydrate and protein, and in accordance with accepted formulae. Pre-injury nutritional status, weight trend, World Health Organization (WHO) growth charts, and indirect calorimetry may be used to personalize this estimate of post-burn caloric needs. If blood glucose exceeds 180mg/dl, insulin supplementation (under the care of a specialist) can be used to restabilize blood glucose to 150mg/dl.
- In burn patients 18 and younger after burn resuscitation, a nonselective beta-adrenergic blocker may be given via oral or enteral route to reduce heart rate. Heart rate monitoring (at least pulse oximetry) should accompany dosage titration to achieve 75% of the admission heart rate.
- Propranolol has been amply demonstrated to modulate post-burn hypermetabolism in children. The clearest evidence indicates a reduction in heart rate, cardiac work, and post-burn hepatomegaly. Additional effects may include beneficial immune modulation.
- Additionally, oxandrolone can be considered as adjunctive therapy to preserve body and muscle mass after burn injury.
- Care should be taken in children less than 2 years of age, where cardiac output may be heart-rate dependent, and for patients with inhalation injury, as beta blockade has the potential to be problematic. Beta blocker therapy should be delayed in patients who are hypotensive due to inadequate resuscitation until normovolemia is established and hypotension resolved. If oxandrolone is used, liver function studies should be monitored weekly to ensure that there is no increase in transaminase levels, which can occur with oxandrolone therapy[11].

Mobility, exercise, and physical function

The return to exercise and early mobilization should be initiated rapidly and progressively after the burn injury.

a. Mobility

- Patients with lower extremity skin grafts should use supportive compression to the legs when mobilizing in upright positions.
- Assistive devices and machines may be used to facilitate mobilization or ambulation after burn injury in order to improve feasibility, safety and independence of mobilization.

b. Exercise

- Burn survivors should follow a wide spectrum of exercise programs including range of motion, strengthening and cardiovascular exercises.
- Exercise programs should be performed for a minimum of 6 weeks and continued until pre-burn motion, strength and endurance are achieved when possible.
- Exercise programs show benefit to the burn survivor when initiated as early as discharge from acute care but may have benefit if implemented sooner. Physiologic response of the burn survivor to exercise should be monitored during exercise performance.

c. Physical function

- Burn survivors should receive rehabilitation for restoration of function to achieve as possible the functional state before the injury.
- Evaluation and treatment planning of functional limitations should be guided by the domains of the WHO's Conceptual Framework of the International Classification of Disability and individualized to the burn survivor's needs.
- Appropriate functional outcome measures should be used to document and monitor a burn survivor's progress and outcome.
- For optimal functional outcomes, a multidisciplinary burn team approach should be used, and physical rehabilitation should include occupational and/or physical therapy initiated upon admission and continued throughout recovery[11].

Pain control

Pain associated with burns combines different facets of psychiatric factors like distress, anxiety, delirium, with situational and emotional factors. Managing and reducing pain is crucial to improve greater health following injury.

- Monitoring the adequacy of pain control is facilitated by regular use of scales and scores during all phases of care. Scales that require human reporting are preferred. Validated pain behavior observation-based scales are useful when the patient is unable to self-report because of mental status impairment or young age.
- Pain management should cover all aspects of a patient's pain like background, breakthrough, procedural, perioperative, and chronic long-term pain. Addressing each of these elements will improve pain control.
- Apart from opioids, non-opioid analgesics, nonsteroidal anti-inflammatory agents and nonpharmacologic maneuvers are recommended in managing burn pain. Each patient is differently evaluated from the other, and thus not all medications suit everyone.
- Dissociative drugs such as ketamine: control of procedural burn pain; Dexmedetomidine and other non-opiate analgesics: reduce acute opiate requirement; non-opioid analgesics, nonsteroidal anti-inflammatory agents, and nonpharmacologic maneuvers: an important adjunct as well as primary therapy for burn pain.
- Psychiatric and neurologic diseases are a major part of pain management, and so it is important to consider the impact of emotional factors and neuropathic sensory change (Gabapentin or pregabalin can be used) so their handling may reduce overall pain medication requirements and complications and may improve the management of pain.
- Nonpharmacologic techniques such as education, distraction, activity-based play therapy, relaxation, guided imagery, music therapy, hypnosis, acupuncture, enhanced patient control, somatosensory approach of motor imagery, meditation and parental participation all have potential individual utility in facilitating control of burn pain in the conscious patient. Their adjunction to pharmacological treatment may improve the experience of burn pain[11].

Anxiety - agitation

Burn patients frequently present with anxiety and agitation that can be related to degradation of clinical outcomes. For this reason, the administration of sedatives is required to treat them.

- The correct diagnosis and treatment of underlying causes of agitation is essential before installing sedatives drug course. If agitation is misdiagnosed, it could lead to wrong medications and then unwanted toxicities.
- Nonpharmacologic interventions like optimizing the environment, sleep provision (via appropriate hospital environment and routines), adequate

analgesia, early mobilization, diversion therapy, and frequent reorientation, should be used in the treatment of anxiety and agitation, it offers great benefits like the avoidance of sedative use with its associated complications, potentially lower cost, universal availability, and adaptability to multiple different cultural environments. The effective application of nonpharmacologic techniques relies on knowledge of the norms and cultures in the burn care environment.

- When sedation is needed, scales and protocols should be used to monitor and adjust sedative administration to the lowest effective dose, and thus provide a reference point. The type of scale and sedation protocol used will vary based on staff training, drug availability, and cultural norms. Light sedation (patient arousable and able to purposefully follow simple commands) is preferred unless medically contraindicated. Lighter sedation is associated with improved outcomes and patient ability to participate in therapy and activities. The choice of agent, route of administration, and local drug availability will determine which sedative agents will be employed in any given setting.
- Nonbenzodiazepine medications are more indicated for sedation than benzodiazepines because of the multiple side effects, tolerance development, and its metabolic profile. Commonly used are propofol which binds to several receptors in the CNS, and dexmedetomidine that is an alpha-2 receptor agonist.
- Burn patients are also at risk for delirium that can increase mortality, hospital stay and cognitive impairment. It's difficult to treat when established, and so prevent it relies on nonpharmacologic therapies like ensuring sleep, increasing mobility, and providing frequent reorientation[11].

Blood transfusion

Blood transfusion is rarely indicated during burn resuscitation unless associated traumatic injury causing significant blood loss is present.

- During hospitalization blood should be transfused based on clinical assessment of the burn patient and families should be informed of the risks of transfusion including include mismatching, transfusion reaction, Transfusion Related Acute Lung Injury (TRALI), Transfusion Associated Circulatory Overload (TACO), Transfusion Related Immunomodulation (TRAMI), electrolyte abnormalities, hypothermia, and transmission of infectious diseases.
- Blood transfusions should be administered one unit at a time unless the patient is hemodynamically unstable or actively bleeding. The more units transfused, the greater the likelihood that the patient will develop antibodies,

have a transfusion reaction, or develop TACO or TRALI. Patients should be reassessed prior to the administration of a second unit of blood.

- Blood type should be confirmed, and blood should be cross-matched prior to transfusion to improve the safety of the transfusion, unless an emergent need (such as massive hemorrhage) is present.
- Blood tests are only prescribed in necessary cases, and the blood quantity should be minimized to reduce risks of anemia and the need for transfusion. Laboratory resources and patient status may impact the blood tests maintenance.
- Using erythropoietin as a factor to reduce transfusion requirements has not been recommended for burn patients.
- During massive surgical blood loss, consideration should be given to administering plasma and platelets in a 1:1 ratio if resources permit[11].

Deep venous thrombosis (DVT)

Scientists report the development of DVT in 0.25% to 1.77% of symptomatic burn patients. It was at 8% in young adults with a TBSA >40% and not receiving any chemoprophylaxis.

- Adult burn patients should be evaluated for DVT risk, and patients with moderate-to-high risk should receive chemoprophylaxis unless medically counter-indicated.
- No consensus has been made concerning the substance to use, but it has been shown in studies that low-molecular weight heparin (LMWH) can be considered as a prophylactic choice. In the only study realized, enoxaparin used at 30mg twice a day with no DVT showed promising results. No evidence supports an improvement in DVT prophylaxis for pneumatic compression devices via rapid inflation, high pressures, or graded sequential intermittent compression systems.
- Putting back patients to mobilization helps decrease risk of DVT[11].

Psychiatric disorders

Patients screened for psychiatric or social risk factors may help determine their impact on safety and well-being.

- And so, screening: 1) Upon admission: mechanism of injury (self-inflicted or abuse/ neglect), social support resources, housing and food resources, blood alcohol level; 2) During inpatient hospitalization: depression, acute stress disorder (ASD)/post-traumatic stress disorder (PTSD), anxiety, substance use

disorder; and 3) Within the first month of hospital discharge, then as needed thereafter: depression, ASD/PTSD, anxiety, substance use disorder.

- If screened positive for psychiatric disorders, patient should be set up with a specialist and offered treatment within the burn care center[11].

Outpatient burn care

Outpatient care should be integrated into the burn-center service region.

- Burn centers must provide outpatient care for small burns and for follow-up of large burns patients after hospitalization.
- Burn centers must incorporate multidisciplinary burn care programs for patients unable to travel to other regions.
- As previous point, outpatient care should include everything a patient needs outside hospital, as in wound care, scar management, functional activities, and psychosocial consultations[11].

1.1.2 World Health Organization (WHO) Burn Management Guidelines (2020)

According to the WHO, burn patients should be treated like all other trauma patients. Special considerations should be taken for different groups that will be detailed posteriorly.

The burn severity is graded by surface area, depth, and others. The risk of morbidity increases with surface area and age. If burns exceed 15% of the surface area in adults, 10% in children or burn injury in any of the extreme ages, it needs to be managed as an emergency.

Body surface area

Considering the surface area, the burned surface can be estimated with the Rule of 9s, where the body surface is divided according to anatomical regions that represent 9% or multiples of 9%. In the case of a small burn, the surface can be estimated according to the outstretched palm and fingers that reaches 1% of total body surface. In children, this rule is modified knowing that surface proportions differ[4].

Depth of burn

This parameter needs to be measured and determined in order to assess the burn grade and to prepare an appropriate treatment plan (table 3).

Another wound type that could be found is a mix of all types of burns within the same wound. Depth can change over time, particularly in the presence of infection.

Emergency burns

Some types of burns require an immediate hospitalization, the cases are the following:

- A burned surface area exceeding 15% in adults
- A burned surface area exceeding 10% in pediatric patients
- Any burn in extreme ages or infirm patients
- A third or a fourth-degree burn
- Some sensitive regions like the face, ears, eyes, hands, feet, perineum
- Circumferential burns
- Burns caused by electricity of high-intensity (high-voltage)
- Burns caused by inhalation
- Burns accompanied with other types of diseases like trauma or preexisting diseases like diabetes[4]

Table 3. Description of Burn Degrees According to Aspect and Sensation. Adapted from the WHO 2020 Guideline.

Depth of Burn	Aspect	Sensation
First degree	Red Blanches when pressure applied Dehydrated No blisters	Hurtful
Second degree – superficial ***(Partial thickness)***	Red Blanches when pressure applied Moist, weeping Blisters	Hurtful to temperature and air
Second degree – deep ***(Partial thickness)***	Variable color No blanching when pressure applied Wet, waxy or dry Blisters (easily unroofed)	Perceptive of pressure only

Third degree ***(Full thickness)***	Waxy white, leathery gray, charred or black No blanching with pressure Dry, inelastic	Deep pressure only
Fourth degree	As with third degree, but extends in depth into fascia and/or muscle	Deep pressure

Wound care

First aid care is the first mandatory care practiced on burn patients, either on spot or in the burn care facility.

- Cool the wound with water to limit damage.
- Burned clothes need to be removed if possible.
- In the case of a localized burn, pain, edema and tissue damage can be limited by immersing the wound in cold water for half an hour.
- In the case of an enlarged burn, sterile bands should be applied around the burned area (or whole patient) to limit and mostly prevent systemic heat loss and hypothermia, that can be a big risk in pediatric children.
- Following injury, the first 6h can be the most critical, and thus the patient needs immediate transport to a hospital.

Following these steps, the **initial treatment** is recommended to increase healing speed and prevent infections since the burn is sterile at the beginning.

- Tetanus prophylaxis should be given in any burn type encountered.
- Bullae needs to be debrided except in very small burns. Adherent necrotic tissue should be initially excised and continue with all necrotic tissue in the next few days. Necrotic tissue can be removed via gentle scrubbing.
- Following this step, the wound should be cleaned with 0.25% chlorhexidine solution, 0.1% cetrimide solution or another mild water-based antiseptic. All alcohol-based solutions should not be used.
- Silver sulfadiazine cream should be applied on the wound or dry gauze should be used to cover the wound, and the dressing should be thick enough to prevent seepage to the outer layers.
- The development of cellulitis may be a marker of infection, in contrast to fever which is not a specific parameter.

After these first two treatments, the wound should be entertained with a **daily treatment** consisting of:

- The change of the dressing is a daily activity (bi-daily if possible, or more if needed) accompanied with loose tissue removal if found.
- Wounds should always be checked for any change of color or bleeding that might indicate a possible infection.
- If hemolytic streptococcal wound infection or septicemia is faced, systemic antibiotics should be used. If *Pseudomonas aeruginosa* infection is encountered, it can be rapidly deadly, and so systemic aminoglycosides are recommended.
- Like the initial treatment, topical antibiotics should be used, one example is the silver nitrate (0.5% aqueous) known as the cheapest topic, is applied with occlusive dressings but does not penetrate the wound or eschar. In addition, it decreases the electrolytes levels and colors the site of application.
- Silver sulfadiazine ointment (1% miscible) should be used with a single dressing layer. Contrarily to silver nitrate, it enters the eschar on a limited level and might cause a decrease in neutrophils count.
- Compared to the first two topicals, mafenide acetate ointment (11% miscible) is applied with any dressing on it. It enters the eschar but develops acidosis. Other agents can be used.
- If hands are burned, specific steps should be followed to preserve its function: hands should be covered with silver sulfadiazine and covered with loose polyethylene gloves or bags locked at the wrist with a crepe bandage. Hands should be elevated for the first 48h to then start exercising them after that period. Once a day or more, hands can be bathed, check the burn, and reapply silver sulfadiazine after removing the gloves. The latter can be re-put on after silver sulfadiazine application.
- If skin grafting is necessary, consider treatment by a specialist after healthy granulation tissue appears.

Finally, the depth and surface of the burn can have an impact on the time of healing phase. If no infection is detected, superficial wounds can heal quickly. Split thickness skin grafts can be applied to full-thickness burns after wound excision or the appearance of healthy granulation tissue. Long term care should be discussed and available for the patient.

Burn scars evolve over time, maturate, and become hypertrophic and form keloids. They flatten, soften and fade with time, but this duration cannot be determined and can take up to two years.

On the face, burn scars can cause cosmetic deformation, ectropion, and contractures about the lips. Ectropion can push the development of keratitis and blindness; lips deformity restricts food intake and mouth care. Specialized care is needed in these cases[4].

Children cases

In children, the scars can interfere with growth if they develop contractures. Therefore, these contractures should be removed by early surgery.

Nutrition

Due to the excess of trauma catabolism, heat loss, infection and call for tissue regeneration, patients will require a higher intake of energy and proteins. If needed, adequate energy intake can be accorded through a nasogastric tube (up to 6000 kcal a day).

If malnutrition and anemia are encountered, they can slow down or stop the healing process and may cause a failure of skin grafts. Eggs and peanut oil are good, locally available supplements[4].

1.3 North American Guidelines

1.3.1 American Burn Association (ABA) Guidelines (2017, 2020)

These guidelines cover specific burn care including under austere conditions, precisely blast injuries. And so, these guidelines were dedicated to disaster preparedness for the US Army. The other aspect includes the management of acute pain in adult patients that consists of an update from the last guidelines.

This section focuses on the recommendations outlined in the ABA guidelines for diagnosing burn types, management, and relative supportive care. All recommendations in this section are of good evidence unless otherwise indicated[36].

A. Burn care under austere conditions: blast, radiation, and chemical injuries

Austere conditions are referred to war conditions enveloping the army that can be of different types: blasts, radiation, and toxic industrial chemicals. The burn care of each type will be detailed posteriorly.

a. Blast injuries

Blast injuries occur during explosions. They're classified depending on the exposure to the blast. Primary blast injury is more common in explosion survivors inside structures or vehicles because of blast-wave physics. By far, secondary blast injury is more common. According to a study on US service members, the most common

injuries were mild traumatic brain injuries (mTBI), open wounds in the lower extremity, and open wounds of the face.

In the body, both stress and shear waves induce tissue damage. Stress refers to microscopic effects at interfaces between tissues of different densities, of which spalling is displacement and fragmentation of denser into less dense tissue, and implosion is the opposite. Shear is macroscopic tissue damage which occurs as energy travels at different velocities through adjacent tissues of different densities. The most striking effect of a blast wave on the body occurs in organs with air–water interfaces, which is why the tympanic membranes, lungs, and the gastro-intestinal (GI) tract are vulnerable.

These concepts are dramatically impacted by the circumstances surrounding the explosion. The use of helmets and torso body armor influences the injury pattern by altering both overpressure and wave shape/duration. Explosions within buildings or vehicles are more lethal than explosions in the open air because structures focus and reflect blast waves, generate more secondary fragments, ignite secondary fires, and create the risk of entrapment or of structural collapse.

And so, each type of injury requires a special treatment that will be described posteriorly.

Emergency care

The immediate action of the body in response to a blast involves bradycardia, apnea and hypotension. To avoid the development of barotrauma which can exacerbate pulmonary injury or induce arterial gas embolism (AGE). Fluid resuscitation of the patient with primary blast injury must strike a balance between over-resuscitation, which will worsen pulmonary edema, and under-resuscitation, which is poorly tolerated in animal models of blast injury accompanied by hemorrhage.

Traumatic brain injury (TBI)

Screening for TBI using a brief survey should be done on all persons exposed to an explosion to assess the potential of developing TBI. The real diagnosis remains primarily clinical.

Otologic injuries

Otologic examination is required in patients injured in explosions. Since the tympanic membrane is the most sensitive component in the body to blasts, it should be checked for rupture, knowing that 50% of exposed persons get injured. A confirmed rupture should lead to examination of delayed-onset lung or intestinal injury. However, a normal membrane should not exclude the probability of injury of other drugs.

Rupture is impacted by head position relative to the blast and by ear canal contents.

A big majority of tympanic membrane ruptures heal spontaneously; most within 3 months of injury. The surface area of rupture predicts spontaneous healing success. Healing is unlikely without surgery if the area is greater than 80%. Other otologic blast injuries may include hearing loss (temporary or permanent), tinnitus, otalgia, otorrhea, and bleeding from the ear. Patients should be examined for bilateral hearing acuity, for sensorineural hearing loss with a tuning fork, and for facial nerve injury. Long-term follow-up, to include audiometry, should be performed for all persons exposed to explosions.

Blast lung

Blast lung syndrome represents the second most common primary blast injury encountered, and it involves the characteristic symptoms of dyspnea, cough, and hypoxia. The clinical aspects include alveolar-capillary disruption, intraparenchymal hemorrhage, hemo- and pneumothorax, pneumomediastinum, subcutaneous emphysema, and/or bronchopleural fistula.

Blast lung injury can manifest up to 6–8 hours after injury; thus, asymptomatic but at-risk patients should be put under observation for delayed onset of symptoms for 6-8h. The chest radiograph typically shows bilateral hilar infiltrates in a “butterfly” pattern. Blast lung injury may also cause AGE, manifested, for example, by focal neurologic deficits. Physical findings of AGE may include retinal arterial air on ophthalmoscopy, tongue blanching, or livedo reticularis. Likewise, all these findings may be absent.

Intestinal injuries

According to a study performed on 1040 survivors of air-blast explosion showed that intestinal injuries constituted around 3% of total injuries. The top injured parts of the intestinal tract were the terminal ileum and cecum. Intestinal injury can manifest as sub-serosal hemorrhage, which, on histopathology, is shown to be submucosal. With increased blood loading, immediate perforation may occur. Lesions which do not perforate right away may (in about 5% of cases) undergo necrosis and delayed perforation, most often more than the ensuing 3–5 days. In the absence of perforation, diagnosis by CT scan may be erroneous, and frequent reexamination of the patient is recommended.

Eye injuries

Patients’ victims of an explosion should have their eyes examined. According to the US Army clinical practice guidelines:

- Examination and documentation of visual acuity

- Examination of the corneas with fluorescein using Wood's Lamp
- Globe penetration careful examination
- Use of a metal Fox shield and avoidance of pressure or dressings to protect the patient with an open globe injury.
- Suspected globe injured patients should be referred to a specialist.

Extremity and pelvic/perineal injuries

Extremities are the most body members exposed to blasts. High rates of Gustilo-Anderson open tibia fractures grades IIIB and IIIC are observed in war casualties. And so, some of the solutions include aggressive debridement and early amputation.

On the other hand, pelvic and perineal injuries occur at high rates like pelvic fractures and / or bilateral high above-the-knee amputations. Thus, immediate activation of a massive transfusion protocol, rapid transportation to the operating room, a multiple-team approach to surgery, damage control laparotomy with proximal vascular control, and pelvic external fixation are among the maneuvers that may be required to salvage such patients.

Triage of multiple casualties

Several settings can lead to multiple blast injuries. And so, care involves an initial evaluation often supplemented with CT imaging, multiple surgical procedures, critical care, and blood-bank resources. Patients suffering blast are at risk for delayed manifestations of their injuries and therefore require monitoring over time by skilled providers.

Initial surgical care is determined by physical exam and patient stability. When imaging is not available, examination of wounds and body cavities must be made based on physical findings. Blast-injured patients that are transported from the scene of injury early after the incident are at risk for delayed manifestation of life-threatening injuries, particularly to the lung or bowel and should be so monitored during transport[36].

b. Radiation injuries

Radiation injuries occur in the setting of nuclear reactor accidents, military grade thermonuclear detonations, and terrorist deployment of an improvised nuclear devise or radiologic dispersal device. And so, these conditions differ from the medical setting encountered every day and thus need special care. In the US, the Radiation Injury Treatment Network (RITN) is specialized in the treatment of those injuries and in hematopoietic stem cell transplantation (HSCT). The amount of exposure determines the treatment to put in place.

In radiation blasts, several types of radiation are encountered including α, β, and γ radiation. A and β are contaminants of the environment, they're very small particles and so can be distributed on a big surface. Alpha radiation penetrates only a few microns, is easily shielded, and therefore does not pose a threat on normal skin. Beta particles are moderately penetrating but can be shielded by a sheet of foil. Beta radiation has the potential to cause significant burns even on normal skin. The top threat encountered with these particles is their impact through inhalation and ingestion; their irradiation of sensitive tissues of the eye, respiratory tract, and GI mucosa, or contaminated wounds which could delay or prevent wound healing.

And so, contamination with radioactive particles should be detected as soon as possible, better before transport or entry of a health care facility, to ensure the safety of the personnel taking care of the patient using the standard personal protective equipment following the ALARA (As Low As Reasonably Achievable) principles:

- time restriction in the presence of radioactive particles
- distance between the personnel and radioactive materials should be as big as possible
- shielding from the radioactive materials should be maximized

Care should be taken to limit contamination of ambulances and health care facilities; and medical and surgical treatment in life-threatening conditions should be initiated even if contamination is present.

The detection of radioactive particles can be done through a radiation meter such as a Geiger-Mueller meter with a pancake probe. If detectors are not available, patients need to be considered contaminated and appropriate protocol should be initiated to protect personnel and decontaminate patients. If patient's face might be contaminated lung contamination should be checked, and internal decontamination must be performed like bronchoalveolar / gastric lavage, and decorporation therapy (drug specific decontamination therapy) if inhalation exceeds the annual threshold allowed. However, these procedures might not be possible in austere conditions, and only the detection of radioactivity can be possible. No alternative to decorporation is available. Patients should be isolated, and entry should be limited to non-pregnant employees and badged with thermoluminescent dosimeter.

Radiation burns

The incidence increases if the patient was on ground zero of a thermonuclear detonation. Cutaneous radiation injuries develop beginning from 3Gy exposure, and so, visible skin degradation can be observed. Phases of manifest illness in cutaneous radiation syndrome with associated acute doses and timing of onset are described in table 4.

Table 4. Cutaneous Radiation Phases. Adapted from the ABA 2017 Guideline.

Cutaneous phases	Radiation intensity	Timing of onset
Epilation	3 Gy	~ 17 days
Erythema	6 Gy	2-3 weeks*
Dry desquamation	10-15 Gy	2-3 weeks
Wet desquamation	>~ 20 Gy	2-3 weeks
Blisters	~25 Gy	Days / weeks
Ulceration / radionecrosis	>~30 Gy	Days / weeks

**May have early erythema that disappears after 24-48h and then recurs in 2-3 weeks*

Decontamination recommendations

Burn surface and depth are estimated using the same methods for thermal burns. Decontamination should be performed in the case of detected contamination or unavailable tools for detection; it should be gentle avoiding sharp debridement. In the event of embedded radioactive shrapnel, special care should be taken to limit the spread of radioactive contaminants during irrigation and debridement. This can be done with waterproof dressings and drapes. It should also be assumed that these fragments will cause uptake (internal contamination).

Steps regarding wound decontamination should include the following:

- Detection of radiation if methods available
- Irrigate with water or normal saline
- Scrub gently with a cloth and tepid soapy water
- In the presence of debris in the burn / wound perform minor debridement
- Contain runoff and supplies contacting the wound (gauze, cloths) in a plastic garbage bag or similar, marked as contaminated, and disposed of accordingly.

Burn care in the field, similar to care of thermal burns, involves clean dressings, topical antimicrobials (silver sulfadiazine, bacitracin), elevation of burn extremities and traditional surgical burn intervention if resources permit.

Other aspects related to radiation could manifest, like Acute Radiation Syndrome, GI syndrome, Hematopoietic syndrome and Neurovascular Syndrome will not be discussed in this report[36].

c. Chemical injuries

Chemical injuries occur generally by accident exposure to toxic industrial chemicals (TICs), and these are described by inhalation of TICs that causes burns. Treatment of this kind of injury is similar to the one for smoke inhalation injury. It involves airway management, lung-protective ventilation, pulmonary cleaning, and avoidance of volume overload or excessively rapid fluid infusion that might worsen pulmonary edema. Vigilance is required for the manifestation of acute lung injury and ventilator-associated pneumonia. Treatment might include an antidote and transfer to a specialized healthcare facility.

Chlorine (Cl_2)

Chlorine is one of the most gases used in industry, and one of the gases used as war weapons against civilians and military individuals. In fact, this agent could cause a high number of deaths. Long-term exposure or health effects could be respiratory disorders (airway and alveolar diseases), cutaneous burns and post-traumatic stress disorder. Treatment related to this intoxication could include:

- Nebulized or IV corticosteroids
- Nebulized sodium bicarbonate in water (e.g., 3.75-4.2%) – not clear if beneficial
- Nebulized beta-agonists
- New research: IV and aerosolized ascorbic and deferoxamine since chlorine decreases levels of endogenous antioxidants

Phosgene ($COCl_2$)

This agent is largely used in the plastic, drugs, pesticides, isocyanates, and polyurethane industries; known to have a new-mown hay smell. Like chlorine, it was also used as a war weapon. The characteristic of this chemical is its delayed onset of action, like a delayed-onset pulmonary edema (where the patient develops hypovolemia due to rapid loss of plasma volume into the lungs) that cannot be detected before 6-12h. And so close monitoring should be performed.

Treatment related to this intoxication might include:

- IV corticosteroids if the patient presents soon after exposure
- Give bronchodilators
- Due to the development of oxidative stress and neutrophils influx into the lungs: N-acetylcysteine, ibuprofen, aminophylline, isoproterenol, and colchicine – not proved beneficial in humans yet.

Hydrogen Sulfide (H_2S)

This “rotten eggs” smelly gas is found in petroleum, natural gas, animal husbandry and waste management industries.

This gas finds its way to the bloodstream via the lungs and deprives cells of oxygen by inhibiting the cytochrome C oxidase implicated in the respiratory chain. At elevated doses, it creates reactive oxygen species. Like the mother molecule, its metabolite, thiosulfate, combines with hemoglobin to form sulfhemoglobin. Sudden loss of consciousness and an arrest of breathing could be noticed due to the impact of the gas on brainstem mitochondria.

Other aspects of H_2S intoxication are seizures, myocardial ischemia, pulmonary edema and keratoconjunctivitis.

Treatment related to this intoxication may include:

- IV fluids, oxygen, and if available mechanical ventilation*
- Antidotes: IV sodium nitrite (induces hypotension and low levels of methemoglobinemia); hydroxocobalamin was also used (no clear evidence if these antidotes are beneficial or not)

**Following resuscitation, long time unconscious patients can experience brain anoxia, acute lung injury and/or multiorgan failure.*

Anhydrous Ammonia (NH_3)

This strong odor liquid agent is found in fertilizer, refrigeration, food processing, petroleum, and explosives industries. It can form NH_4 on release that is water soluble. It can induce alkali skin and eye burns, severe tracheobronchial or pulmonary inflammation and obstruction if inhaled, and after that pulmonary edema. In addition, it can cause frostbite.

Treatment related to this intoxication can rely on:

- Intubation, ventilation, and decontamination of the patient
- Irrigation of any alkali injury including skin and eye.
- (Inhaled corticosteroids were not found effective in animal trials)

Mustard Agent (HD)

Used as chemotherapeutic agent (nitrogen mustard) and chemical weapon (sulfur mustard: HD), the latter is a threatening agent due to its easy fabrication and stock in third world countries; its symptomatic effect can be delayed from 2 to 24h after exposure; it can persist in the environment and pollute it for a long time, thus developing cross-contamination; it induces impairment in casualties rather than deaths; and no targeted antidote have been developed yet.

This component impacts moist areas of the body including eyes, airways, axilla and groin. It disrupts DNA and causes damage and cell death and mutations. In addition, it forms reactive oxygen species, decreases glutathione levels, generates reactive nitrogen species, and induces the formation of proinflammatory molecules like TNF α. It also impacts rapidly dividing cells in the GI tract and bone marrow. Additionally, skin injuries can be noticed, like dermal-epidermal separation; healing duration is much longer than thermal burns.

Management of this intoxication involves:

- Protection of healthcare professionals and patients, decontamination of exposed patients
- Detection of high-dose HD exposed victims must follow the upcoming criteria: 1) rapid onset of pulmonary symptoms, that is, within 2 to 6 hours; 2) ≥25% TBSA cutaneous injury (not just erythema); 3) heavy vomiting within 24 hours of exposure; or 4) a lymphocyte drop of ≥ 50% within 24 hours of exposure
- Treatment involves respiratory support, surveillance of those with lung injuries for pneumonia, ophthalmology assessment, atropine and antiemetics for vomiting, cutaneous management based on depth of injury, and granulocyte-colony-stimulating factor (GCSF) for those with decreased lymphocyte counts. Lymphopenia is an early marker for impending pancytopenia; the main effect of GCSF is to prevent neutropenia.

Hydrogen Fluoride

Hydrogen fluoride (HF) and hydrofluoric acid (water soluble form) are heavily found in gasoline, glassware, and semi-conductor industries. HF can dissolve in epithelium and form hydrofluoric acid. A small dose can induce pulmonary irritation and high doses can induce bronchial and pulmonary parenchymal deterioration. Systemic toxicity can occur and provoke hypocalcemia and hyperkalemia leading to cardiac arrest.

Airway support is needed to manage pulmonary disorders. IV calcium is used to reverse the systemic toxicity, and local burns are treated with topical calcium. As for HF inhalation injuries, nebulized calcium can be a treatment choice.

Others

Other agents, citing hydrogen chloride gas and isocyanates, are also pulmonary toxic agents found in polymer industries. No treatment has been discussed.

Summary of targeted therapies

And so, specific therapies and antidotes have been designed to get out of the toxic profiles imposed by chemical agents. And small summary is presented in table 5[36].

Table 5. Summary of Principle Toxic Chemical Agents and Specific Therapies Involved. Adapted from the ABA 2017 Guideline.

Toxic chemical agent	Therapy / antidote
Chlorine (Cl_2)	Antioxidants
Phosgene ($COCl_2$)	Early IV corticosteroids, surveillance for delayed onset pulmonary edema
Hydrogen sulfide (H_2S)	Hydroxocobalamin or nitrites
Ammonia (NH_3)	Prolonged decontamination
Mustard agent (HD)	Surveillance of lymphocyte count, GCSF for lymphopenia
Hydrogen fluoride (HF)	Calcium

B. Burn care under austere conditions: special care topics

Austere conditions are referred to war conditions enveloping the army. The first part described specific etiologies related to blast, radiation, and chemical injuries. The upcoming part will be focusing on special topics included in the burn care management like pain management, nutrition, rehabilitation, pediatric considerations, and palliative care.

a. Pain management

Pain management has been debated for a long time now, covering the use of different molecules approved or not by authorities as medical treatment of pain, like opium etc.

In the US, the Strategic National Stockpile (SNS) is a powerful resource for drug supply. And so, several analgesic drugs are prescribed for the treatment of burn pain.

Ketamine, an anesthetic with limited impact on respiratory depression, can be used as an operative and postoperative analgesic, in IV/IM/SubQ (the latter as a local anesthetic or infusion agent if the vein cannot be accessed) forms if needed.

Fentanyl, used in spontaneous pain management and procedural pain in IV and intraoral formulations.

Morphine, known for its multiple uses in IV, IM and PO formulations.

Methadone is preferably used for long-duration treatment and small risk of addiction. **Hydrocodone** gives a step-down option,

Lorazepam can reduce anxiety and prevent hallucinations in adults using ketamine.

Butorphanol, a 1:5 equivalent analgesic to morphine, can be used under IV and IM formulations. Intranasal formulation can be an alternative for IV use. **Nalbuphine,** a

1:1 equivalent analgesic to morphine, has similar properties of butorphanol with the intranasal option. **Buprenorphine,** a 1:40 equivalent analgesic to morphine, can be used under several formulations (sublingual, transdermal, injectable), can cause withdrawal symptoms in concomitant use with narcotics.

Nonnarcotic adjunctive agents, such as **Gabapentin,** cover neuropathic pain, reduces narcotics use in adult and pediatric patients, improve pain management, and sometimes decreases pruritis in patients. Another drug, **Pregabalin**, can decrease acute pain, pruritis, surface pain, procedural pain, but does not interfere with the opioid consumption in adult burn survivors. Anxiolytics, another type of nonnarcotic adjunctive agents, can be considered. Clonidine and Amitriptyline can reduce pain and anxiety and improve sleep and overall affect as well respectively.

Finally, **Cannabis**, a legalized drug in several states and countries, is being debated as a new pain manager in patients[37].

b. Nutrition

Nutritional intake may need to be increased after burn injuries due to the metabolic effects of the burn; patients with large burns (10%-20% TBSA), mechanical ventilation, severe oral or facial burns will need to increase their nutritional intake by oral supplementation or enteral nutrition (tube nutrition).

An initial intake of 2100 kcal is recommended, susceptible to increase. 50%-60% need to be given in the first week following the injury.

Patients with 10-20% TBSA can increase the amount of food intake or vary the consummation to higher protein value diet, and so they will need to eat whenever possible.

Patients unable to meet the required number of calories by oral intake may benefit from the tube feeding. The decision to start tube feedings will depend on how well patients eat and whether feeding tubes are available, can be placed, and if appropriate formulas/blended food are available. Gastric or small bowel nutrition feedings may be used to provide nutrition. Gastric feeding tubes can be inserted without specialized equipment and are generally easier to initiate than small bowel feeds. If marketed formulas are not available, foods may be blended and given through the feeding tube. Adding soy, dairy products, or other protein-rich foods increases protein intake; pureed fruits (or juice) and vegetables (particularly green or dark yellow) will add vitamins.

Parenteral nutrition requires highly specialized formulations and sterile mixing.

Parenteral and supplemental nutrition may not be possible in austere conditions, and so, patients need to be transfer[37].

c. Rehabilitation

Rehabilitation assistance after burn injury may involve physical and occupational therapy. In austere conditions, using available resources creatively **and** training the family to assist may provide the essentials to facilitate and enhance the chances of a successful outcome after a burn injury.

- Elevate limbs if they have significant swelling
- Position shoulders away from the body with elbows straight
- Position hands to avoid fisting
- Position legs away from the body with knees straight
- Position ankles at a right angle
- Stretch skin at least twice per day
- Train family to assist in therapy, if able
- Encourage sitting and walking as soon as possible[37]

d. Pediatric considerations

Children, considered fragile patients (due to their difference from adults in physiology, BSA, lung development, fluid requirements, ability to heal, response to sepsis, susceptibility to infection, language skills, and socialization), may be at risk to severe physical and psychological sequelae, and mortality in disaster situations. Additionally, in post disaster situations, children may be subject to refugee conditions, with lack of sanitation and hygiene, nutrition, and healthcare, exposing them to more diseases. Moreover, the absence of a parental figure to provide or advocate for these essential need places the child at further risk for disease and injury.

Fluid resuscitation is an essential component of oral and IV rehydration. If IV route cannot be accessed, intraosseous access can sometimes be easier to obtain. If the presentation is very delayed and wounds are granulated or grossly infected, treatment of septic shock with rehydration may be necessary. Children with burns are more vulnerable to dehydration and respiratory insufficiency secondary to infection and hypothermia than adults in a similar situation. Children have a higher BSA to weight ratio than adults, and risk hypothermia with exposure to cold environments. Hypothermia increases fluid requirements and the inflammatory response. Infants have limited ability to thermoregulate.

Protection of small children and infants from exposure to the elements is warranted, particularly in the presence of burn injury and during operative interventions. In some cases, this can be achieved by co-sleeping with the mother, extra blankets, and avoidance of unnecessary baths.

Concerning nutrition in nursing children, if the mother is not available, the location of donor milk or a local wet nurse is useful. Breast milk varies in nutritional and electrolyte composition. Beyond the early postpartum period, average measurements list human milk sodium at 141mg/L, potassium at 480mg/L, and chloride at 452mg/L. The nutritional content varies as well, depending on the mother, her nutritional state, and the volume of milk produced per day. Reported averages for breast milk contents list 3 to 5% fat, 0.8 to 0.9% protein, 6.9 to 7.2% carbohydrate as lactose, and caloric content as 60 to 75 kcal/100ml. For older children, oral rehydration, and nutritional supplementation with high protein products such as peanut paste are central elements of resuscitation and acute care of the burned child in austere circumstances.

For burns, topical therapy can be enormously effective for pain reduction. First aid with cool water is the first step in pain control. Following this, application of a petroleum-based ointment such as bacitracin or petroleum jelly or burn creams such as silver sulfadiazine with an occlusive dressing can greatly reduce the pain of a second-degree burn. Application of ointment without covering with dressing to areas such as the face is also effective in reducing pain. Prevention of infection is important for pain control, as infected wounds are painful. Readily available or easily manufactured solutions such as Dakin's are useful. Homeopathic remedies such as honey can be used as astringents to reduce discomfort associated with swelling and some even have anti-infective properties. Root and plant products such as aloe or tea tree oil are thought to improve healing from burns, but this is not always supported in the literature.

Elevation of the burned area decreases swelling, pain, and the subsequent development of complications. Protecting the wound from exposure to the air and the environment is important in reducing pain and the risk of infection.

Children have limited glucose stores and are susceptible to hypoglycemia with infection.

Infection can present as hypothermia in a small child rather than fever, and limitations in laboratory analysis could force reliance solely on physical examination to assess progress.

As previously discussed, the use of ketamine for bedside procedures can be extremely useful in austere settings as airway protective reflexes and respiratory drive are better maintained, and limit pain. Distraction techniques help reduce pain and anxiety around procedural interventions.

During operative intervention, limit blood loss using tourniquets and epinephrine clysis prior to excising burns and harvesting grafts.

Assign temporary names and guardians to unidentified preverbal children and preserve information on how and where they were found[37].

e. Palliative care

According to the guidelines, “the goal of palliative care is to prevent and relieve suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies”.

In the case of insufficient beds in the facility, patients should be transferred to another one if appropriate. Regardless of location, palliative care should be provided at a site that is as comfortable and as private as possible allowing the patient’s family/significant others to be present. It is critical that parents or guardians be allowed to be with their children. Promoting patient comfort should be the highest priority.

Pain and anxiety

Parenteral opioids have the most rapid action on pain. Oral opioids may be useful if parenteral opioids are unavailable, and the patient is able to ingest them. Transdermal opioids may also be a viable alternative if there is an area of intact skin, and no other routes can be accessed. The sublingual route should also be considered. All opioids need to be titrated to an effective dosage, implementing a pain scale to assess effectiveness.

Nonopioids such as acetaminophen and nonsteroidal anti-inflammatory drugs are an option if there are no available opioids. Acetaminophen may be administered rectally and some nonsteroidal anti-inflammatory drugs parenterally if necessary.

Adjuncts such as anxiolytics (lorazepam) and anesthetic agents (nitrous oxide or ketamine) may also be considered. In situations where resources are severely limited, local herbal remedies or alternative care methods may be the only interventions readily available for patient comfort and should be considered.

Airway and wound care

Airways support, supplemental oxygen, and bronchodilators and anxiolytics if available may be beneficial for the prevention/management of air insufficiency.

Clean wound and oral nutrition should be correctly provided.

Privacy, family, and spiritual supports should be provided for a better comfort[37].

C. Burn care guidelines on the management of acute pain in the adult burn patient

Pain is a process involving complex biochemical and electrophysiological mechanisms utilizing numerous receptors, cells, fibers, and neurotransmitters. The painful sensation is processed in the central nervous system from nociceptors on the surface of the skin to the spinal cord to the CNS. Knowledge of specific pathways

and players involved in the process leads us to consider potential pharmacologic and nonpharmacologic treatments.

The ABA published updated recommendations on the management of acute pain in burn patients[5]. They are summarized below.

Pain assessment

- Evaluation of pain should be done more than once a day and in the different phases of healing and care. (Level A)
- Evaluation of pain should be planned and documented by the physician and the nurses during the different phases of care to ensure language stability in the assessment of pain. (Level B)
- Tools of the pain evaluation should be used when patient conditions permit (Level C)
- The Burn Specific Pain Anxiety Scale (BSPAS) should be included as one of the pain assessments used during an acute burn hospitalization as it is a validated tool for the burn patient population and includes evaluation of anxiety. (Level C)
- Critical Care Pain Observation Tool (CPOT) can be used if a patient is unable to interact or communicate their individual assessment of pain. (Level D)

Opioid pain medications

- Appropriate opioid pain medications should be chosen according to pharmacology, physiology, and physician experience given the limited amount of high-quality data available. (Level C)
- Opioid therapy should be tailored to each patient and continuously adjusted during their care due to the high spectrum of individual responses, side effects, and the narrow therapeutic window of opioids. (Level D)
- Alternation between opioid equivalents should be done as needed to achieve the desired level of pain control. (Level C)
- Opioid pain medications should always be adjunct to nonopioid medication and other pain medications during the healing. (Level D)
- Recipients of opioids should receive some knowledge about these medications during the healing process. (Level D)

Nonopioid pain medications

- Acetaminophen might be administered to all burn patients, with vigilance regarding the maximal daily dose. (Level D)

- The decision of including NSAIDs to the patient's treatment should depend on the patient's profile including comorbidities and kidney function, as well as the surgeon's preferences. Generally, it is administered to all patients (Level D)
- In patients with neuropathic pain or who are refractory to standard therapy, agents approved for the treatment of neuropathic pain like gabapentin and pregabalin should be used as adjunctive therapies to opioids to treat this condition. (Level C)
- Ketamine can be considered for procedural sedation but needs to be administered by a competent physician or nursing staff. (Level B)
- Low-dose ketamine should be considered as an adjunct to opioid therapy in patients who could benefit from reduced opioid consumption, particularly in the postoperative period. (Level D)
- Dexmedetomidine and clonidine are recommended as adjunct agents in pain management, particularly in patients showing signs of withdrawal or prominent anxiety symptoms and as a first-line sedative in the intubated burn patient. (Level D)
- The administration of IV lidocaine is kept as a second- or third-line agent. (Level D)
- The use of cannabinoids in the treatment of acute burn pain is still debated due to legal and political obstacles. (Level D)

Regional anesthesia

- Regional anesthesia for burn pain management has the potential to provide improved pain relief, patient satisfaction, and opioid use reduction without serious risks or complications. (Level C)

Nonpharmacologic treatments

- All patients should receive a nonpharmacological pain control technique, at least as an adjunctive measure to their pain control regimen. When the expertise and/ or equipment is available, cognitive-behavioral therapy, hypnosis and virtual reality have the strongest evidence. (Level A)

1.4 European Guidelines

1.4.1 European Burns Association (EBA) European Practice Guidelines for Burn Care (2017)

These guidelines, published in 2017, offer the new updates concerning burn management in the different sectors related to the burn management (nursing, physiotherapy, medicine….). It also discussed the essentials of a burn care center and its characteristics[3].

This section focuses on the recommendations outlined in the EBA guidelines for diagnosing burn types, management, and relative supportive care. The accepted principles of treatment are based on a very high degree of clinical certainty supported by Class I evidence (based on prospective, randomized controlled clinical studies) ; guidelines are based on moderate clinical certainty supported by Class II evidence (retrospective studies with relatively clear results); They are possible ways of treatment based on personal clinical observation and/or Class III evidence (clinical series, case reports, expert opinions, etc.).

A. Provisional Burn Care

The principal features concerning Burn Care Provision are the burn center and the transfer criteria to the burn center.

The Burn Center

The Burn Center is the most structured and specialized organism in burn management among other healthcare facilities.

- It has well defined spaces and arrangements
- Can be found in a hospital
- Has all materials needed to burn care
- Covers all aspects and extends of burns in all ages
- Is directed by a medical and administrative staff focusing on burn care
- Is specialized and shows a very high level of expertise in patient treatment and care.
- Conducts a certain minimal number of acute procedures and consequent reconstructive surgical procedures per year.

Transferal criteria to a burn center

Detection of patients who need to be transferred to a burn center is essential for the management of patients. Patients with superficial dermal on more than:

- 5% of TBSA in children under 2 yo
- 10% of TBSA in children of 3-10 yo
- 15% of TBSA in children of 10-15 yo
- 20% of TBSA in adults
- 10% of TBSA in seniors over 65 yo
- Patients in the need of burn shock resuscitation
- Patients experiencing burns on sensitive areas like face, hands, genitalia, or major joints
- Deep partial and full thickness burns of any age group and any extent
- Circumferential burns in all ages
- Burns of any size with concurrent trauma or diseases, which might complicate treatment, prolong recovery or affect mortality
- Patients that might experience inhalation injury
- Any type of burns where there is question marks about the treatment
- Burn patients in the need of special social, emotional or long-term rehabilitation support
- Major electrical or chemical burns
- In the case of 10% TBSA in children and elderly and 15% TBSA in adults with concomitant diseases like toxic epidermal necrolysis, necrotizing fasciitis, staphylococcal scalded child syndrome; or if there are question marks about the treatment[3].

B. Nursing Guidelines

These guidelines cover essentially the nursing duties towards patients on nutritional, pain management, fluid resuscitation and wound care levels.

Nutrition

It is recommended that the nurses have knowledge regarding patients' nutrition recommendations and collaborate with the burn team to ensure the patient has the appropriate amount, time, way, and quality feeding. Assessment concerning feeding should be done on a regular basis.

Pain management

These guidelines are not Class I evidence.

- Guidelines for burn-pain management must be broad in scope to allow for variations in analgesic needs across all patient populations and phases of burn recovery.
- Nurses should regularly assess the patient's pain using tools (scales example VAS) including pain-related anxiety to surveil the evolution of pain.
- Medication, particularly opioids, needs to be continuously under radar to assess their effects and adjust in case of side effects, not reaching the targeted concentrations or reducing in case of pain resolution.
- Aggressive pain management should be relied on in the first case.
- Before dressing the wound, analgesia needs to be administered (1/2 to 1H)
- Anxiety medication can be a good adjunct to pain killers.
- In the case of itching antihistaminic medication can be administered
- The purpose for the patient should be to stay conscious with all senses and comfortable at the same time.
- Nonpharmacological therapy such as hypnosis, rapid induction analgesia and distraction relaxation can be recommended as adjunctive therapy to medication.

Fluid resuscitation

- Estimation of fluid management is essential for the patient's life with enlarged burns, to prevent hypovolemia and/or burn shock. This should be initiated by the nurse in collaboration with the MD.
- Fluid resuscitation relies on the patient's parameters such as the extent of the burn, the body size and hemodynamic status.
- Ringer Lactate should be titrated based on urine output. And so, the latter should be continuously monitored.
- Target values of urine output are: 0.5 cc/kg/hr for adults, 1cc/kg/hr for children <30kg and 1 to 2 cc/kg/hr for high voltage burns.
- The first 8h post burn patients should not receive colloids.
- Administer maintenance fluid with resuscitation due to limited glycogen stores in young children.

Wound care

- Quick wound healing with the best possible functional and aesthetic outcome.
- Fighting off infections Less inflammation, better scarring, and ultimately lower morbidity and mortality are the results of sepsis, SIRS, MODS, and/or biofilm formation.
- A faster rate of wound healing will be the result of any wound treatment.
- The etiology, size, depth, location, and degree of exudation all affect the dressing option. Costs and pollution levels. Considering this, think twice before using, and use your imagination clinically sound justification for selecting one dressing over another.
- There is only weak evidence that foam dressings have an impact on secondary healing wounds, benefit in terms of patient satisfaction, pain management, and treatment time.
- Topical creams - Should be effective against microbes without increasing the risk of resistance allergy symptoms, etc. They must provide good care and not leave any slough on the wound bed and have a clear view of the wound bed. They must avoid drying out the wound, while on the other. Hands absorb sufficient exudates to maintain the equilibrium for moist healing without maceration of the adjacent (unharmed) skin.
- Blisters: Clinical practice recommendation based on the best available research regarding the optimum approach, various clinical applications and recommendations have been made, procedures for treating burn blisters brought on by partial-thickness burns. Arguments in favor of keeping intact blisters include the notion that they naturally whereas the debridement of blisters has been recommended, occurring biologic protection because fewer wound infections and consequences are reportedly occurring. In this discussion, recurring themes in burn wound care are taken into account, include patient comfort, ease of recovery, functional and cosmetic results, infection, and clothing with care and saving money. Care should be taken to treat burn blisters backed up by proof in each of these six categories, should correspond to the level of competence of the provider, and they ought to make advantage of the tools at their disposal.
- Evidence exists for a link between stress and slower wound healing between stress and the various kinds of wounds' ability to heal. The effects of stress on the psychological and physical healing process. as a wound can aid in reducing psychological stress, measuring wound healing, and successful wound treatment. Pain may lessen patient anxiety and facilitate quicker recovery from acute and persistent wounds.

- Wound-tissue temperature – The temperature of the wound-tissue should remain above 33°C. Fibroblast and epithelial cell activity are reduced below this temperature. The date should not be greater than 3 to 4 degrees Celsius for hypothermic cells to resume mitotic cell division. As much as feasible, wound bed temperature should be maintained throughout dressing modifications to promote recovery. To this knowledge, adjustments should be made.

D. Physiotherapy and occupational-therapy guidelines

These guidelines cover essentially the recommendations concerning oedema management, splinting and positioning, scar management, exercise and mobilization and hand rehabilitation.

Oedema management

In burns patients, the therapist must communicate with the burn team to limit the risk of oedema development and implicate to ensure maximal oedema reduction. For this, the therapist must know the essentials of vascular and lymphatic circulation, must know which factors predispose to oedema development, and must know how to evaluate and grade the type and stage of oedema. Techniques need to be performed to decrease pain sensation, stiffness, and contracture:

1. Positioning, compression, and mobility rationale associated with oedema decrease. Here the therapist should know the essentials of compression application, surveil the evolution of the oedema during the compression treatment and evaluate the contraindications of compression treatment.
2. Production of devices for patient positioning to decrease oedema (e.g., foam, thermoplastics, neoprene).
3. Design of programs for joint and limb active/passive movements to limit stiffness and contractures.

Splinting and positioning

The therapist must have knowledge of the rationale for splinting and the need to initiate an appropriate splinting program (of course knowing the essentials of splint planning and production) to limit contracture development, damage to anatomical and assist graft or skin substitute and/or wound closure. On the other hand, the therapist needs to stay alerted of the risks and complications associated with splinting.

The therapist needs to regularly evaluate the implementation requirements, safety, and time positioning during the recovery period.

The therapist needs to stay alerted of burn pathology and its relevance to positioning requirements.

Scar management

The therapist needs to continuously evaluate the evolutional stage of the wound with objective and subjective measures, considering the factors contributing to scar management and functional impact of scar formation, and come up with the appropriate time to initiate the scar management methods after evaluating understanding the indications for scar management. Treatment methods can regroup massage, pressure therapy/silicone gel therapy/facial and neck conforming collars and masks/splinting. The latter should be applied taking into consideration the patient and caregiver factors.

Surveillance should be done to constantly evaluate progress taking into consideration the psychological impact of scar formation, the complications, and contraindications of the various treatment methods.

Exercise and mobilization

Specialized rehabilitation is an essential component of the patient's recovery after burns. Rehabilitation starts directly in the ICU where the patient is pushed to mobilize him/herself.

The goals of this physical treatment are to focus on:

- Recovering or maintaining range of motion (ROM), strength and physical fitness (endurance).
- Recovering pre-injury (or improving post-injury) mobility e.g., transferring and ambulation.
- Recovering pre-injury (or improve post-injury) functioning in activities of daily living (ADL)

Regular analgesia is essential for the treatment as it may improve the exercise quality.

Monitoring of the patient's profile needs to be done by continuous meetings, including using of audit tools/quality indicators to assess the improvement.

Hand rehabilitation

Burn hands are a severe and urgent injury to be treated rapidly and with precision, threatening to lose the hands functionality. And so, rehabilitation starts directly in the ICU where the patient is pushed to mobilize his/her hands.

The goals of this physical treatment are to focus on:

- Recovering or maintaining range of motion (ROM)
- Recovering hand function and application in daily life activities
- Limit oedema
- Prevent contractures
- Limit scar formation
- Recover senses and decrease hypersensitivity

Regular functioning and multifaced treatment pain management should be installed to improve exercise/rehabilitation performance and outcome.

Monitoring of the patient's profile concerning rehabilitation needs to be imperatively done by continuous meetings.

Use meaningful audit tools and outcome measures[3].

E. Rehabilitation guidelines

Preparations for discharge from a burn center (adult's case)

Since their entry to the burn center, patients and families need to have an idea about the length of stay depending on the case.

Discharge is a process that requires precision, caution, and personalization. It will be accorded after the consent of a multidisciplinary team that will be evaluating multiple criteria: wound healing, overall health status (including cognitive), activities of daily living independent accomplishment and functional status, adaptable home to the patient's situation (stairs, cleanliness…), family's availability as caregiver and support, ability to get medications (and have some knowledge about them) and services, ability to transport from burn center to home and for follow-up visits.

The patient and caregiver need to be informed about[3]:

- Wound care and healing
- Skin care, vulnerable skin, blisters
- Scar formation, mouvements restriction
- Scar care like massage, silicone application if available and necessary
- Splints with indication when and how long to wear
- Daily program on mobilization exercises
- Pain (medication, relaxation and breathing techniques, distraction, etc)
- Itch (medication, lotion, cool environment etc)
- Fatigue, reduction of general health

- Nutrition requirements
- Permissions and contraindications
- Psychological impact (distress, concentration loss, poor sleep, fear)
- Interaction with family, friends, strangers (how to handle the altered appearance)
- Role within the family (rediscover the balance in-between the family)
- Role at work
- Peer contact

F. Psycho-social guidelines

Anxiety

No specific guidelines have been established in patients due to lack of research. However, some considerations might be useful in clinical reasoning in anxiety-related problems:

- Professionals should be aware of the relationship between physical and psychological factors that can interfere with and contribute to anxiety.
- Professionals need to be skilled in burn-specific pain anxiety evaluation, symptoms evaluation, lifetime psychiatric disorders and personality traits that can contribute to the initiation of PTSD.
- Professionals are required to know the options of possible treatments (pharmacological and psychotherapeutic) and so or to initiate the appropriate treatment or recommend referral to available psychological and/or psychiatric care. Non-pharmacological pain interventions can be adjunct to routine pain management treatment to reduce pain-related anxiety.

Depression

Related-burn depression is a quality-of-life deteriorating psychiatric disease that develops frequently in burn patients. According to studies, several factors might come along and increase this risk: A history of emotional disorder, Personality (neuroticism, trait anxiety and hypochondria), psychiatric history of:

- Poor psychological adjustment
- Alcohol and other substance abuse
- Self-inflicted burns
- Medical illness
- Behavioral self-blame for the burn accident

- Employment status at the time of the burn
- Pain intensity
- Physical disabilities, mental status, and social adaptability
- Female gender (especially in combination with facial and/or breast disfigurement)
- Burn visibility (namely head, neck and hands burns)
- Maladaptive coping strategies
- PTSD
- Loss of function
- Prolonged stay in hospital and complicated surgical course
- Symptoms of depression in the hospital.

In addition, patients and staff need to have clear communication to exchange information about the case.

Pain assessment and management are essential to evaluate the improvement.

Cognitive-behavioral interventions and psychotherapeutic interventions can be performed in order to reduce depression for seen and hidden scars.

Delirium

Delirium is defined in the DSM-5 as a multisymptomatic disorder regrouping: a disturbance in attention that commonly develops over a short lap of time, and tends to fluctuate during the day, a change in cognition, a possible correlation between a current medical condition/substance intoxication/substance withdrawal and the development of delirium. Three different delirium types could manifest (hyperactive delirium, hypoactive delirium, mixed delirium).

This condition should be surveilled every day in critically ill burn patients and reported on delirium score instruments documentation at least twice a day. Surveillance of pain and sedation is a must. Pain meds should be given before sedatives, and the latter may be given if the patient status does not refuse it. To avoid over- or under- sedation, targeted levels of pain and sedation need to be personalized and prescribed individually.

In the patients in need of ventilator support, a protocol should be implemented as soon as possible.

Early exercise and mobilization should be installed, and sleep and rest need to be given more access by controlling light, noise, pain, discomfort, etc.

Educate patients and relatives about the condition.

Quality of life – adults

Quality of life (QOL) is the person's perception of their position regarding daily life in every aspect. Burn professionals meeting with multi-disciplinary team should act to preserve QOL known as one of the essential components of patient recovery.

QOL should be evaluation form patient's admission till the end of rehabilitation, sometimes lifetime in severe cases.

Burn professionals should take into consideration how QOL is important for patient's improvement, including the return to work and going back to work processes[3].

G. Pediatric guidelines

This first part will briefly cover *pediatric occupational therapy*.

Recovery of manual skills and dexterity

Splint should be applied to restrict the provenance of contracture, and if child is active during the day so applied at night, and so to avoid wrong positioning of the limb.

Passive mobilization exercises of the child can be done under anesthesia (with caution in respect of the vulnerable tissues) and in awake children (considering the pain and stress factors) as long as needed. Active mobilization exercises can be done with dynamic splinting with maximal, but cautious stretching of scars over joints. Splints must be worn 30-60min per day, possibly 3 times daily. For circumferential areas of involvement, alternating the position and slow and controlled stretch is indicated.

The scar should be covered with cream two time a day with daily mobilization; silicon might be applied if available; also, if compression garments are available compression therapy can be performed, and if not with elastic wrapping with foam, especially in concavities.

Pain and stress management

Non-pharmacological strategies that help decrease stress can be performed, such as distraction, imagery, hypnosis, relaxation methods, comfort positioning during painful procedures as well as age-appropriate information and illustrations. These methods can be combined to the painful occupational therapy measures.

Recovery of self-competence and selfcare skills according to the child's age

Since the hard task of inducing active mobilization in children, attractive activities that require hand function are mandatory in pediatric hand therapy. Re-education of selfcare skills depending on child's age, re-encountering of individual's skills.

Enablement and involvement of parents

Parents should gain knowledge about the child's case, goals of the treatment and therapeutical considerations. They also need to be involved and if possible, enablement in specific parts of the treatment, like passive mobilization, splinting and scar management, meaningful and purposeful activities for the child; parents can also teach, coach, supervise and support the child.

Discharge, re-integration and out-patient setting

Before the patient is discharged, the patient's parents should be prepared, capable, and confident in their ability to continue with the prescribed hand therapy, including splint- and scar-management. In the event of doubts, they must understand when and where to turn.

Splints and scars must be frequently and periodically reassessed as youngsters grow, and revised. Scar and splint expert monitoring must be planned, either with a burn center or a suitable expert near the site of the patient's family's home.

The child's self-aptitude, performance in a job, manual abilities, and self-confidence and the level of social activity engagement must be investigated and repeatedly assessed. Support for reintegration in school, in the community, and off-site patients.

This second part will briefly cover *the diversity of patient's family backgrounds in pediatrics.*

Conditions for an effective diversity process with reference to parent collaboration

- The capacity to efficiently provide medical services that address patients' social, cultural, and language needs is known as cross-cultural competency.
- Appreciation of the potential, as well as the diversity and dynamic development in society cultural distinctions, as well as social and economic issues, may have an impact identity and conduct.
- Recognize the effects of exile and migration on people and families.
- Understanding the potential sources of discrimination
- The capacity and willingness to consider things from multiple angles
- An understanding of parallels and contrasts
- Understanding one's own cultural circumstances, attitudes, and values through self-reflection presumptions, assumptions

- Avoiding the use of cultural determinism or cultural attribution to a person's needs
- Refraining from using racial and cultural stereotypes
- Ambiguity tolerance, or the capacity to deal with ambiguities.

The procedure for promoting professional diversity in regard to the patient's family

- Acceptance of diversity without bias
- The awareness of an investigation of parallels without bias
- Goals, capacities, resources, and requirements are mutually clarified by involving a variety of various viewpoints (professional, familial, juvenile, etc.)
- Examine and overcome institutional biases, both personal and organizational structures that make discriminating easier
- Clarification of the priorities, expectations, and expectations of the family in favor of their hurt child
- Offer a secure space and the intimacy required for meditation or other spiritual retreats, support in locating spiritual care in accordance with the family's religious or spiritual preferences needs, about which the family was questioned directly
- Acceptance of religious dietary restrictions and taboos
- The establishment of a common ground based on similarities, especially when those commonalities very straightforward and fundamental), where mutual respect and trust may be built as the foundation for a robust and long-lasting collaboration
- Attempting to reach a consensus with people and families by involving
- Educating parents will enable them to participate in decision-making
- Deliver information and teaching in a linguistically and educationally relevant manner.

This third part will briefly cover the *painful procedures and non-pharmacological approaches in children*

Adequate and mindful communication with the child:

- Using a calm voice and careful word choice to create an atmosphere of peace, comfort, and hope as much as feasible.
- Quickly providing practical, competent, and sympathetic responses to a child's suffering manner
- Speaking in terms that children can understand
- Encouraging the parent or caregiver to stay with the kid until the discomfort has passed control (if a parent cannot exercise this kind of control, try to persuade the parent to do so for her/his responsibility to provide consolation in particular circumstances)

Introducing and teaching techniques for managing pain without drugs

- Examining the best treatment option for each individual child (this can depend on personal preferences, the stage of the treatment plan, daily circumstances, etc.).
- Techniques for relaxation (belly breathing, body scan, mindfulness, guided imagery)
- Distraction techniques (avoid competitive and level-bound computer games as they raise stress levels; bubbles, hidden-object games, memory games, virtual reality, etc.)
- Pediatric hypnosis and teaching a kid, teenager, or parent how to hypnotize themselves are two techniques that can be combined and modified for use.

Child appropriate information

- Information, illustrations, and directions detailing the intended processes that are age- and child-appropriate and take into account the child's circumstances.
- Roll-play with plush animals, dolls, etc.
- A description of how pain processing differs depending on the child's intellectual development and how it might be modified.

Pediatric occupational therapy

- Enhancement of self-competence, autonomy, and capacity for self-care. Facilitation of the child's conception of "magical helpers," which may be developed with occupational therapy's assistance.
- The discovery and development of new skills.

- The integration of functional goals into enjoyable and fulfilling activities for the specific child (play, crafts, even cooking or baking).
- The support of a child-appropriate environment with regard to privacy and personality as well as the opportunity for play and social interactions[3].

H. Best practice guidelines for burn practitioners

a. Initial management of burns wounds

Main concepts for burn wound management

1. *Aims of burn wound management*

We advise taking immediate action to close burn wounds, as well as measures to lessen discomfort, avoid infection, and maximize function and cosmesis.

The goal should be to closure burn wounds as quickly as possible because there is a well-established correlation between time to healing and the likelihood of developing hypertrophic scars in both adult and pediatric patients. Early wound closure also reduces the need for frequent dressing changes, as well as pain and mental anguish.

2. *Prehospital burn wound management*

- We advise removing any jewelry that may be restricting, as well as any burned clothing (unless it is adhered to the patient).
- We advise providing cool running water to the burn wound for 20 minutes as part of immediate first aid.
- We advise that the burn wound be covered with a non-adherent simple dressing in the pre-hospital setting in order to prevent hypothermia, especially in youngsters.
- For pre-hospital dressing, plastic food wrap (also known as polyvinyl chloride film, or "cling film") is a good option.
- We advise keeping the patient warm while transporting them to an appropriate hospital for a professional evaluation of the burn lesion.

By lowering intradermal temperature and possibly protecting the zone of stasis, proper first aid lessens discomfort and can restrict the depth and extent of the burn lesion. In an animal model, first aid using cool running water for 20 minutes within three hours of the accident improves the results, including the duration of stay, the necessity for surgery, and the degree of scarring. Gels that provide less effective cooling have been tried.

The general public and non-specialist physicians should be warned against using additional first aid techniques, such as the administration of cold or materials like toothpaste, egg, or butter that could harm the burn wound.

Topical cream usage should be avoided prior to admission to the hospital as it could impede later wound examination.

3. *Wound management in the burn center*

- We recommend that all burn wounds be evaluated by a qualified clinician and that adults and children should utilize the Lund and Browder charts for measuring burn size.
- We advise treating all patients in a comfortable setting that takes into account the ambient temperature, their comfort, and their analgesia.
- When appropriate and practical, we advise using adjuncts to clinical assessment, such as Laser Doppler Imaging for mixed depth burns. We also advise meticulous recording of the burn wound and subsequent care, including clinical photographs.

Optimal management of circumferential burns

- We advise thoroughly examining the burn patient to check for circumferential burns.
- We advise maintaining a semi-seated position (elevation of the torso) in the event of chest or abdominal circumferential burns.
- We advise elevating the affected limbs.
- We advise routine evaluations of peripheral circulation, abdominal hypertension symptoms, and breathing.
- When circumferential burns impair respiration, circulation, or result in abdominal hypertension, we advise doing escharotomies.
- Escharotomies and fasciotomies should be carried out by appropriately qualified clinicians when symptoms of compression continue after an escharotomy, particularly in cases of high voltage injury or extremely severe thermal burns.

b. Burn wound dressings

Cleaning and debridement of burn wound

1. *Wound cleaning*

Before applying a proper dressing, we advise thoroughly cleaning burn wounds.

In the acute setting (i.e., 48 hours after injury), we advise cleaning burn wounds with normal saline or filtered tap water. Outside of the acute setting, we advise cleaning burn wounds with an antiseptic solution that is effective against likely contaminant microorganisms, like chlorhexidine or acetic acid.

2. *Wound debridement*

We advise debriding burn wounds to get rid of any dead tissue and speed up healing. Debridement can be carried out by enzymatic, surgical, or physical methods.

We advise removing blisters from burn victims.

Debridement is necessary to remove necrotic or nonviable tissue from the wound bed in burn wounds. To do this, dressings, surgical eschar debridement, or the use of enzymatic debriding chemicals may be used.

The best way to treat blisters in burn wounds is a topic of intense discussion. The comfort of the patient, the avoidance of infection and the worsening of burn wounds, the evaluation of the underlying wound, and the opportunity for antimicrobial dressings to come into direct touch with the wound bed are all reasons for deroofing. According to the comfort of the patient, very small or adherent blisters, such those on the palmar surface of the fingers, may be left intact or broken up.

Burn wound enzymatic debridement is becoming more and more common, despite being a labor-intensive treatment with a learning curve. Deep partial thickness or full thickness burns, including those to the hands and face, have been described as being treatable using a bromelain-based enzyme. In comparison to standard of care, a multicenter randomized controlled trial indicated a decreased requirement for surgical excision and autografting (5). When local competence is available, enzymatic debridement should be taken into account as a potential alternative to surgical excision in certain cases.

Burn wound dressing

We recommend covering burn wounds with an appropriate occlusive dressing until they heal, suggesting antimicrobial dressings for burn wounds at risk of infection and colonization, and considering temporary biosynthetic skin substitutes for

dressings when necessary, such as for children with confluent superficial burn injuries.

As more dressings become available, we advise burn services to routinely assess the ones they use.

Main features of burn wound infection

We advise using clinical evaluation coupled with qualitative or quantitative microbiological analysis to evaluate potential wound infections.

We advise against routinely administering prophylactic antibiotics for severe burn victims.

We advise using antimicrobial dressings when necessary to lower the risk of burn wound infection.

c. Management of burn shock

Main concepts for burn shock management

- We advise doctors to evaluate burn shock based on the patient's clinical response to first resuscitation, the mechanism and severity of the burn damage, and their understanding of the physiopathology of burn shock.
- We propose that the institutional expertise and unique technology of each burn center serve as the foundation for guidelines for measuring and monitoring burn shock.
- We propose that more than one metric should be used to guide the evaluation and monitoring of burn shock.
- The therapeutic measures should focus on restoring tissue oxygenation, and doctors should aim to prevent both under- and over-resuscitating patients.

Due to the disturbance of normal homeostasis brought on by both local and systemic responses, including the release of cytokines and other inflammatory mediators, burn shock develops in significant burn injuries.

The ensuing circulatory failure is a special mix of distributive and hypovolemic shock, with the latter being characterized by intravascular volume loss, elevated systemic vascular resistance, and compromised cardiac function. Dysoxia of the tissues occurs as a result of inadequate oxygen delivery and/or use.

Burn shock usually peaked 12 to 24 hours after the first injury and lasted throughout the first 24 to 72 hours.

After this time, circulatory failure in burn patients should be further examined and interpreted because their physiopathology is different and therefore require various therapeutic approaches.

There is no one reliable scoring method that can accurately predict the likelihood and severity of burn shock or the requirement for large volume fluid administration or replacement.

However, the degree of burn injuries serves as a crucial screening tool for locating people who are at risk for shock. A "critical burn size" is defined by data from the literature as a threshold of 15-20% total body surface area (TBSA) non-superficial (2nd and 3rd degree) burn injury that requires IV fluid resuscitation. Additionally, the clinical therapy should be determined by the injury's etiology, the patient's physiology, and their reaction to first resuscitation.

The clinical evaluation and the estimate of physiological parameters are useful tools for determining the severity of hemodynamic damage following burn injury.

Recent consensus recommendations advise performing a clinical examination of three organs easily accessible to the assessment of tissue perfusion: skin (examining the degree of cutaneous perfusion); kidneys (measuring urine output); and brain (assessing mental status) in order to evaluate the hemodynamic status and to guide therapeutic interventions. However, several restrictions may make it difficult to apply these clinical criteria to burns. Patients with severe burns or circular limb injuries may not exhibit skin perfusion signs of decreased microcirculation (acrocyanosis, mottled skin, slow capillary refill time, and elevated central-to-peripheral temperature gradient). Similarly, abdominal hypertension in those with severe burns may cause irregular urine output.

Finally, because burn patients frequently need sedation and analgesia to control their pain and maintain an adequate airway, it may be difficult to determine their mental state.

Consequently, further hemodynamic evaluation must direct treatment approaches in burn shock. Multiple parameters should be looked at and taken into account due to the intricacy of burn shock physiopathology and presentation. Clinicians are required to use the monitoring equipment that is available at their facility since they are familiar with how to operate it and interpret the measurements it provides.

Finally, it is crucial to focus treatment on tissue perfusion, which is the main goal of shock management, rather than normalizing a particular measure and losing the larger clinical context. No single approach or endpoint has been shown to be superior to the others in guiding fluid resuscitation in severe burns, and both excess and under resuscitation have been shown to have major negative effects.

Optimal initial assessment of burn shock

1. *Invasive arterial pressure monitoring*

When shock is refractory to first treatment, necessitating a vasopressor infusion, or a patient has significant burns on both arms, we advise arterial catheter insertion.

We advise patients without a history of hypertension to aim for a MAP of roughly 65 mmHg at first.

We advise tailoring the target blood pressure during shock resuscitation to each patient.

2. *Lactate levels, base deficit*

We advise using tests of serum lactate and/or base deficit to gauge the severity of shock and assess the impact of treatment.

We propose that blood lactate levels above 2 mmol/L be used as a gauge for insufficient tissue perfusion.

In burn patients, determining lactate and/or base deficit may be very crucial. The physiological independence between oxygen delivery and oxygen consumption is lost as a result of burn shock, resulting in tissue hypoperfusion and increased lactate levels.

The severity of burn injuries has been demonstrated to be significantly correlated with lactate levels, and lactate levels appear to have a better predictive value than blood pressure. In fact, it appears that patients with circulatory shock who had lactate levels between 1.5 and 2 mmol/L have higher mortality.

The first base deficit has been demonstrated as an independent predictor of death in patients with burn shock, similar to the predictive value of lactate levels.

3. *Urine output*

We propose that fluid resuscitation be guided by the integration of urine output with other clinical indicators, particularly when monitoring tools are scarce.

4. *Central venous catheter: central venous pressure, central venous oxygen saturation*

We advise against using central venous pressure for the estimation of preload and for directing fluid resuscitation in severe burns. Instead, we recommend inserting a central venous catheter in cases of shock that are unresponsive to initial therapy and/or require a vasopressor infusion.

In order to evaluate tissue perfusion in patients who already have a central venous catheter in place, we advise measuring central venous oxygen saturation.

Hemodynamic measurements in burn shock

We recommend using dynamic parameters for fluid resuscitation when additional hemodynamic measurements are required, and only in severe burns that are not responding to initial therapy or in complicated situations (such as coexisting trauma or preexisting comorbidities).

We advise against estimating preload using static data and predicting fluid responsiveness.

We propose that the selection of the monitoring technique is based on institutional knowledge and the patient's unique characteristics.

Therapeutic interventions to improve perfusion in burn patients with shock

1. *Fluids*

We advise beginning fluid resuscitation in patients with burns more than 20% total burn surface area (TBSA) in adults and greater than 10% TBSA in children.

In the first 24 hours, we advise prescribing 2 to 4 ml/kg/% TBSA.

We advise utilizing crystalloid solutions as a first line of defense.

We advise against using regular (0.9%) saline.

Although colloids, especially synthetic ones, should not be used routinely, they can be used as salvage therapy. We advise fluid de-escalation after the first 24 hours.

2. *Vasopressors and inotropic agents*

We advise the treatment of vasopressors when there is life-threatening hypotension despite adequate fluid replacement, and we base our recommendation on a precise hemodynamic assessment.

If there are still visible symptoms of tissue hypoperfusion while receiving adequate fluid resuscitation and vasopressor therapy, we advise adding an inotropic drug.

Restrictive strategy for fluid administration

We advise cautious fluid titration and/or de-escalation, particularly when there are increased intravascular filling pressures or extravascular lung water[3].

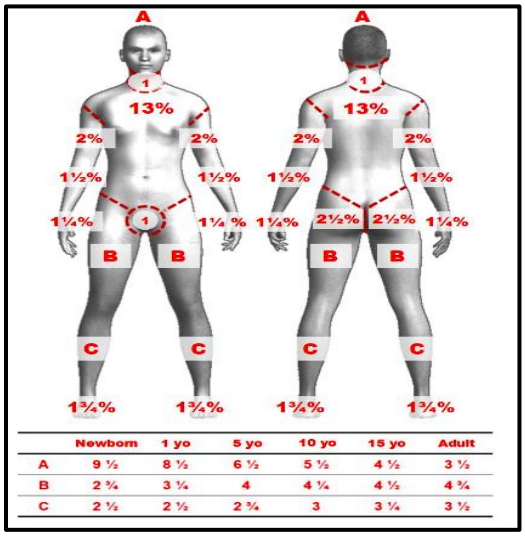
1.4.2 Société Française d'Anesthésie et de Réanimation (SFAR) Management of Severe Thermal Burns in the Acute Phase in Adults and Children (2020)

The aim of these guidelines is to build a framework for the management of thermal burns in the acute phase in six predefined fields (that will be detailed shortly) without covering the well-known ground recommendations in clinical practice[6].

And so, this report describes the main management principles of patients in acute phase in restricted fields. Recommendations are presented according to the GRADE method (Grade of Recommendation Assessment, Development and Evaluation).

Field 1: Assessment, admission to specialized centers, and telemedicine

- For suitable measures of the burned TBSA, experts' advice the use of the Lund and Browder method that according to studies, is the most accurate one for adults and children, but must be repeated during initial management (Figure 1); in addition, an E-Burn application has been developed to measure TBSA using the Lund and Browder method via smartphones. Other methods: the serial halving method in prehospital setting or in mass victim situation; the open hand (where TBSA equals 1%) and so easy to measure.



	Newborn	1 yo	5 yo	10 yo	15 yo	Adult
A	9 ½	8 ½	6 ½	5 ½	4 ½	3 ½
B	2 ¾	3 ¼	4	4 ¼	4 ½	4 ¾
C	2 ½	2 ½	2 ¾	3	3 ¼	3 ½

Figure 1. *Lund and Browder chart for TBSA measures in burned patients. Retrieved from the SFAR 2020 guidelines.*

- The experts advise consulting a burn specialist to assess whether the patient needs to be admitted to a burns center: they should assess the extent of the burn, quantify the amount of TSBA burnt, start a suitable fluid resuscitation, and make sure the patient is managed and referred properly. Burns to certain anatomical regions, such as the face, hands, feet, flexure lines, genitalia, or perineum, also need specialized advice. Additionally, unique circumstances like hyperalgesia or the requirement for specialized medical-social care or long-term rehabilitation necessitate the use of an expert opinion.
- The specialists advise using telemedicine to enhance the early evaluation of badly burnt patients: suited for burns that don't pose a life-threatening risk or when the severity of the burn is unclear. Telemedicine also prevents unnecessary patient transfers, which are linked to a higher mortality risk.
- The specialists advise that the patient be admitted straight to the burns center if there are any indications that admission is necessary.
- If a deep burn causes compartment syndrome in the limbs or trunk that impairs the airways, respiration, and/or circulation, the experts advise

performing an escharotomy. The escharotomy should ideally be carried out at a burns center by a qualified medical professional.

Third-degree burns that are circumferential might cause constriction, which raises pressure inside the afflicted anatomical compartment. This pressure can cause various physiological effects, including decreased cardiac output and pulmonary compliance, hypoxia, hypercapnia, acute renal failure, and mesenteric ischemia, depending on the area of the body that is affected. It can also cause acute limb ischemia, which can result in neurological problems and downstream necrosis.

Escharotomy can be used to decompress the subcutaneous tissue in third-degree circumferential burn patients (and occasionally deep second-degree instances). Escharotomy's impact on compartment syndromes associated with burn injuries has not been examined in any randomized controlled studies. Escharotomy is comparatively seldom performed, however it can lower intra-compartmental pressure and can treat and prevent compartment syndrome, as well as reduce morbidity. Escharotomy is comparatively uncommonly performed, but it does lower intra-compartmental pressure and can both treat and prevent compartment syndrome, decrease morbidity, and improve functional outcomes. This is despite the majority of the studies being retrospective and using small sample sizes. Escharotomy timing is hardly discussed in the literature. Escharotomy is rarely necessary immediately, and the main urgent indication is reduced airway movement and/or respiration, according to what appears to be global consensus. It is also accepted that patients with circulatory dysfunction or intraabdominal hypertension should have an escharotomy within 48 hours of the onset of these illnesses.

Escharotomy involves a risk of complications, including infection and hemorrhage. Increased morbidity is also linked to an ineffective escharotomy. Therefore, the professionals advise that this surgery must be carried out at a Burns Center. Before conducting an escharotomy if it is not possible to transport the patient to a burns center soon, it is advised to consult a specialist[6].

Field 2: Hemodynamic management

- The experts advise giving 20 mL/kg of an intravenous crystalloid solution within the first hour of treatment to adult burn patients with a total burned body surface area of greater than or equal to 10% and pediatric burn patients with a total burned body surface area of greater than or equal to 10%.
- The professionals advise using balanced crystalloid solutions (Ringer’s Lactate solution).

- The experts advise calculating the first crystalloid infusion rate using a formula that at the very least takes into account the body weight and total surface area of the body that has been burnt (table 6).

  One of the fundamental practices in the initial administration of a lot of burns. many prediction formulas. There are fluid needs. These equations calculate fluid a minimum of 2 to 4 mL/kg/%TBSA throughout the first 24 hours after the burn. Sadly, these formulas have never been thoroughly verified, and none of them proved to produce superior results than others. An example of an alternative to these conventional equations, which is most appropriate for the initial hours of treatment and the prehospital stage. There hasn't been clinically tested (just in silico testing).

- Numerous formulas have been presented to determine the total amount of fluid consumption needed in the first 48 hours in children. All comprise TBSA. None of them have undergone rigorous evaluation, and there haven't been any studies that compare them. Formulas created for adults are probably not relevant to children since they have a larger body surface area/weight ratio than adults do. In fact, children who have been burnt require more total fluid intake than adults do during the first 48 hours. According to two retrospective investigations, children needed roughly 6 mL/kg/% TBSA in total fluids during that time. According to the modified Parkland formula (between 3 and 4 mL/kg/%TBSA), several centers handle these pediatric specificities for children with a burned TBSA of over 10% by calculating the daily basal fluid intake requirement in accordance with the 4-2-1 rule proposed by Holliday and Segar. However, two retrospective investigations show that lowering total fluid intake levels is related with a shorter hospital stay and a lower requirement for skin grafts in the subgroup of children with 10–20% burnt TBSA.

- The experts advise that the infusion rate should be altered as quickly as feasible depending on clinical and hemodynamic data in fluid resuscitation for severe burns (tables 7 and 8).

  To prevent either inadequate or excessive fluid infusion (known as "fluid creep"), which are both linked to greater morbidity, actual infusion rates must be adjusted to the clinical response and hemodynamic parameters.

  Based on hourly urine output, fluid resuscitation rates may be changed most easily and quickly. Although not technically defined, people with thermal burns are frequently targeted for a urine production of 0.5–1 mL/kg/h. Urinary output may be combined with other variables, such as arterial lactate concentration or sophisticated hemodynamic monitoring techniques including echocardiography, cardiac output monitoring, and measurements of central venous pressure. These appear to be especially helpful in individuals

who continue to have oliguria after resuscitation or who have hemodynamic instability. It is unknown how addressing particular hemodynamic parameters may affect the outcome.

A computer-based decision support system may reduce the danger of over-resuscitation and assist in decision-making during the early resuscitation period. Vasopressors can be utilized if hypotension persists after the proper fluid resuscitation.

However, it is likely best to assess the heart function and intravascular volume status as quickly as possible using echocardiography or another hemodynamic monitoring method.

For kids, there is a comparable danger of both inadequate and excessive resuscitation. According to retrospective research, patients who had a positive fluid balance on Day 3 were in the hospital longer and required more mechanical breathing. The amount of urine produced is thought to be a crucial indicator when administering fluids to youngsters. Hemodynamic monitoring utilizing transpulmonary thermodilution was related with less fluid and decreased morbidity, according to retrospective research in children with TBSA > 30%.

Table 6. Prehospital and Initial Hospital Regimen for IV Liquid Resuscitation with Standardized Formula Without Delay. Adapted from the SFAR 2020 Guidelines.

	Proposed Formulas	***Alternative: "Rule of Tens"***
H0-H1	Balanced crystalloid: 20ml/kg	Patient weight <80kg: (10 x %TBSA) ml/hour Patient weight >80kg: (ditto+100ml/10kg over 80kg) ml/h
H0-H8	Balanced crystalloid: 1-2ml/kg/%TBSA. (rate per hour including for prehospital fluids)	
H8-H24	1-2ml/kg/%TBSA	

Table 7. Hospital Regimen for Hemodynamic Resuscitation in Children with Severe Burns. Adapted from the SFAR 2020 Guidelines.

Modified Parkland formula	**Fluid resuscitation H0-H24**	**Fluid resuscitation H24-H48**

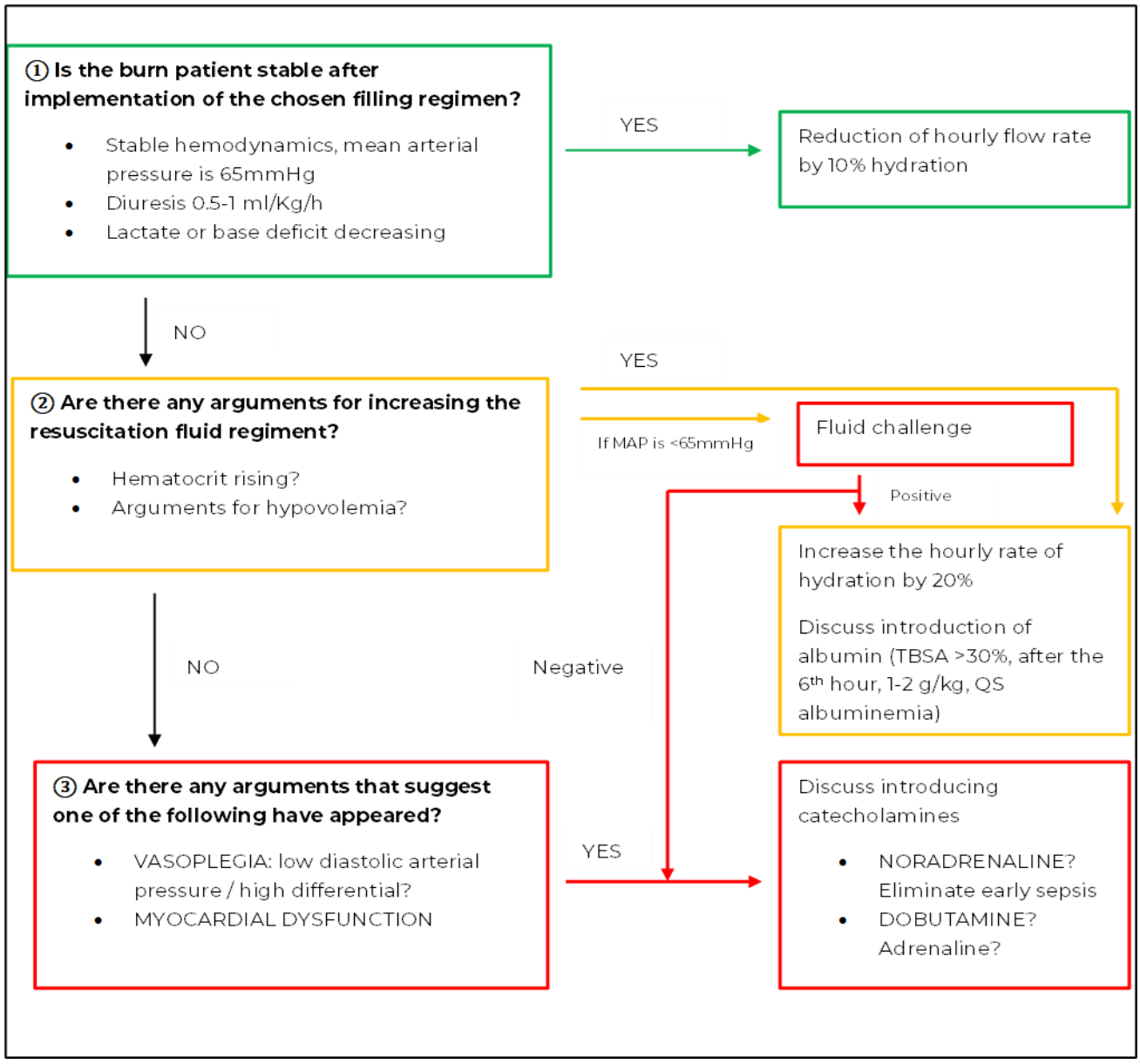
Hourly rate	• **3ml x TBSA (%) x weight (kg)**
	  • 50% in the first 8h
	  • 50% in the following 16h
		• **1.5ml x TBSA (%) x weight (kg)**
		  • To distribute over 24h
		
		  +

	+
	• **Basic inputs, with hourly rate calculated on the basis of the '4-2-1' rule**:
	  • 4ml/kg for the first 10kg, plus
	  • 2ml/kg for the kilos 10-20, plus
	  • 1ml/kg for the kilos >20kg
		• **Basic inputs, with hourly rate calculated on the basis of the '4-2-1' rule:**
		  • 4ml/kg for the first 10kg, plus
		  • 2ml/kg for the kilos 10-20, plus
		  • 1ml/kg for the kilos >20kg

Infusion solutions	• **Infant (<1y):**
	  • 50% Ringer's Lactate
	  • 50% GS5%
	• **Child >1y:**
	  • 2/3 Ringer's Lactate
	  • 1/3 GS5%	

Monitoring and adaptation	• Hemodynamic variables • Hourly diuresis: between 0.5 and 1.5ml/kg/h • Urinary density: between 1010 and 1020 • Natremia, glycemia, osmolarity	

Table 8. Hemodynamic Resuscitation Algorithm in Adults with Severe Burns. Adapted from the SFAR 2020 Guidelines.



- After the initial six hours of care, the experts advise giving human albumin to patients with severe burns who have a total burnt body surface area of above 30%.

  Theoretically, colloids can raise oncotic pressure, lowering fluid loss and the number of crystalloids used in the first stage of treating severe burns. Colloid injection therefore has the potential to improve prognosis by reducing problems linked to fluid overload, such as acute respiratory distress syndrome, congestive acute renal damage, and abdominal compartment syndrome.

Additionally, human albumin may have antioxidant and anti-inflammatory properties.

For patients with a TBSA of 20–30%, 5% albumin administration decreased administered crystalloid quantities, decreased the likelihood of organ failure, and decreased death, according to many studies, the majority of which were observational.

Notably, 20% albumin treatment (with a serum albumin goal of > 30 g/L) did not lower mortality compared to the control group in multicenter research on patients without burns who had severe sepsis or septic shock.

The experts advise that patients with severe burns should receive enough albumin to keep albumin levels at > 30 g/L since the extremely large doses of crystalloids given to burns patients are linked to iatrogenic damage. This is often accomplished with albumin dosages of 1-2 g/kg/day. This might aid in reducing the amount of crystalloid infused and the subsequent morbidity.

Albumin administration has been experimentally added to certain resuscitation strategies in pediatric settings. Although it is still debatable, this strategy appears to lessen the requirement for fluids in children. In contrast to late administration (12 hours after burning), early administration (8–12 hours after burning) of 5% albumin lowered the need for crystalloids, the incidence of fluid creep, and the length of hospitalization in children with TBSAs of > 15%[6].

Field 3: Airway management and smoke inhalation

- The doctors advise against frequently intubating patients who have burns on their face or neck.
- If one (or more) of the following characteristics are also present, the experts do advise to consider intubating patients with burns covering the full face:
    1. A deep, circular burn on the neck
    2. Signs of airway blockage (such as a change in voice or laryngeal dyspnea); and
    3. The extent of the burns (i.e., 40% of the total body surface area burnt).
- To prevent transfer delays, the specialists advise against doing bronchial fibroscopy outside of burns centers if smoke inhalation is suspected.

  For diagnosing smoke inhalation, bronchial flexible fibroscopy is typically regarded as the gold standard. Blood gas analyses and chest X-rays are not diagnostic tools. According to grading ratings, the morbidity, length of stay in the intensive care unit, time spent on mechanical breathing, and degree of hypoxemia are all connected to the severity of the lesions seen during

bronchoscopy. However, proximal airway abnormalities play a major role in an urgent justification for intubation. Although it is a standard technique, it is unclear how fibroscopy affects results. Due to the possibility of clinical worsening following the surgery, fibroscopy should usually only be carried out on patients who have previously been intubated. Once more, its usage in kids, which can be challenging for small kids, must not impede effective care of these patients.

- The specialists advise against frequently giving hydroxocobalamin to anyone who has inhaled tobacco.
- The specialists advise that only adult patients with smoke inhalation and a strong suspicion of severe cyanide poisoning, as well as children with smoke intoxication and moderate cyanide intoxication, should receive hydroxocobalamin (very low level of evidence).

  Hydroxocobalamin does not appear to increase survival following smoke inhalation. Furthermore, nephrotoxicity brought on by oxalate nephropathy has been linked to hydroxocobalamin. As a result, the use of hydroxocobalamin therapy should generally be limited to cases of smoke inhalation when there is a strong suspicion of significant cyanide poisoning, including cardiac or respiratory arrest, shock, and/or coma. Since plasma lactate concentration and plasma cyanide concentration are connected, measuring plasma lactate may help determine whether to provide hydroxocobalamin. According to a cohort study, 83% of cyanide poisoning patients had plasma hyperlactatemia over 8 mmol/L. Adults should take 5 g, and 10 g is advised for cardiac arrest.

  Compared to adults, children have a lower body mass index and a greater alveolar ventilation per minute. These variations make them more susceptible to cyanide toxicity following smoke inhalation. Given the severity of this poisoning, prehospital administration of hydroxocobalamin (70 mg/kg, maximum 5 g) is advised for children who have smoke inhalation symptoms and show signs of moderate cyanide poisoning (GCS score 13, confusion, stridor, hoarseness, polypnea, dyspnea, soot particles in the airways) or severe cyanide poisoning (GCS score 8, seizures, coma, mydriasis, severe hemodynamic disorders, collapse, respiratory depression)
- The specialists advise against routinely using hyperbaric oxygen treatment in situations of suspected carbon monoxide poisoning following smoke inhalation.

  Two hypothesized reasons for one or more sessions of hyperbaric oxygen therapy (HBOT) in patients who have suffered severe burns have been put forth. The first is when carbon monoxide (CO) poisoning caused by smoke

inhalation is suspected or confirmed; in such circumstances, HBOT is believed to prevent or lessen the neurological aftereffects of this poison. The second reason is to encourage burn wound healing (grade B evidence).

Regardless of their carboxyhemoglobin level upon admission, patients with CO poisoning who have a high risk of medium or long-term neurological sequelae should get HBOT, according to the European Committee of Hyperbaric Medicine (ECHM). These individuals have neurological, respiratory, cardiac, or psychiatric symptoms as well as an altered state of consciousness. For pregnant women who have been exposed to CO, HBOT is also advised regardless of how they appear clinically when they are admitted. They claimed that due to frequent hemodynamic or respiratory instability in the acute period, which creates technical challenges with HBOT and carries significant hazards, HBOT is frequently contraindicated in patients with severe burns. The current recommendations' specialists advise that each individual case should be considered when determining whether HBOT is indicated.

These evaluations should take into account the patient's age and whether she is pregnant or not, the severity of the burn and poisoning, the patient's stability, whether HBOT equipment can be started quickly enough, and whether a specialized team is present to ensure the best safety conditions. As a result, all patients who have experienced CO poisoning from smoke inhalation should receive immediate treatment with oxygen via a high concentration mask or 100% FiO2 for 6 to 12 hours if they are mechanically ventilated. Early HBOT (within the first six hours) could be an optional therapy for second-degree burns involving > 20% TBSA, particularly if the burns affect the face, neck, or perineum, according to the ECHM's 2016 statement (very low level of evidence) It was thought that HBOT in this situation could lessen deep burn extension and enhance recovery. Any child suspected of having CO poisoning should start receiving 100% oxygen right away, according to the ECHM, starting with first assistance (grade C evidence). Furthermore, regardless of the carboxyhemoglobin level at hospital admission, the ECHM recommends treating all children with CO intoxication who display decreased awareness and/or neurological, cardiac, respiratory, or psychosocial symptoms with HBOT[6] (grade C evidence).

Field 4: Anesthesia and analgesia

- Multimodal analgesia, according to the experts, is an option, but all analgesic drugs should be dosed in accordance with proven comfort and analgesia assessment measures.
- The doctors advise combining additional analgesics with titrated intravenous ketamine to treat extremely painful burns.

- The doctors advise combining nonpharmacological treatments with analgesic medications for dressings as necessary if the patient is stable.

  Burn injuries cause inflammation, hypermetabolism, and capillary leakage, all of which result in hypovolemia and raise the possibility of negative side effects from sedatives or analgesics. Therefore, titrating medications are expected to lower the possibility of under- and overdose. Ketamine reduces morphine intake while being an effective treatment for burn-related pain.

  Lidocaine's lack of high-quality evidence makes it unable to provide recommendations for its use in burn patients.

  When appropriate, patients with burns may get local anesthesia care.

  Finally, non-pharmacological approaches to pain management may be more effective, such as chilling the limited injured surfaces and treating burns with a fatty substance (such as Vaseline). Hypnosis or virtual reality therapies may also lessen the patient's anxiety and discomfort level. The burn management conditions for patients with non-life-threatening injuries must be modified in order to apply these techniques. Burns or dressing changes frequently result in pain that is fleeting.

  The most effective medications for treating pain brought on by burns are likely ketamine and short-acting opioids. Nitrous oxide inhalation can be helpful, particularly when there is no IV access available. Alpha-2 receptor agonists are challenging to utilize in the acute period due to their hemodynamic effects. Finally, general anesthesia is a good choice for painful injuries or treatments[6].

Field 5: Local treatment

- According to specialists, burns in adults with a total burned body surface area of less than 20% and burns in children with a total burned body surface area of less than 10% should be cooled without shock.

  Several studies suggest that **cooling** was associated with a reduced need for skin grafting, reduced depth of burns using tap water, reduced pain, shorter hospital stay, lower risk of admission to continuing care, lower need for grafts in burns with <25% TBSA. However, this practice can increase the risk of hypothermia. In children with a TBSA > 10-15% and adults with > 20-25% TBSA, cooling is not recommended.

- To lessen the risk of hypothermia and microbiological contamination, the specialists advise covering burn wounds during the initial stage. Up until professional guidance can be sought, the dressing should be kept in place.

Care for burn wounds should be administered in a sterile setting and typically calls for general anesthesia or deep analgesia. Before putting on the dressing, the wounds need to be washed with tap water, isotonic saline solution, or an antiseptic solution. The type of dressing is determined by the TBSA, how the wound appears locally, and the patient's overall health (figure 2). There isn't much proof that one kind of clothing is better than another. However, it appears that if used for a long time on superficial burns, silver sulfadiazine is linked to delayed healing. Large or infected burns may benefit from an antiseptic dressing. Topical antibiotics should only be used on infected wounds and not as first-line therapy.

It's important to avoid creating a tourniquet effect when putting the dressing, especially on the limbs. Circular dressings require monitoring of distal perfusion. Dressings should ideally be reviewed every day.

To reduce the danger of hypothermia, external cooling devices like Water-Jel dressings shouldn't be utilized for extended periods of time.

Therefore, patients with serious burns shouldn't be brought to the hospital while using external cooling devices. In the prehospital stage, burn wounds can be wrapped with sterile gauze, interface dressings, or non-adhesive dressings. However, using such straightforward dressings shouldn't cause further resuscitation measures to be delayed.

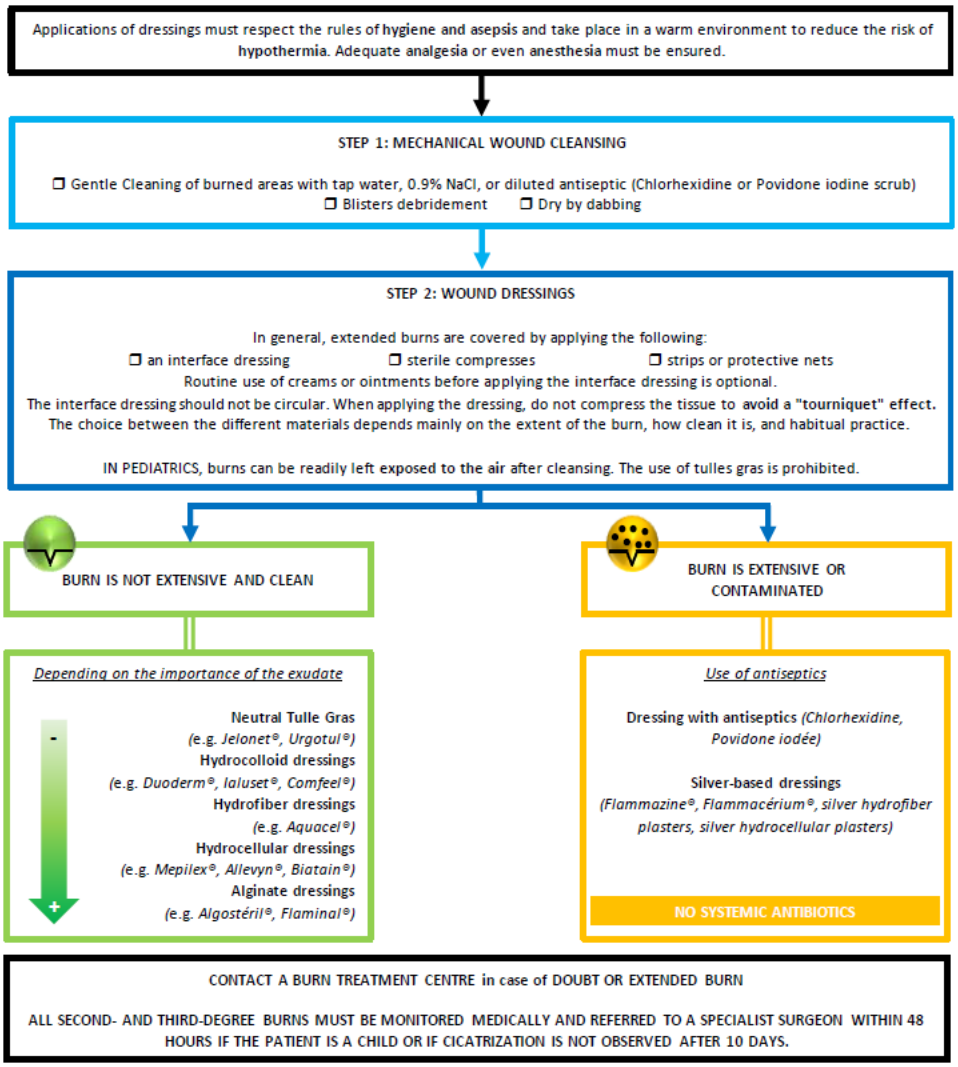


Figure 2. *Wound care and dressings. Retrieved from the SFAR 2020 guidelines.*

- According to the specialists, individuals with burns shouldn't typically receive antibiotic prophylaxis.

  It is still unknown whether patients with burns should get local antibioprophylaxis, systemic antibiotic prophylaxis prior to surgery, systemic antibiotic prophylaxis throughout the perioperative period, and/or systemic antibioprophylaxis after surgery.

  The specialists advise against using systemic antibiotic prophylaxis, particularly considering the possibility of selecting multidrug-resistant microorganisms in patients with severe burns[6].

Field 6: Other treatments

- After a burn injury, the specialists advise beginning nutritional supplementation within 12 hours. Parenteral routes are recommended over oral or enteral methods.

  Early oral or enteral nutrition initiation (within the first 6 to 12 hours) is linked to decreased neuro-hormonal stress response, decreased hypermetabolic response, increased immunoglobulin production, decreased incidence of stress ulcers, and decreased risk of energy and protein deficiency. The amount of energy needed each day is calculated using prediction formulae designed specifically for burn victims. The Schofield formula is used for youngsters, whereas the Toronto formula is used for adults (Rf Table 8). Adult protein needs range from 1.5 to 2 g/kg per day, whereas children's protein needs might reach 3 g/kg per day.

  Supplementing with glutamine (or alpha-ketoglutarate) seems to be linked to lower levels of gram-negative bacteremia, shorter stays in the hospital, and lower rates of hospital mortality. Micronutrient supplementation should probably be started early in both adults and children. Copper, zinc, and selenium are the three principal trace elements. Vitamins B, C, D, and E should be the major supplements taken.

- Early thromboprophylaxis should be regularly provided for patients with severe burns.

  Deep vein thrombosis occurs more frequently in burns patients without thromboembolic prophylaxis (0.9–5.9%), according to retrospective cohort studies.

  Age, TBSA, the depth of burns, the presence of central venous access (including femoral access), the duration of mechanical breathing, the necessity for intensive care hospitalization, and the requirement for numerous transfusions all enhance the risk of thromboembolic events. Enoxaparin has been recommended as an effective prophylactic drug. In individuals who have a contraindication to heparin, mechanical thromboprophylaxis might be performed for the unburned region.

  In pediatrics, pubescent kids and those with a central venous catheter should get thromboprophylaxis[6].

1.4.3 Royal Manchester Children's Hospital Update on the Management of Burns in Pediatrics (2020)

Burns in children are frequently encountered, especially thermal burns. It can damage the skin and expose to different types of complications like infections, and increase in hospital stay length, and psychological disorders. Multiple specialists may be involved in the child's case like anesthetists, dermatologist, infectiologist…

These guidelines cover the essentials of pediatric burn management and relative support care, updated. Recommendations are mentioned with the corresponding evidence level.

A. Initial management

The child should be treated initially according to the principles of Advanced Pediatric Life Support, using an "airway, breathing, circulation, disability and exposure" (ABCDE) strategy and being alert for any further injuries in addition to the burn. When treating critically burnt children, anesthetists will be involved to offer airway assessment and management, IV access, sedation/analgesia, and transfer.

To inform early care, it is critical to comprehend the injury's process. Burns from an enclosed fire will cause smoke inhalation, and the resulting airway damage will be exacerbated by soot, toxic materials, and hypoxia. Since airway oedema will spread quickly, tracheal intubation must be done as soon as possible in severe instances. Children who are not physically capable of moving about freely, such as babies or children with physical limitations, may suffer more serious scald injuries.

Accuracy is crucial since the secondary survey's evaluation of the burn's size and depth directs both fluid resuscitation and the placement of follow-up therapy. By recognizing the damage to the epidermis and dermis skin layers, one may gauge the depth of the burn.

The depth of a burn might be superficial, partial, or complete. This evaluation aids in determining the anticipated recovery timeframe.

The Lund and Browder burns chart, which indicates the proportion of body surface and varies with child age, has traditionally been used to calculate the TBSA of a burn. The patient's palm and fingers make up 1% of the body surface, according to another criterion. To quickly assess if a patient needs to be sent to a specialized center, the "rule of nines" is utilized. Once more, this has been modified for pediatric burns. The amount of the burn is frequently overestimated, especially in youngsters, despite the existence of these many techniques for TBSA estimation.

Using the Mersey Burns app, a user may input the patient's age and weight and color in the regions of full- and partial-thickness burns to assist assess the extent of a burn.

It is crucial to decide whether to transfer the kid to a specialist center once the first diagnostic and resuscitation procedure has begun. Children are sent to a specialized burns unit based on the following factors: burns with a TBSA of greater than 5%, burns over a joint, on the perineum, hands, feet, or circumference, burns brought on by inhalational injuries, electrical burns, and chemical burns.

If a child unfortunately sustains serious burns, care should be taken to determine if transfer to a burns center is even appropriate. It is important to find a balance between a child's and family's end-of-life demands and the likelihood of recovery if moved to a center of expertise. Having said that, it is significant to highlight that more patients with serious burns are surviving, and a conversation with the specialized center is necessary. The improvement in burns care is a significant factor in the survival of more severely burned individuals. Improved resuscitation, surgical skill, less blood loss, early antibiotic medication (including topical), and critical care management are some of these advancements.

But severe burns may have a crippling effect on a person's quality of life, both physically and emotionally. Therefore, it is crucial that rehabilitation and therapy continue to advance. Even children with quite severe burns frequently recover surprisingly well over time.

The Baux score is a well-liked rating method for burns. It originally gained popularity in the 1960s and calculated projected death by multiplying the patient's age by the proportion of burns they had (age % TBSA). A score of 100 would indicate a 100% anticipated death rate. Given the advancements in burn management and therapy, this may now be contested. According to some extensive research, a 100% expected death rate would be closer to a score of 160 than 100. This would imply that all children may live, even those who had the most serious injuries[7].

B. Fluids

Increased vascular permeability following burn damage causes considerable fluid changes that result in intravascular volume loss. Patients frequently have decreased vascular resistance and may develop systemic inflammatory response syndrome, which can cause myocardial depression at first. Additionally, systemic oedema, which starts to appear 4 hours after the injury and lasts for 36 hours, is present in patients with TBSA >25%. These modifications lower cardiac output, cause hypoperfusion, and, in extreme circumstances, circulatory shock. Fluid resuscitation must begin quickly. The risks of acute renal failure, multiple organ dysfunction, a lengthy hospital stay, and death can all increase because of delays in fluid resuscitation. This could happen as a result of challenging IV access. The intra-osseous pathway should be quickly established in such circumstances. A bolus of 20 ml kg of crystalloid should be administered to children who present with circulatory shock.

Anyone with more than 10% TBSA burns must get formal fluid resuscitation. A formulaic strategy that is tailored depending on physiological endpoints is encouraged, just like with adults. There are formulations available for children. These take into account the physiological variations in pediatric patients. The Parkland formula, which is expressed in milliliters, is the one that is most frequently used. This is equivalent to 3–4 ml kg x TBSA% burns throughout a day. Half of the amount is distributed throughout the first 8 hours following the burn, and the other half over the next 16 hours. Other formulae, such the modified Brooke formula, have been used as fluid regimes have become more stringent. Clinicians must utilize their knowledge to support continuous fluid control and modify infusions as necessary. This can be established by using the resuscitation and hydration endpoints (strong evidence)

The 'fluid creep' phenomenon, in which patients get much more fluids than anticipated, has been recognized recently. Over-resuscitation with intravenous fluids can be harmful, just as under-resuscitation can result in complications. Acute respiratory distress syndrome (ARDS), multi-organ failure, abdominal and limb compartment syndrome, and cerebral oedema are a few problems that can result from excessive resuscitation.

If dosages of medications, such antibiotics, and electrolyte supplements, like magnesium, are not taken into account, fluid creep may happen[7].

C. Intraoperative management

Burn victims may require several trips to the operation room. Dressing changes, skin grafts, and wound cleansing and debridement are frequent treatments. Escharotomies may be necessary in circumferential burns to prevent compartment syndrome and neurovascular impairment.

Physiological changes

Multiple physiological changes in pediatric burn patients must be considered throughout the perioperative phase. The anesthetist must assess if the patient has gained some stability during the initial resuscitation period. This will be ascertained by the use of inotropic drugs, vital signs, urine output, hydration status, and urine output.

After the first 24 hours, individuals with burn injuries experience a hypermetabolic and inflammatory response. This may endure for a considerable amount of time (some sources have estimated up to two years). The intensity of this response will often be correlated with the severity of the burns. Catecholamines and other stress hormones are released, which increases basal energy expenditure, cardiac output, oxygen consumption, and refractory tachycardia. It is important to keep in mind that

a very ill child may experience circulatory collapse as a result of catecholamine depletion during induction of anesthesia.

Airway

Particularly in cases of face and inhalational injuries, a difficult intubation should be taken into consideration if the airway is not already secured. It's important to take airway oedema seriously, especially in the first 48 hours. In these situations, video-laryngoscopy is frequently used. Loss of the airway may result in death. There should be the tools and staff necessary to execute an emergency tracheostomy.

Temperature

Controlling the temperature is crucial for pediatric burn sufferers.

Burns jeopardize the skin's integrity and can result in considerable heat loss. In the operating room, continuous core temperature monitoring is crucial. Rectal, esophageal, or bladder temperature probes are frequently employed. 24-48 hours after the time of the accident, post-burn pyrexia in children is a problem that can happen. Antibiotics shouldn't be started unless there is convincing evidence to suggest differently because it is frequently unrelated to infection. The basal metabolic rate and energy consumption are significantly increased by fever. For temperature regulation in serious situations, hemofiltration is necessary.

Monitoring

The anesthetist must be creative as well as practical when deciding how and where to put standard monitoring devices like an oxygen saturation probe, ECG leads, and blood pressure cuffs. Both arterial gas sampling and blood pressure monitoring benefit from an arterial catheter. This is crucial in instances with severe burns.

An hourly assessment and a urinary catheter are crucial since fluid loss might be significant. The use of cardiac output monitoring is growing, and it predicts considerable fluid movements. A variety of cardiac output monitors have pediatric use licenses. Esophageal Doppler and LiDCO are some of them.

During surgical operations, blood loss must be closely monitored. It might be challenging to estimate actual blood loss.

According to one research, 1% of a TBSA burn may be removed for every 3-5% predicted blood loss. The following formula may be used to calculate the amount of blood needed for a certain procedure: 3 x weight (kg) x %burn. Surgical methods to lessen blood loss include the use of tourniquets, swabs soaked in adrenaline, and subcutaneous adrenaline injections prior to excision (1:100,000). Bupivacaine and adrenaline sub eschar injection (clysis) might also lessen blood loss. Bupivacaine

(0.001%) and adrenaline (1:500,000) are injected into the sub eschar and donor sites after being diluted in saline 0.9% or Hartmann's solution.

Special circumstances

In a variety of circumstances, a sick kid may require special care that must be maintained throughout surgery. Renal replacement treatment (RRT) and high-frequency oscillation breathing are examples of this.

Acute renal failure in burn patients can occur for a variety of causes. Severe metabolic acidosis, fluid overload, and electrolyte imbalance are a few examples. Continuous venovenous hemofiltration and continuous venovenous hemodiafiltration are two forms of continuous RRT that are often utilized in pediatrics. The Pediatric Intensive Care Unit (PICU) must be staffed with skilled, committed personnel to supervise this. While in the operating room, it would be anticipated that the same crew would continue to supervise this. Prior planning and coordination with the PICU staff are required. The vascular catheter that is being utilized must be straight and operating at adequate flow rates. Before transfer, an arterial blood gas should be done to make sure there is some level of stability.

When conventional ventilation has failed to treat respiratory failure, high-frequency oscillation ventilation is performed. Reverting back to traditional ventilation using the anesthetic machine in such circumstances, if it was determined that the patients must travel to the operating room, is likely to make their condition worse. These patients frequently develop ARDS; thus, their respiratory health must be carefully monitored.

Infection risk

Antibiotics should be used empirically if an acute infection is suspected. It's crucial to rule out infections from places other than the wound, such as the urinary and respiratory systems. During the perioperative period, antibiotics should be maintained.

Analgesia

It's crucial yet frequently difficult to manage pain in burn damage patients since it can be impacted by a variety of circumstances. These include physical activity, surgical and non-surgical procedures, the location, size, and depth of the burn, as well as its progression. Both central and peripheral mechanisms can mediate pain.

Simple analgesics and opioids are the mainstay of pain management throughout the postoperative period. Commonly prescribed medications include regular paracetamol and morphine as needed. It is administered intravenously or orally using continuous or PCA pumps. Oxycodone is a substitute for individuals who

cannot take morphine. It has greater bioavailability and is preferred in individuals with renal insufficiency.

NSAIDs should only be used with extreme caution in burn victims. Despite being potent analgesics that may lessen the need for opioids, they may not always be recommended because side effects include renal toxicity, stomach ulcers, and antiplatelet effects. Gabapentin, ketamine, and a2 agonists (such clonidine and dexmedetomidine) are other helpful medications[7].

D. Procedural sedation and analgesia

Care for burns frequently involves several unpleasant treatments that may be safely carried out outside the operating room. Examples that are frequently used are showers, dressing changes, and staple removal. A multimodal strategy that uses hypnosis, guided imagery, play therapy, and both pharmaceutical and non-pharmacological therapies is crucial.

The management of background and procedural pain is crucial for maintaining treatment compliance and reducing psychological suffering.

Ketamine, propofol, benzodiazepines, and opioids are frequently used medications for procedural sedation and analgesia in burn patients. For more than 40 years, ketamine has been used widely in burn treatment. It is perfect for procedural sedation due to its potent analgesic effects, preservation of airway reflexes, and cardiorespiratory profile. Agitation, hallucinations, and emerging symptoms are some of the negative consequences.

Because of this, a second medication—such as a benzodiazepine—is administered in addition.

Dexmedetomidine has recently received attention for its usage in PICU sedation as well as procedural sedation.

Given that pediatric burn patients must undergo painful treatments, its combination of analgesia, sedation, quick onset, and offset makes it a beneficial medicine to take into consideration. Propofol and opioids are commonly used for procedural sedation and analgesia. This can result in several negative side effects, including an obstructed airway and cardiorespiratory impairment. This has made it possible to employ other medications, including dexmedetomidine.

Dexmedetomidine predominantly affects the locus coeruleus of the pons by acting as an agonist on a2 adrenergic receptors.

It induces a drowsiness similar to that of natural sleep and barely affects breathing directly. It has biphasic effects on the heart. Both bradycardia and hypotension may result from it. It can cause hypertension by activating vascular smooth muscle a2b receptors at greater blood concentrations.

Due to its analgesic qualities, dexmedetomidine's usage as a single agent is constrained. In painful treatments, it has been used well in conjunction with ketamine. They can all work together to produce amnesia, hemodynamic stability, sedation, and analgesia. Dexmedetomidine has been successfully utilized for sedation in radiological imaging, for example, using boluses of 0.5-2 microg kg-1 followed by infusions of 0.2-1 microg kg-1 h-1. An IV bolus of 100–300 microg kg-1 followed by an infusion at 0–5 microg kg-1min-1 is a typical ketamine dosage for procedural sedation.

Bolus dosage and infusion rates must be utilized with care when combined. Dexmedetomidine's growing use during procedures and throughout operations should help solidify its position as a worthwhile substitute for the more traditional medications already in use[7].

1.4.4 British Burn Association (BBA)

1.4.4.1 First Aid Clinical Practice Guidelines (2018)

It has been demonstrated that providing first aid for burns quickly and efficiently improves the prognosis of the burn by halting more tissue damage and lowering eventual morbidity. The first aid recommendations that are now available for the treatment of burns and scalds, however, differ greatly. Based on data from a thorough literature analysis, the following guidelines provide a minimal standard of care for the practical and efficient management of burns and scalds in first aid settings[8].

A. Thermal burns

Cease the burning procedure

When it's safe to do so, remove the person or people from the burn's source. Put out burning garments with water or the "Stop, Drop, and Roll" technique. STOP where you are, DROP to the ground, and use your hands to cover your mouth and eyes.

When trying rescue, roll over and back and forth until the flames go out. If it's safe to do so, isolate electrical power sources. Prevent chemical cross-contamination.

Take off clothes and jewelry

If at all possible, take off any polluted, burnt, moist, or confining clothing.

If possible, take out any jewelry, contact lenses, and diapers that are close to the burnt area.

Discard any liquefied or sticky garments.

Relieve the burn

If water is available, cool down as soon as possible.

Within three hours after the injury, cool the burn with cool running tap water for twenty minutes.

Try to chill for a full twenty minutes. Hypothermia may result after further cooling attempts, particularly in young people, the elderly, or in cases of severe burns.

When there is a limited supply of water, apply a cool water compress using any clean, wet, lint-free cloth. Change the compress frequently over the course of 20 minutes. If there isn't any water available right away, burns should be covered with cling film and cooled as soon as possible within three hours of the injury.

Although hydrogels are sold, there is little proof of their effectiveness. Avoid cooling with ice or ice-filled water.

Warm up the sufferer.

"Warm the patient but cool the burn."

Children and the elderly are particularly vulnerable to hypothermia; therefore, the patient must be kept warm. Cover non-burned regions when cooling and keep them warm throughout care interventions.

Cover the burn

Apply a wet compress to chemical injuries that have been fully decontaminated and irrigated.

Do not wrap cling film circumferentially around limbs or other burned areas.

Cover the cooled burn with loose longitudinal strips of cling film or any clean, lint-free cloth or non-adherent dressing[8].

B. Chemical burns

Since the length of the chemical's contact with the skin is a significant factor in determining the severity of the burn, it is imperative that chemical injuries be immediately decontaminated and diluted by irrigation.

Take out the chemical agent

Put on the proper personal protection gear to reduce the possibility of cross-contamination.

Before wet decontamination, brush off dry dust, remove pieces of solid chemical compounds, and throw away contaminated garments.

Irrigate

Regardless of the patient's presenting delay, do not postpone starting irrigation until after completing a thorough examination of the patient or obtaining a specific irrigation fluid.

Apply a sterile isotonic solution (such as Hartmann's or Normal Saline), an amphoteric solution, or room-temperature running water to the skin and eyes immediately.

Keep the patient submerged until he/she no longer feels pain or burning in the wound, or until a burn professional has evaluated them.

Avoid irrigating elemental metals, concentrated sulfuric acid, phenols, muriatic acid, and dry lime with water.

Because of the possibility of an exothermic reaction that might worsen tissue damage, avoid attempting to neutralize the chemical.

Treat

Manage any systemic toxicity or anticipated side effects of a chemical agent. Obtain agent-specific decontamination and treatment information from the National Poisons Information Service/TOXBASE. If necessary, administer antidote therapy for particular chemicals[8].

C. Electrical burns

Immediately cool the injury site(s) with cold running tap water for 20 minutes within 3 hours of the injury (after the electrical source has been controlled). Prioritize and handle life-threatening situations in accordance with established ATLS procedure.

Prolonged monitoring is not necessary if there is no history of cardiac arrest, unconsciousness, or aberrant rate or rhythm (normal ECG)[8].

D. Tar and bitumen burns

Within three hours after the damage, cool the molten agent and the injured area(s) entirely by pouring cool tap water over them for 20 minutes. Once cool, emulsify the tar using solvents that contain liquid paraffin or any other oily material. Tar removal may wait until you go to the burn service and is not an emergency[8].

E. Cold burns (frostbite)

Give life-threatening situations, such as hypothermia or severe trauma, priority over the existence of localized cold injuries.

Only start local rewarming in the pre-hospital management of cold injuries if refreezing won't happen during travel. If there is field melting, do not refreeze.

Within 12 hours of the injury, quickly and continuously rewarm the area in circulating water at 37°C to 39°C while using a weak antibacterial agent (povidone-iodine or chlorhexidine) for at least 30 minutes.

When all wounded tissues appear reddish-purple, feel malleable and soft to the touch, and have restored feeling, the process of rewarming is considered complete.

Avoid using dry heat as it might make the wound worse.

Avoid applying pressure, massaging, or rubbing the afflicted region to prevent further tissue injury.

Elevate the injured area to reduce any developing swelling[8].

1.4.4.2 Clinical Practice Guidelines for the Management of Burn Blisters (2018)

Healthcare workers required to handle patients with burn blisters in pre-hospital, emergency, primary, or secondary services can find direction from the BBA guidelines, which are developed based on the best available evidence for burn blister management.

A. Burn blisters

Burn injuries cause increased capillary permeability, which leads to the creation of oedema and the separation of the epidermis from the underlying dermis. This process causes burn blisters. Burn blisters can form on top of deeper burns, however they are more common in superficial partial thickness burns[9].

B. Criteria for deroofing

Deroofing is a process that requires the description of the wound before initiating it. Sometimes the wound doesn't need deroofing[9].

Table 9. Blister Criteria That Lead to Possible Deroofing. Adapted from the BBA 2018 Guideline.

LEAVE INTACT	Non-tense and small blisters (<6mm)	Natural method of pain control. Unlikely to rupture spontaneously, damage underlying tissue, or impede healing
	Deroofing is not the priority in care for severe and extensive burns	

DEROOF	Thick-walled blisters on fingertips, palms, and soles of feet	These regions are prone to pain and restricted motion when there are blisters. An alternative approach to care is to cut a sizable "window" to allow for fluid removal and wound evaluation.
	Large (>6mm) and thin-walled blisters	Most likely to occur on hair-lined surfaces and rupture spontaneously, which increases the risk of infection
	Ruptured blisters and loose skin	Removes any necrotic and possibly contaminated material from the wound

C. Rationale for deroofing

- Makes it possible to accurately analyze the burn depth, including capillary refill time and feeling, and to see the wound bed in order to choose the best course of action.
- Reduces the chance of scarring and speeds up wound healing by removing non-viable tissue from the wound bed.
- Removes blister fluid that might impair the patient's systemic and local immune response, strengthening their defenses against infection.
- Lowers the chance of wound infection brought on by uncontrollably rupturing blisters and the protracted presence of non-viable tissue.
- Avoids applying pressure to the underlying tissue, maintaining the microcirculation of the wound, and stopping the advancement of burn depth.
- Promotes joint mobility, lowering the risk of burn contracture.
- Enhances the effectiveness of topical wound care[9].

1.4.4.3 Initial Management of Ocular Burns (2021)

A. Preparation

Apply topical anesthetic eye drops as needed to make irrigation and inspection easier.

Take out any scabs, debris, particle matter, or exudate from the eye; if possible, remove contact lenses.

Measure corneal pH (tears have an average pH of 7.6)[38].

B. First Aid

Regardless of the delay in presentation, do not postpone the prompt irrigation of the eye in order to get a specific irrigation fluid or to conduct a thorough examination of the patient.

- Use water, an amphoteric solution (Diphoterine®), or a sterile isotonic solution (Hartmann's or Normal Saline) to start an immediate irrigation.
- Water for as long as it's safe and feasible to do so. Keep the patient warm to avoid hypothermia; the elderly and young are particularly vulnerable.
- To prevent cross-contamination, keep the unaffected eye above all others.
- Move from the inside corner outward. The sterile fluid should be applied over the eye using a Morgan lens or the end of an IV tube.
- Thoroughly rinse the deep fornices and the eye. Lift the eyelids if at all possible.
- If there are chemical injuries, conduct another pH test as soon as the irrigation stops and again after 30 minutes[38].

C. Assessment

Check for chemical or thermal burns on the face and lids; reapply topical anesthetic as necessary to enable proper evaluation.

Rule out any foreign body or chemical that is in the eyes, intraocular, or intraorbital.

The following tests are performed on the cornea: fluorescein corneal staining; corneal clouding and perilimbal blanching; visual acuity evaluation (with input from ophthalmology); intraocular pressure (with input from ophthalmology)[38].

D. Treatment

Examine whether the patient has received a tetanus vaccination.

Cut any singed or scorched eyelashes.

Use chloramphenicol ointment to burnt eyelids and the ocular surface to lower the risk of infection.

Sit the patient up to minimize oedema in the face and eyelids and consult the local ophthalmology and burns service[38].

1.4.4.4 Management of Burns in Pre-Hospital Trauma Care (2019)

Following a conference at Queen Elizabeth Hospital in Birmingham, a multidisciplinary panel including members of the British Burn Association (BBA) and the Faculty of Pre-Hospital Care (FPHC) reviewed the relevant data and reached an agreement[10].

It serves to update the existing consensus for burns care from the FPHC, in collaboration with the BBA, and to offer guidelines for the pre-hospital management of burn injuries.

It is crucial to emphasize the significance of not ignoring crucial pre-hospital care components such as scene safety, putting out flames, and preventing the cross-contamination of chemicals, corrosives, and causal agents before providing clinical management guidelines (IV).

A. Airway management

Any burn patient's initial evaluation must rule out airway burns or inhalational injuries. There are two anatomical groups of airway burns: supraglottic and infraglottic.

Because the upper airways are so powerful at exchanging heat, most airway burns will be supraglottic, confined to the larynx and Naso/Oropharynx.

Certain situations, such as inhaling steam or aspirating boiling liquid, blast injuries, combustible gases under pressure, or chemical aerosolization, should be taken into consideration while evaluating infraglottic airway burns [IV].

Impaired ciliary activity, erythema, hypersecretion, oedema, mucosal ulceration, and bronchial spasm are among the characteristics of infraglottic airway burns [IV].

If intubation fails, practitioners should be equipped to execute a surgical airway as part of the Rapid Sequence Intubation (RSI) checklist.

Setting up equipment and identifying landmarks are necessary steps before starting the RSI. Due to tissue oedema or underlying burned skin, a direct transverse incision through the skin and cricothyroid membrane may not be successful in obese patients or in cases where the anatomy is difficult to palpate.

In this case, it is advised to make a transverse incision into the cricothyroid membrane after a longitudinal skin incision to reveal the anatomy [IV][10].

B. Breathing

The goal of treatment should be to achieve oxygen saturations between 94% and 98% [IV] by using a non-rebreathing reservoir mask at a rate of 10 to 15 l/min. Asphyxiant inhalation should be taken into consideration in addition to standard

respiratory assessments, particularly if patients have been imprisoned in a smoke-filled confined space. Pre-hospital clinicians should assess a variety of signs and symptoms in addition to pulse oximetry to rule out asphyxiant inhalation. These consist of CNS depression, widespread muscular weakness, acute temporal headache, irritability, and lethargy.

After carbon monoxide (CO) or cyanide (CN) poisoning, cyanosis may often be absent; thus, a high index of suspicion should be maintained to prevent missing such diagnoses. It is uncommon to see cherry red discoloration after breathing in an asphyxiant [III]. Because of their comparable absorbances (extinction coefficients), standard pulse oximeters are unable to distinguish between carboxyhemoglobin (COHb) and oxyhemoglobin (O2Hb) until COHB levels are more than 40%. As a result, pulse oximeters are unable to show decreased pulse oximetry since they measure COHb similarly to O2Hb. Even with normal pulse oximetry readings, carbon monoxide poisoning may exist [III]. Carbon monoxide meters, if accessible, can help with diagnosis; a reading of more than 30% suggests serious poisoning.

High flow oxygen [IV] remains the first treatment. the delivery of 100% normobaric oxygen until the patient's CO poisoning symptoms have subsided and COHb is normal (<3%) [IV]. Carbamyl hemoglobin has a half-life of 320 minutes while breathing air. This can be lowered to inhaling 100% oxygen [IV] for 80 minutes. Inhaling smoke or asphyxiants may cause altered mental state and depression in the central nervous system (CNS). Since there is evidence linking elevated blood levels of cyanide (CN) and carbon monoxide (CO) to burn injuries and smoke inhalation, as well as cardiac arrest, routine conscious level monitoring of these parameters should be performed in all burn patients [III].

Treatment with hydroxycobalamin has been linked to better survival rates in the treatment of acute cyanide poisoning brought on by smoke inhalation, as well as a risk-benefit ratio that makes it appropriate for usage prior to hospitalization [III].

It is advised to give high flow oxygen and cyanide poisoning antidotes (hydroxycobalamin 5 mg intravenously) to burn patients who appear to have been exposed to smoke and have altered mental status or unstable heart rhythm. IV].

In addition to medical comorbidities, self-inflicted poisoning, and occult trauma should be considered as potential causes of low consciousness. About 1.5–6% of all burn injuries are caused by self-infliction (or suicidal intent) [III], therefore wherever feasible, a focused history should be taken from the patient[10].

C. Circulation

After significant burns, placing IV access can often be challenging. Consider intraosseous circulatory access if two attempts are unsuccessful.

It is possible to provide enough fluid quantities for burn injury resuscitation when intraosseous (IO) vascular access is used [IIb].

Without the use of a pressure bag, infusion rates vary from 5 to 10 ml/min, depending on the anatomical location and underlying state of hypovolemia [IIb]. Therefore, in order to provide larger fluid amounts, dual IO access could be necessary[10].

D. Temperature

It has been demonstrated that hypothermia in burn patients is independently linked to death [III], hence efforts to actively warm patients should be taken to prevent hypothermia [IIb].

In order to accurately assess the severity of their burns, patients must be fully exposed; however, this must only be done for the shortest length of time necessary, exposing only the region under examination, and body temperature must be taken on a frequent basis to prevent heat loss[10].

E. Burn severity

It has been demonstrated that the most trustworthy technique for precisely estimating burn TBSA severity is to utilize the Lund & Browder chart [IV].

Additionally, it has been shown that using electronic versions to calculate burn TBSA is both more effective and efficient [II]. To provide an accurate assessment, a supine patient's posterior surfaces must be thoroughly examined. Only burns of partial or full thickness should be included, excluding areas with superficial burn characteristics such as erythema, dry skin, blistering, intact skin, and skin blanching with brisk capillary refill.

A properly scaled pediatric burns chart should be used to estimate the number of burns since children have a distinct anatomical surface area.

In order to guide pre-hospital treatment techniques, estimations just need to provide a simplistic demarcation between those burn TBSA <20%, 20-50%, and >50%. This is because the burn area may change over time and with standard of care. Whether a burn is small (<20%) or serious (>20%) will dictate how further care should be administered, including whether fluid resuscitation is required and whether the patient should be triaged to a burn center[10].

F. Burn cooling

The best way to cool burns has been shown to be under cold flowing water, which also improves the course of burn healing [III]. Twenty minutes is the ideal burn cooling time [III/IIb].

Less than 20 minutes of cool water treatment has no impact on better burn healing results [III]. The ideal healing temperature for cool water is around 12°C [Ib]. Cool water should not be warmer than 20°C. Because of the increased tissue necrosis, ice water (<8oC) should be avoided [Ib].

To lower the danger of wound infection, water should ideally be drinkable; non-potable water should not be used for burn cooling.

To provide efficient cooling, fluid quantities ranging from 20 to 120 liters of water may be needed, applied to the burn area(s) at a minimum rate of 1 to 1.5 liters per minute [IIb].

Burn cooling should be done as soon as possible, ideally within 10 minutes of the injury, even if it is beneficial for up to three hours after the damage [III]. Only in situations when there is an urgent threat to life or serious sequelae from trauma should cooling be postponed or avoided.

Remove any jewelry and any clothes that covers the burned regions. Any substance that sticks to the skin should be left there, although cooling should still proceed [IV].

Hypothermia in patients does not seem to be directly caused by burn cooling [III]. But at the pre-hospital stage of care, burn cooling therapy should be closely watched, and as mentioned above, steps should be taken to aggressively warm patients to prevent hypothermia [IIb][10].

G. Chemical burns

Amphoteric treatments have shown promise in the management of burn injuries caused by chemicals. Amphoteric solutions have been demonstrated to reduce tissue damage, increase analgesia, and resolve pH more quickly in both experimental and clinical investigations, with no negative side effects [Ia/IV].

Nevertheless, these studies' reporting and methods are subpar or exhibit a substantial risk of bias [Ia]. The in-hospital administration of amphoteric solutions did not significantly alter the duration of hospital stay, the time to healing, or the requirement for surgery in a single unaffiliated clinical series [III].

It is advised to use an amphoteric solution for chemical burns as it is likely to be both safer and more effective than alternative irrigation solutions [Ia/IV].

A particular amphoteric eye wash should be utilized for ocular chemical burn injuries [Ia].

Regardless of the irrigation solution chosen, immediate irrigation is essential and should preferably be done within 10 minutes of the injury as this has been proven to reduce hospital length of stay by half and result in a five-fold decrease in whole thickness severity [III].

Hartmann's or Normal Saline solutions should be used for irrigation if amphoteric solutions are not available. Use bottled or tap water for irrigation if neither is available [Ia][10].

H. Burn dressing

To help with wound care, burn wounds should be wrapped loosely with polyvinyl chloride dressings (cling film) [IV]. To prevent a constriction, cling film should be put over the incision rather than entirely circumferentially. Wounds can be treated with non-adherent dressings [Ia/IV] or a clean, wet towel if cling film is not available.

Hydrogel dressings are not advised for usage. There isn't much data to support the effectiveness of hydrogels over water in burn cooling [Ia]. It is not possible to reach cold enough temperatures to promote healing [IIb], hence these dressings must be exposed to allow air to circulate and promote cooling [III][10].

I. Fluid resuscitation

In patients with burn injuries encompassing more than 20% of their adult body surface area, prehospital fluid resuscitation ought to be commenced [III].

However, excessive resuscitation can also negatively impact fluid creep [IV], airway oedema [IV], abdominal compartment syndrome [III], mortality, and morbidity.

Numerous fluid resuscitation protocols have been documented, taking into account precise TBSA, weight, and age. Although it is not practical in most pre-hospital care settings, fluid administration should ideally be directed by monitoring for appropriate rates of urine output (adults: 0.3 – 1 ml/kg/hr; children: 1 – 1.5 ml/kg/hr). Burn patients are frequently under resuscitated whereas burn TBSA is frequently overestimated [III]. Children with more than 20% TBSA burns should get fluid resuscitation.

It is advised that this be done in accordance with adult guidelines in order to reduce ambiguity and maximize fluid resuscitation. Weight-based fluid resuscitation is still used. Age-based estimate can be computed in the event when precise body weight is not available. This has to start right away, be precisely documented, and have its titration well watched. The ideal fluid for pediatric patients undergoing fluid resuscitation is 0.9% saline, which has the maximum salt concentration when available (IV)[10].

J. Burn analgesia

All burn treatment phases require adequate pain management [IV]. Full thickness burns result in a minor reduction in pain intensity, although most patients still feel a great deal of agony. It is not appropriate to rule out full thickness burns based just on the existence of discomfort [IV].

The use of a bandage over the burn will relieve pain. The patient's pain score should be taken into consideration while selecting an analgesic. The effectiveness of morphine and fentanyl against methoxyflurane has been shown, and there is no evidence to support the use of any specific opiate drug for burns [III].

Optimizing the recovery of a kid suffering from a burn injury requires effective pain management.

The delivery of pre-hospital analgesia for pediatric patients falls short of expectations [III], and the most frequent reason for not administering opiate analgesia is the incapacity to evaluate pain. For this reason, pediatric pain treatment needs to be started as soon as possible. Because of their effects on acute renal damage, wound healing, and the mediation of the inflammatory response, non-steroidal anti-inflammatory drugs (NSAIDs) are not advised for use in burn patients needing fluid resuscitation [III][10].

K. Burn safeguarding

Pre-hospital practitioners can get crucial information regarding burn injuries and should take into account non-accidental injury (NAI) in all situations. This is particularly true for pediatric burns, where 10–20% of burn injuries are thought to have an NAI etiology [III/Ia], albeit this number is probably underestimated due to the challenges in correctly identifying these instances. To enable a comprehensive inquiry, all information about the surroundings and events leading to the accident should be shared with the hospital's pediatric staff.
The pre-hospital practitioner's duty should also include highlighting the danger of non-accidental burn injuries in elderly or fragile adult patients, as well as in pediatric burns[10].

L. Escharotomy

Chest escharotomy increases systolic blood pressure and serum oxygen concentration by a significant amount while decompressing the restriction on chest wall expansion and helping to decompress intra-abdominal hypertension, carbon dioxide retention, and central venous and inferior vena cava pressures [III].

In the pre-hospital context, chest escharotomies are not always necessary.

The physiologic alterations resulting from an emergency chest escharotomy are thought to be potentially lifesaving in this patient population, who already has a very

high mortality rate [III], even though there are no high-level studies of patient outcomes following this treatment.

Pre-hospital chest escharotomies (including those of the neck, where necessary) should only be performed in situations with near-circumferential eschar and respiratory compromise, either imminent or already present, resulting from thoraco-abdominal burns[10].

Section 2.0 Drug Therapy

2.1 Topical Agents

2.1.1 Chlorhexidine Gluconate

Table 10. Chlorhexidine Gluconate Drug Information

SCIENTIFIC NAME CHLORHEXIDINE GLU0CONATE - topical	
Trade Name(s) on Saudi Market	HIBISCRUB ® SOLUTION 4% W-V
SFDA Legal status	OTC
SFDA	Registered, labeled indication
FDA	Registered (April 2005), labeled indication
EMA	Not registered
MHRA (UK Market)	Registered, labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Antiseptic
Drug Sub-Class	Organochlorine compound and a D-gluconate adduct
ATC Code	B05CA02
Pharmacological Class (ASHP)	52:04.92 Anti-infectives, Miscellaneous
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	Topical
Dose (Adult) [DDD]*	• Preoperative skin preparation: Apply generously and swab the surgery site for at least two minutes. Dry with a clean towel. Repeat the process (swab for a further two minutes and dry with a sterile cloth). • Wound care and general skin cleansing: Rinse area with water, then apply minimum amount necessary to cover skin or wound

	area and wash gently. Rinse again thoroughly.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Infants <2 months** Preoperative skin preparation: Solution: Apply liberally to surgical site and swab for at least 2 minutes. Dry with a sterile towel. Repeat procedure (swab for additional 2 minutes and dry with sterile towel). Wound care and general skin cleansing: Rinse area with water, then apply the minimum amount of chlorhexidine necessary to cover skin or wound area and wash gently. Rinse again thoroughly. **Infants ≥ 2 months, Children, and Adolescents: Topical solution:** Preoperative skin preparation: Solution: Apply liberally to surgical site and swab for at least 2 minutes. Dry with a sterile towel. Repeat procedure (swab for additional 2 minutes and dry with sterile towel). Wound care and general skin cleansing: Rinse area with water, then apply the minimum amount of chlorhexidine necessary to cover skin or wound area and wash gently. Rinse again thoroughly.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment: No adjustment required. • Hepatic impairment: No adjustment required. • Elderly: No adjustment required. • Pediatrics:

	Refer to adult dosing, in normal conditions and in renal and hepatic impairment.
Prescribing Edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	• Dermatologic: allergic sensitization, erythema, hypersensitivity reaction, rough skin, xeroderma • Anaphylaxis • Dyspnea • Facial edema • Nasal congestion
Drug Interactions (Contraindicated)	There are no known significant interactions.
Special populations	N/A
Pregnancy	Even though chlorhexidine is often used during delivery and in the neonate, no reports of unfavorable effects on infants have been made. In addition, very little disinfectant gets to the fetus and the mother's bloodstream. (Category B)
Lactation	Unknown if excreted in breast milk
Contraindications	• Hypersensitivity to chlorhexidine or any other ingredient in the product • In contact with meninges • In genital areas

	• Electrocautery procedures (ChloraPrep) • Open skin wounds or as general skin cleanser (ChloraPrep)
Monitoring Requirements	N/A
Precautions	• Hypersensitivity reactions: have been reported. • Only for localized usage. Keep out of the eyes, ears, and mouth; if contact happens, flush the affected area with cold water as once. If the agent gets into the eye and stays there, it might cause irreversible eye damage. Following instillation via ruptured ear drums into the middle ear, deafness has been documented. Applying too heavily to wounds that go deeper than the epidermis is not advised. Avoid using it repeatedly to clean big areas' skin (unless it's really required for the condition). Not to be used on lumbar puncture sites or for preoperative preparation of the face or head. Solutions may be combustible (items may include alcohol); postpone using an open flame or other ignition source (such as electrocautery) until they are totally dry; and avoid applying to hairy regions because this may cause the drying process to take much longer. Due to the possibility for enhanced absorption and the danger of irritation or chemical burns, use with caution in children under 2 months of age. If there is enough chlorine present from specific laundry detergents

	used during the laundering process, chlorhexidine gluconate bonded to fabric may cause discoloration of clothes (brown stain). • Suitable use: Topical: Improper application might result in product contamination when used as a topical antiseptic. Product contamination has been linked to reports of localized and systemic diseases, notwithstanding their rarity. Make sure antiseptic goods are used in accordance with the directions on the label, refrain from dilution after opening, apply single-use containers only once to a patient, and discard any unused solution to decrease the risk of infection. • Data is lacking concerning premature infants. Chlorhexidine-containing products may irritate or burn preterm neonates and babies under two months of age, according to the manufacturer's instructions. Dermal burns are more common in newborns under 1,500 g according to a US NICU chlorhexidine usage survey. Some people advise utilizing sterile water or ordinary saline to eliminate excess disinfectant after operations may help prevent chemical burns if utilized for newborn skin site washing.
Black Box Warning	-N/A
REMS*	-N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of burns treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS) for chlorhexidine gluconate.

Table 11. Chlorhexidine Gluconate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Chlorhexidine Gluconate	NICE	Chlorhexidine solution based on alcohol: At the time of publication (April 2019), 2.0% chlorhexidine in 70% alcohol applicators (ChloraPrep) were licensed for "disinfection of the skin prior to invasive medical procedures" and 0.5% chlorhexidine in 70% alcohol solution (Hydrex; Prevase) was licensed for "preoperative skin disinfection prior to minor surgical procedures." Some chlorhexidine in alcohol formulations were used outside of their intended uses. First choice unless contraindicated or the surgical site is next to a mucous membrane[18].
	HAS	With an AMM offered on May 3rd 2013, its only indication covers skin disinfection before invasive procedures[17].
	CADTH	According to few studies, chlorhexidine gluconate is indicated for surgical site infection and wound healing; indeed, prospective cohort studies suggested that the use of chlorhexidine gluconate was preferred to saline in superficial surgical infections only, and not the deep ones. In addition, it was also proposed that chlorhexidine gluconate has a better effect on primary healing (closed wound) than secondary healing (open wound) than saline group. Furthermore, the mean time to healing was shortened compared to saline groups. Cost-effectiveness of: • Antimicrobial or antiseptic wound cleansers: it cost 99.94 USD to avoid wound-related complications. • Antimicrobial or antiseptic wound cleansers vs antimicrobial dressings / different types of

		antimicrobial or antiseptic wound cleansers: no data available[19].

Conclusion statement – CHLORHEXIDINE GLUCONATE

This antiseptic solution is recommended as the first line antiseptic solution to be applied on wounds during initial treatment of burns, and in between dressing changing. In addition, it can be used on surgical wounds.

According to NICE and HAS, on one hand, this product can be applied on skin subject to invasive procedures. On the other hand, CADTH suggests it can be indicated for surgical site infection and wound healing.

2.1.2 Silver Sulfadiazine

Table 12. Silver Sulfadiazine

SCIENTIFIC NAME SILVER SULFADIAZINE cream	
Trade Name(s) on Saudi Market	FLAMAZINE® cream 1%, HYALO4 PLUS®
SFDA Legal status	OTC
SFDA	Registered, labeled indication
FDA	Registered (1973), labeled indication
EMA	Not registered
MHRA (UK Market)	Registered, labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Antibiotics
Drug Sub-Class	Sulfonamide
ATC Code	D06BA01 D03AX05
Pharmacological Class (ASHP)	84:04.92 Local Anti-infectives, Miscellaneous
DRUG INFORMATION	
Dosage Form	Cream
Route of Administration	Topical
Dose (Adult) [DDD]*	Apply once or twice daily to a thickness of 1/16 inch; reapply as necessary to regions where the cream is removed by patient activity since the burnt area should always be covered with cream.

	Use until the burn site is suitable for grafting or healing has taken place. If there is a chance of infection, don't stop taking your medication until a serious side effect has happened.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Burn treatment:** Infants >2 months, Children, and Adolescents: Limited data available in infants and children: Topical: Apply to a thickness of 1/16 inch once or twice daily; reapply as needed; burned area should be covered with cream at all times.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment No adjustment required • Hepatic impairment No adjustment required • Elderly No adjustment required • Pediatrics For dosing refer to adult's recommendations, as well as for hepatic and renal dysfunction • Interactions Concomitant drug use with silver sulfadiazine may be subject to interactions – check before use
Prescribing Edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	

SAFETY	
Main Adverse Drug Reactions (Most common)	• Dermatologic: Erythema multiforme, pruritus, skin discoloration, skin photosensitivity, skin rash • Hematologic & oncologic: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia • Hepatitis • Hypersensitivity: Hypersensitivity reaction (may be related to sulfa component) • Renal: Interstitial nephritis
Drug Interactions (Contraindicated)	There are no known significant interactions.
Special populations	N/A
Pregnancy	Contraindicated near term, premature infants, newborn during the first 2m: theoretical increased risk for hyperbilirubinemia and kernicterus,
Lactation	The manufacturer advises that a choice be made on whether to stop nursing or to stop taking the medication, taking into account the significance of therapy to the mother, due to the possibility of significant adverse effects in the nursing child.
Contraindications	• Hypersensitivity to silver sulfadiazine or ingredient of the product • Pregnant women approaching or at term • Premature infants or neonates < 2m of age
Monitoring Requirements	Serum electrolytes, urinalysis, renal function tests, CBC in patients with extensive burns on long-term treatment. Serum sulfa concentrations, if clinically indicated.

Precautions	• Sulfonamide allergy: However, there is a chance of a cross-reaction in patients who have allergies to any of these substances; avoid usage if a prior response has been severe. usage in patients with sulfonamide allergy is expressly contraindicated on the product label. • C. diff superinfection due to prolonged use • Systemic absorption may be significant and adverse reactions may occur. • Hemolysis may develop in people with G6PD deficiency; use with care. • Hepatic impairment: Sulfadiazine may accumulate in people with hepatic impairment; use with care. • Renal impairment: Sulfadiazine may accumulate in people with renal impairment; use with care. • Propylene glycol: This substance is included in some dosage forms but is potentially dangerous in large doses and has been linked to hyperosmolality, lactic acidosis, convulsions, and respiratory depression. • Proper usage: Only for topical use. Avoid eye contact.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of burn treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), and Haute Autorité de Santé (HAS) for silver sulfadiazine.

Table 13. Silver Sulfadiazine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Silver Sulfadiazine	NICE	Overall, the authors of the Cochrane review considered that there was insufficient evidence to support the use of silver-containing dressings or creams because, generally, they did not promote wound healing or prevent wound infections[21].
	HAS	Approved since 1977; Burn infection infections can be prevented and treated with FLAMMAZINE cream (silver sulfadiazine). Given the lack of very robust clinical efficacy data supporting the efficacy of silver sulfadiazine in the prevention and treatment of infections in the context of the management of second-degree or more severe burns and a risk of serious adverse effects, though rare in view of the cumulated exposure, the efficacy/adverse effects ratio of this medicinal product in this indication is at best low. In the context of managing second-degree or more severe burns in adults and children beginning at the age of two months, this patented medication is a first-line treatment for the prevention and treatment of infections[22].
	CADTH	It has only been mentioned that silver can be impregnated in dressing to limit infections. Cost-effectiveness of: • Antimicrobial or antiseptic wound cleansers: it costs 99.94 USD to avoid wound-related complications. • Antimicrobial or antiseptic wound cleansers vs antimicrobial dressings / different types of antimicrobial or antiseptic wound cleansers: no data available[19].

Conclusion statement – SILVER SULFADIAZINE

Silver sulfadiazine is largely indicated in the initial treatment and management of wounds as THE first topical antibiotic to apply on post-burn skins. It can be used for superficial and deep burns and can be a specific agent to use on delicate patients, like the hands-burned patient and pediatric patient. It is usually applied on dressings after burn as an initial treatment step (+ according to CADTH)

As reported by HAS, this ingredient can also be used as an infection prophylactic agent on second-degree or severe burns, with not important side effects.

2.2 Analgesics

The following table outlines the analgesics used in pain management for burns.

For more detailed information regarding side effects, interactions, precautions, etc., please refer to the separate indication report on pain management.

Table 14. Analgesics Drug Information

Drug	Indication	Dosing	Prescribing edits	HTA Analysis
Paracetamol (Acetaminophen)	Pain management	**Adults** **- Oral:** 325 to 650 mg every 4 to 6 hours as needed or 1 g every 6 hours as needed; maximum dose: 4 g/day **- IV:** - ≥50 kg: 650 mg every 4 hours or 1 g every 6 hours; maximum single dose: 1 g/dose; maximum daily dose: 4 g/day. - <50 kg: 12.5 mg/kg every 4 hours or 15 mg/kg every 6 hours; maximum single dose: 15 mg/kg/dose (≤750 mg/dose); maximum daily dose: 75 mg/kg/day (≤3.75 g/day). Note: Some experts recommend this reduced dosing if used in patients with chronic alcoholism, malnutrition, or dehydration regardless of weight **- Rectal:** 325 to 650 mg every 4 to 6 hours as needed; maximum daily dose: 3.9 g/day.	**ST:** Nonopioids such as acetaminophen and nonsteroidal anti-inflammatory drugs are an option if there are no available opioids	**NICE:** This drug should not be started to manage chronic primary pain in 16-year-olds and above[23] **CADTH:** Limited data shows that IV acetaminophen may provide better pain relief within the first hour of delivery in individuals with moderate to severe pain in the ED, but equivalent pain reductions after 4 hours when compared to oral acetaminophen. In people in the ED with moderate to severe pain, intravenous acetaminophen

		Pediatric **- Oral:** Weight-directed dosing: Infants, Children, and Adolescents: 10 to 15 mg/kg/dose every 4 to 6 hours as needed ;do not exceed 5 doses in 24 hours; maximum daily dose: 75 mg/kg/day not to exceed 4,000 mg/day. **- IV:** Infants and Children <2 years: Manufacturer's labeling: Fever: 15 mg/kg/dose every 6 hours; maximum daily dose: 60 mg/kg/day. Alternate dosing: Limited data available: Pain and fever: 7.5 to 15 mg/kg/dose every 6 hours; maximum daily dose: 60 mg/kg/day. **Children ≥2 years:** - <50 kg: 15 mg/kg/dose every 6 hours or 12.5 mg/kg/dose every 4 hours; maximum single dose: 15 mg/kg up to 750 mg; maximum daily dose: 75 mg/kg/day not to exceed 3,750 mg/day. - ≥50 kg: 15 mg/kg/dose every 6 hours or 12.5 mg/kg/dose		and intravenous NSAIDs reduce pain after 30 minutes in a clinically comparable way. NSAIDs may provide somewhat better pain relief than IV acetaminophen after 60 minutes, although the difference is not clinically significant. While there were conflicting results regarding pain alleviation, the majority of the research comparing IV acetaminophen with IV opioids found no statistically or clinically significant differences in pain

		every 4 hours; maximum single dose: 15 mg/kg up to 1,000 mg; maximum daily dose: 75 mg/kg/day not to exceed 4,000 mg/day. **Adolescents:** - <50 kg: 15 mg/kg/dose every 6 hours or 12.5 mg/kg/dose every 4 hours; maximum single dose: 15 mg/kg up to 750 mg; maximum daily dose: 75 mg/kg/day not to exceed 3,750 mg/day. - ≥50 kg: 1,000 mg every 6 hours or 650 mg every 4 hours; maximum single dose: 1,000 mg; maximum daily dose: 4,000 mg/day. **- Rectal:** Weight-directed dosing: Limited data available: Infants and Children <12 years: 10 to 20 mg/kg/dose every 4 to 6 hours as needed; do not exceed 5 doses in 24 hours ; maximum daily dose: 75 mg/kg/day not to exceed 1,625 mg/day.		between the groups. Regarding IV acetaminophen's cost-effectiveness, no pertinent data could be found[24]
Buprenorphine	Pain management	1:40 equivalent analgesic to morphine	**MD:** Should be prescribed by a	There are no recommendations

		Acute pain (moderate to severe): **Adults:** **IR injection: IM or slow IV:** Initial: 0.3 mg every 6 to 8 hours as needed; initial dose (up to 0.3 mg) may be repeated once 30 to 60 minutes after the initial dose. **Pediatric:** - Children ≥2 years: IM, slow IV injection: Initial: Opioid-naive: 2 to 6 **mcg**/kg/dose every 4 to 6 hours - Adolescents: IM, slow IV injection: Initial: Opioid-naive: 0.3 mg every 6 to 8 hours as needed; initial dose may be repeated once in 30 to 60 minutes if clinically needed.	pain specialist physician.	issued by the HTA bodies for Buprenorphine.
Fentanyl	Pain management and procedural pain	**Acute pain, patient-controlled analgesia (alternative agent):** **Adults:** **Example IV Patient-Controlled Analgesia Initial Dose Ranges for Opioid-Naive Patients** **IV: Demand dose:** 5 to 20 mcg **Lockout interval:** 5 to 10 minutes	**ST:** Used as an alternative if other opioids have failed. **MD:** Should be prescribed by a pain specialist physician.	**CADTH**: 2015 recommendations from the Italian Intersociety recommend IV paracetamol for pain management morphine and fentanyl for severe pain[26].

		Maximum cumulative dose: 300 mcg within a 4-hour period **Procedural sedation and analgesia:** ✓ **Outside the operating room (alternative agent) (off-label use):** **IV:** 0.5 to 1 mcg/kg every 2 minutes until desired level of sedation and analgesia achieved; generally, the maximum total dose is 250 mcg. If administered with other sedatives (eg, etomidate, propofol, midazolam), do not exceed single doses of 0.5 mcg/kg. **Intranasal (using parenteral solution [50 mcg/mL]) (off-label route):** 1 to 2 mcg/kg as a single dose; administer half the dose in each nostril; maximum total dose: 100 mcg (50 mcg per nostril; based on volume). ✓ Analgesia during monitored anesthesia care or regional anesthesia: IV: Usual initial dose range: 0.5 to 2 mcg/kg, administered in incremental boluses of 25 to 50 mcg, titrated to effect. When		

		used in combination with a sedative (eg, midazolam), consider dosage reduction. **Acute pain, severe (opioid-naive):** **Pediatrics:** **Intermittent IV doses:** **Infants, Children, and Adolescents: Limited data available in <2 years of age:** - Patient weight <50 kg: IV: Initial: 0.5 to 1 mcg/kg/dose; may repeat every 1 to 2 hours; more frequent dosing may be allowed (eg, every 30 minutes) if necessary; usual maximum dose: 50 mcg/dose; a higher maximum dose of 100 mcg/dose may be considered in critically ill patients in the ICU. - Patient weight ≥50 kg: Initial: IV: 25 to 50 mcg; repeat every 1 to 2 hours (more frequent dosing may be needed [eg, every 30 minutes]). **Continuous IV infusion:**		

		Infants, Children, and Adolescents: - Patient weight <50 kg: Limited data available: Continuous IV infusion: Usual range: 0.5 to 2.5 mcg/kg/hour; initiate at the lower end and titrate to effect; an initial rate of 1 mcg/kg/hour has been suggested for critically ill patients in the ICU. - Patient weight ≥50 kg: Limited data available: Continuous IV infusion: Usual range: 25 to 100 mcg/hour; initiate at the lower end of dosage range and titrate to effect; an initial dose of 50 mcg/hour has been suggested for critically ill patients in the ICU. **Intranasal (using parenteral preparation):** Limited data available: Children ≥10 kg and Adolescents: Intranasal: Usual dose: 1.5 to 2 mcg/kg once; maximum dose: 100 mcg/dose; some studies that used an initial dose of 1.5		

		mcg/kg allowed for second dose of 0.5 mcg/kg or 0.75 mcg/kg, at the discretion of the physician, 10 or 20 minutes, respectively, after the first dose.		
Gabapentin	Pain management (neuropathic)	**Neuropathic pain:** **Adults:** Immediate release: Oral: Initial: 100 to 300 mg 1 to 3 times daily; increase dose based on response and tolerability to a target dose range of 300 mg to 1.2 g 3 times daily. Extended release: Oral: Initial: 300 mg at bedtime; increase dose based on response and tolerability to a target dose of 900 mg to 3.6 g once daily. **Pediatrics:** Limited data available: Children and Adolescents: Immediate release: Oral: Initial: 5 mg/kg/dose at bedtime, maximum dose: 300 mg/dose; day 2: Increase to 5 mg/kg/dose twice daily, maximum dose: 300 mg/dose; day 3: Increase to 5 mg/kg/dose 3 times daily, maximum dose: 300 mg/dose; further titrate with dosage	**N/A**	**NICE**: Gabapentin and pregabalin are a first choice and initial treatment in neuropathic pain (except trigeminal neuralgia) in non-specialized settings. Pregabalin and gabapentin are Class C controlled substances (under the Misuse of Drugs Act 1971) and Schedule 3 under the Misuse of Drugs Regulations 2001[27]. **HAS**: the actual benefit of Gabapentin remains

		increases (not frequency) to effect; usual dosage range: 8 to 35 mg/kg/**day** divided into 3 doses daily; maximum daily dose: 3,600 mg/**day**; do not exceed 12 hours between doses with 3-times-daily dosing; a lower initial dose may be considered if concurrent analgesics are also sedating.		significant for neuropathic pain[39]
Pregabalin	Pain management (neuropathic)	**Neuropathic pain:** **General** **Dosing** **Recommendations:** Immediate release: **Oral:** Initial: 25 mg once daily or 50 to 150 mg/day in 2 to 3 divided doses; may increase in increments of 25 to 150 mg/day at weekly intervals based on response and tolerability up to a usual dose of 300 to 600 mg/day in 2 to 3 divided doses	**N/A**	**NICE**: Gabapentin and pregabalin are a first choice and initial treatment in neuropathic pain (except trigeminal neuralgia) in non-specialized settings. Pregabalin and gabapentin are Class C controlled substances (under the Misuse of Drugs Act 1971) and Schedule 3 under the Misuse of Drugs Regulations 2001[27].

				HAS: Pregabalin is indicated in the treatment of peripheral and central neuropathic pain in adults.[40]
Methadone	Long-duration treatment and small risk of addiction	**Chronic pain:** **Adults** **A- Opioid-naive patients:** **Initial:** - **Oral:** 2.5 to 5 mg every 8 to 12 hours. - **IM, IV, SUBQ:** Note: For use only in patients unable to take oral medication (such as during hospitalization). 2.5 to 10 mg every 8 to 12 hours. **Titration and maintenance:** May increase dose by 2.5 mg per dose no more often than every 5 to 7 days (gradual titration) or by 2.5 to 5 mg per dose every 3 days (faster titration in monitored setting). Once a stable dose is reached, the dosing interval may be extended to every 8 to 12 hours or longer.	**MD:** Should be prescribed by a pain specialist physician.	There are no recommendations issued by the HTA bodies for Methadone.

		B- Opioid-tolerant patients: Conversion from oral morphine to oral methadone: 1) There is not a linear relationship when converting to methadone from oral morphine. The higher the daily morphine-equivalent dose the more potent methadone is, and 2) conversion to methadone is more of a process than a calculation. In general, the starting methadone dose should not exceed 30 to 40 mg/day, even in patients on high doses of other opioids. **C- Critically ill patients in the ICU (analgesia and sedation) (alternative agent) (off-label use):** - **Oral:** 10 to 40 mg every 6 to 12 hours. - **IV:** 2.5 to 10 mg every 8 to 12 hours **Pediatric:** **Pain; chronic, severe or palliative care**: Limited data available: Infants >6 months, Children, and Adolescents: - IV (preferred), SUBQ: Initial: 0.05 to 0.1 mg/kg/dose every		

		6 to 24 hours; maximum initial dose: 5 mg/dose; adjust dose and/or interval based on clinical response no more frequently than every 72 hours. - Oral: Initial: 0.05 to 0.2 mg/kg/dose every 6 to 24 hours; maximum initial dose: 5 mg/dose; adjust dose and/or interval based on clinical response no more frequently than every 72 hours.		
Morphine	Pain management	**Acute pain in opioid-naive patients:** **Adults:** - **Oral:** Opioid-naive patients: Immediate release: Oral solution, Tablet: Initial: 10 mg every 4 hours as needed; if pain is not relieved, may increase dose as tolerated. May give up to 30 mg every 4 hours as needed for severe, acute pain in hospitalized patients at low risk for respiratory depression.	**MD:** Should be prescribed by a pain specialist physician.	**HAS**: Morphine has been indicated in "Intense pain and/or unresponsive to lower-level analgesics"[30]. **CADTH**: The 2015 recommendations from the Italian Intersociety recommend IV paracetamol for pain management morphine and

		- **IV:** Opioid-naive patients: Intermittent: Initial: 1 to 4 mg every 1 to 4 hours as needed; if pain is not relieved, may increase dose as tolerated. May give up to 10 mg every 4 hours as needed for severe, acute pain in hospitalized patients at low risk for respiratory depression. For some severe acute pain episodes (eg, trauma), may initially give more frequently (eg, every 5 to 15 minutes) if needed and titrate to pain relief; once pain relief is achieved, reduce frequency (eg, every 3 to 4 hours as needed) - **IM (not recommended for routine use):** Opioid-naive patients: Initial: 5 to 10 mg every 3 to 4 hours as needed; if pain is not relieved, may increase dose as tolerated. **Acute pain, severe (opioid-naive patients)** **Pediatrics:** **Infants ≤6 months:**		fentanyl for severe pain[27].

		Intermittent dosing: - Oral: Oral solution (2 mg/mL or 4 mg/mL): Initial: 0.08 to 0.1 mg/kg/dose every 3 to 4 hours. - IV or SUBQ: Initial: 0.025 to 0.05 mg/kg/dose every 2 to 4 hours. Continuous IV infusion: Initial: 0.008 to 0.02 mg/kg/hour (8 to 20 mcg/kg/hour); titrate carefully to effect. Higher initial doses of 0.05 mg/kg/hour (50 mcg/kg/hour) have been recommended in critically ill patients in the ICU. **Infants >6 months, Children, and Adolescents:** **Intermittent dosing:** **Oral:** - Weight <50 kg: Oral: Immediate-release tablets, oral solution: Initial: 0.15 to 0.3 mg/kg/dose every 3 to 4 hours as needed; some experts have recommended higher initial doses of up to 0.5 mg/kg; usual initial maximum dose: 20 mg/dose.		

		- Weight ≥50 kg: Oral: Immediate-release tablets, oral solution: 10 to 20 mg every 3 to 4 hours as needed. **IV, SUBQ:** - Weight <50 kg: IV, SUBQ: Initial: 0.05 to 0.1 mg/kg/dose every 2 to 4 hours; titrate based on patient response. - Weight ≥50 kg: IV, SUBQ: Initial: 2 to 5 mg every 2 to 4 hours as needed. Use lower end of the dosing range in opioid naive patients; higher doses have been recommended (5 to 8 mg every 2 to 4 hours as needed) **Continuous IV infusion, SUBQ continuous infusion:** - Weight <50 kg: Initial: 0.01 mg/kg/hour (10 mcg/kg/hour); titrate carefully to effect; dosage range: 0.01 to 0.04 mg/kg/hour (10 to 40 mcg/kg/hour). Higher initial doses of 0.05 mg/kg/hour (50 mcg/kg/hour) have been recommended		

		in critically ill patients in the ICU. - Weight ≥50 kg: Initial: 1.5 mg/hour; titrate carefully based on clinical response; usual maintenance dose: 0.8 to 3 mg/hour. Higher initial doses of 2 mg/hour have been recommended in critically ill patients in the ICU.		
Oxycodone	Pain management	**Acute pain in opioid-naive patients:** **Adults:** - **Immediate release:** **Oral:** Initial: 5 mg every 4 to 6 hours as needed; adjust dose according to patient response. Usual dosage range: 5 to 15 mg every 4 to 6 hours as needed. If usual dose and frequency is insufficient, reassess patient and reconsider pain management strategies. For outpatient use, usually up to 20 mg/day for moderate pain or up to 30 mg/day for severe pain will suffice.	**ST:** Used as an alternative for morphine who cannot take morphine. **MD:** Should be prescribed by a pain specialist physician.	**HAS**: with marketing authorization accorded in March 2005, its indication cites: "Severe pain that can only be properly treated by strong opioid painkillers; especially in pain of cancerous origin" [31].

		Dosing is based on severity of pain and patient-specific factors; reduced dosing may be indicated in patients with comorbidities. **Analgesia, moderate to severe pain:** **Pediatrics:** - Infants ≤6 months: Immediate release: Oral solution (1 mg/mL): Oral: Initial dose: 0.025 to 0.05 mg/kg/dose every 4 to 6 hours as needed. - Infants >6 months, Children, and Adolescents: ✓ Patient weight <50 kg: Immediate release: Oral: Initial dose: 0.1 to 0.2 mg/kg/dose every 4 to 6 hours as needed; for severe pain some experts have recommended an initial dose of 0.2 mg/kg; usual maximum dose range: 5 to 10 mg/dose. ✓ Patient weight ≥50 kg: Immediate release: Oral: Initial dose: 5 to 10 mg every		

		4 to 6 hours as needed; for severe pain an initial dose of 10 mg may be used; usual maximum dose: 20 mg/dose.		

2.3 Sedatives and Anesthetics

The following table outlines the sedatives and anesthetics used in burn management.

For more detailed information regarding side effects, interactions, precautions, etc., please refer to the separate indication on anesthesia.

Table 15. Sedatives and Anesthetics Drug Information

Drug	Indication	Dosing	Prescribing edits	HTA Analysis
Ketamine	Procedural sedation; post-operative analgesic	**Procedural sedation (off-label use):** **Adults:** **Note:** Although rarely needed, may consider using midazolam to decrease risk **or** to treat emergence reactions. However, premedication may significantly prolong recovery time. - **IV:** Initial: 1 to 2 mg/kg over 1 to 2 minutes; if initial sedation is inadequate or for longer procedures, repeat dose (0.5 to 1 mg/kg) every 5 to 10 minutes; use lower doses (0.25 to 0.5 mg/kg) depending on concomitant sedation and clinical status.	**CU:** Should be used with propofol. **MD:** Should be prescribed by a pain specialist physician.	**CADTH**: During the short-term period (between 48 hours and two weeks), IV ketamine infusions dramatically lowered pain ratings and had considerably greater positive response rates; however, these effects did not hold true for the longer follow-up period (four to twelve weeks). Ketamine's short-term effects were unaffected by

		Alternatively, may consider an initial dose of 0.375 to 0.75 mg/kg when combined with propofol (as a 1:1 mixture); repeat with ~0.188 to 0.375 mg/kg, as needed. - **IM: Note:** Onset of sedation will be delayed ~5 minutes with this route. Initial: 4 to 5 mg/kg as a single dose; if sedation is inadequate after 5 to 10 minutes, repeat dose (2 to 5 mg/kg) **Sedation/analgesia, procedural: Limited data available:** **Pediatrics:** **Ketamine without propofol: Infants ≥3 months, Children, and Adolescents:** - **IM:** 4 to 5 mg/kg as a single dose; may give a repeat dose (range: 2 to 5 mg/kg) if sedation inadequate after 5 to 10 minutes or if additional doses are required. - **IV:** 1 to 2 mg/kg over 30 to 60 seconds. If initial sedation inadequate or repeated		dosage, the kind of persistent pain, or other medications[28].

		doses are necessary to accomplish a longer procedure, may administer additional doses of 0.5 to 1 mg/kg every 5 to 15 minutes as needed. - **Intranasal:** Note: Use of mucosal atomizer device is recommended: Infants ≥3 months and Children: 3 to 6 mg/kg (half dose per nostril), doses up to 9 mg/kg have been described. - **Oral:** Children and Adolescents: 5 mg/kg with oral midazolam given 30 to 45 minutes before the procedure. - **Ketamine with propofol ("ketofol"):** Infants ≥3 months, Children, and Adolescents: IV: 0.5 to 0.75 mg/kg of each agent. **Analgesia, subanesthetic dosing (off-label use):** **Acute pain:** **Adults:**		

		IV: Initial: 0.25 to 0.5 mg/kg bolus (maximum bolus: 35 mg), followed by 0.05 to 0.25 mg/kg/hour continuous infusion in patients who need a longer duration of analgesia; titrate to pain goal and tolerability; usual dosing range: 0.05 to 1 mg/kg/hour; may need to use doses at the higher range in patients who are opioid-tolerant or with opioid-induced hyperalgesia; duration of infusion: 48 to 72 hours. **Intranasal (off-label route):** 0.2 to 1 mg/kg by administering half dose in each nostril (using 100 mg/mL solution); if necessary, may repeat after 10 to 15 minutes with 0.25 to 0.5 mg/kg; titrate to pain goal and tolerability. Doses up to 40 mg may be reliably administered intranasally; for doses >40 mg, part of the dose will be delivered to the oropharynx and ingested orally due to volume limitations, which may decrease effectiveness. **Analgesia, acute pain (low dose; sub-dissociative):** **Pediatrics:**		

		Very limited data available: Optimal dose not established: Children ≥3 years and Adolescents: Intranasal: Usual: 1 mg/kg/dose, may repeat once; range: 0.5 to 1.5 mg/kg/dose; maximum dose: 100 mg/dose.		
Lidocaine	Local anesthesia	**Anesthesia, local or regional:** **Adults:** - Cutaneous infiltration: Maximum: 4.5 mg/kg/dose not to exceed 300 mg; do not repeat within 2 hours. - Intraosseous line or infusion pain: Lidocaine 1% or 2% preservative-free solution: Intraosseous: Initial dose: 40 mg over 1 to 2 minutes; usual adult dose range and maximum: 20 to 50 mg/dose; after allowing lidocaine to dwell for up to 1 minute, follow with NS flush; immediately following the NS flush, some centers administer a second lower (50% dose reduction) lidocaine dose over 30 to 60 seconds (usual adult	**ST:** Used as 2nd or 3rd line therapy. **MD:** Should be prescribed by a pain specialist physician.	**CADTH**: Lidocaine is indicated in loco-regional anesthesia and intravenously: to prevent pain linked to propofol injection; for the prevention of post-operative pain, particularly in order to speed up recovery intestinal transit after abdominal surgery[41]

		maximum repeat dose: 20 mg/dose); if discomfort reoccurs, may repeat doses at a maximum frequency of every 45 minutes during intraosseous access; maximum total dose not established. **Pediatric:** - Cutaneous infiltration: Children and Adolescents: Typically, solutions with concentration <2% should be used (allow for larger volumes); maximum dose: 5 mg/kg/dose not to exceed the recommended adult maximum dose of 300 mg/dose; do not repeat within 2 hours. - Intraosseous line or infusion pain: Infants, Children, and Adolescents: Lidocaine 1% or 2 % preservative-free solution: Intraosseous: Initial dose: 0.5 mg/kg over 1 to 2 minutes; usual adult dose range and maximum: 20 to 50 mg/dose; follow with NS		

		flush; immediately following the NS flush, some centers administer a second lower (50% dose reduction) lidocaine dose over 30 to 60 seconds (usual adult maximum repeat dose: 20 mg/dose); if discomfort reoccurs, may repeat doses at a maximum frequency of every 45 minutes during intraosseous access; maximum total dose not established, some centers suggest that dose should not exceed: 3 mg/kg/24 hours.		
Dexmedetomidine	Analgesic; and reduces opioid requirement; sedative	**Procedural sedation or monitored anesthesia care (including flexible scope intubation [awake]):** **Adults:** - **IV: Initial:** Loading dose of 0.5 to 1 mcg/kg over 10 minutes (use lower range for less invasive procedures [eg, ophthalmic]), followed by a continuous infusion of 0.2 to	**MD:** Should be prescribed by an anesthesiologist.	**HAS**: With a marketing authorization approved in September 2011, its unique indication cites: "Sedation in ICU (Intensive Care Unit) in adults requiring state of sedation no deeper than that allowing a

		1 mcg/kg/hour; titrate to desired level of sedation. **ICU sedation:** **Pediatrics:** Limited data available: Infants, Children, and Adolescents: - **Loading dose (Optional)**: IV: 0.5 to 1 mcg/kg/dose over 10 minutes; use of loading dose is dependent upon concomitant sedation agents and patient's current and desired level of sedation. - **Maintenance dose:** Note: Although the manufacturer recommends limiting continuous infusions to ≤24 hours in adult patients, duration in pediatric patients has been reported from 2 hours to 103 days; weaning of dexmedetomidine and/or replacement strategies have been recommended. - **Continuous IV infusion: Initial:** 0.2 to 0.5 mcg/kg/hour; increase dose by 0.1 to 0.3 mcg/kg/hour to achieve desired level of		response to a verbal stimulus (corresponding to a score of 0 to -3 on the scale of Richmond Vigilance-Agitation (RASS)"[25]

		sedation; usual dose range: 0.2 to 2.5 mcg/kg/hour. **Sedation/anesthesia, noninvasive procedures: Limited data available:** Infants, Children, and Adolescents: - **Loading dose:** IV: 0.5 to 2 mcg/kg/dose over 10 minutes; may be repeated if sedation is not adequate. - **Maintenance dose:** Continuous IV infusion: Usual initial dose: 0.5 to 1 mcg/kg/hour; an initial dose up to 2 mcg/kg/hour has been reported; titrate to desired level of sedation; dosing based on multiple studies evaluating IV dexmedetomidine administered prior to noninvasive procedures.		
Propofol	Procedural sedation and anesthesia	**Procedural sedation, outside the operating room (off-label use):** **Adults:** - **IV: Initial:** 0.5 to 1 mg/kg, followed by 0.25 to 0.5 mg/kg every 1 to 3 minutes, as needed, to achieve adequate	**MD:** Should be prescribed by a specialized anesthesiologist.	**HAS**: With medication approved since 2002 for the 1% product, in 2007 for the 2% product and 2008 for the 0.5% product,

		sedation. Alternatively, may consider an initial dose of 0.375 to 0.75 mg/kg when combined with ketamine (as a 1:1 mixture); repeat with ~0.188 to 0.375 mg/kg as needed. **Procedural sedation: Limited data available:** **Infants, Children, and Adolescents:** - **Repeated IV bolus method**: **IV:** Initial dose: 1 to 2 mg/kg; higher initial doses of 2 mg/kg are recommended in infants and children <3 years of age; follow initial dose with 0.5 to 1 mg/kg every 3 to 5 minutes as needed until adequate level of sedation achieved. - **IV bolus followed by continuous IV infusion: IV:** Initial bolus: 1 to 2 mg/kg followed by continuous IV infusion: Dose range: 50 to 250 mcg/kg/minute (3 to 15 mg/kg/hour); titrate to desired level of sedation.		indications of this drug include: Induction and maintenance of general anesthesia in adults and children more than 1 month (3yo and beyond), Sedation of ventilated patients aged over 16 in ICU, Sedation during diagnostic or surgical procedures, alone or in combination with local or regional anesthesia in adults and children [32] CADTH: It is advised to use propofol-based sedation to enhance patient safety, comfort, procedural effectiveness, and favorable outcome. Pre-procedural Assessment and Preparation:

		- **Propofol with concurrent ketamine; emergency department procedures: IV:** 0.5 to 0.75 mg/kg.		Patients who take alcohol, barbiturates, benzodiazepines, or anticonvulsants on a regular basis may require higher doses of propofol. (LoE: Observational trials; Grade of recommendation: May be taken into account). Monitoring During Rehab and Release: There must be at least 30 minutes of recovery time after propofol sedation. (LoE: A minimum of one randomization-free case-control or cohort study; Recommendation Grade: Worth taking into account)[33]

2.4 Alpha Adrenergic Agonists

2.4.1 Norepinephrine/Epinephrine

Table 16. Norepinephrine/Epinephrine Drug Information

SCIENTIFIC NAME NOREPINEPHRINE/EPINEPHRINE	
Trade Name(s) on Saudi Market	**NOREPINEPHRINE**: LEVOPHED®, POSICAINE 200® injection, NOREPIRIN® 2mg/ml injection, NEVOLEEN® 1mg/ml ampoule, NORADRENALIN SINTETICA® 4mg/4ml, NOREPINEPHRINE®, NORPHED® **EPINEPHRINE**: ADRENALINE®, EPINEPHRINE®
SFDA Legal status	Prescription
SFDA	Registered, labeled indication
FDA	Registered (1950), labeled indication
EMA	Not registered
MHRA (UK Market)	Registered, labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Alpha adrenergic agonist
Drug Sub-Class	vasoconstrictor
ATC Code	Norepinephrine: C01CA03 Epinephrine/articaine, Norepinephrine/articaine: N01BB58 Epinephrine: C01CA24
Pharmacological Class (ASHP)	12:12.12 alpha- and beta-Adrenergic Agonists
DRUG INFORMATION	
Dosage Form	Solution for injection Injection Concentrate for solution for infusion
Route of Administration	IV / PARENTERAL use
Dose (Adult) [DDD]*	**EPINEPHRINE:** **Hypotension or shock:**

	Septic shock and other vasodilatory shock states (adjunctive agent): Continuous infusion: • Weight-based dosing: IV: Initial: 0.01 to 0.2 mcg/kg/minute; titrate to goal MAP or end-organ perfusion; usual dose range: 0.01 to 0.5 mcg/kg/minute; maximum dose range for refractory shock: 0.5 to 2 mcg/kg/minute. • Non-weight-based dosing: IV: Initial: 1 to 15 mcg/minute; titrate to goal MAP or end-organ perfusion; usual dose range: 1 to 40 mcg/minute; maximum dose range for refractory shock: 40 to 160 mcg/minute (doses calculated and rounded for an 80 kg patient based on weight-based dosing) **NOREPINEPHRINE:** **Septic shock and other vasodilatory shock states:** Continuous infusion: • Weight-based dosing: IV: Initial: 0.05 to 0.15 mcg/**kg**/minute; titrate to goal MAP; usual dose range: 0.025 to 1 mcg/**kg**/minute; maximum dose range for refractory shock: 1 to 3.3 mcg/**kg**/minute. **Note:** While available data describe a wide range of initial dosing (0.01 to 0.5 mcg/kg/minute), initial dosing provided is a reasonable starting point for most patients. • Non–weight-based dosing (based on ~80 kg patient): IV: Initial: 5 to 15 mcg/minute; titrate to goal MAP; usual dose range: 2 to 80 mcg/minute; maximum dose range for refractory shock: 80 to

	250 mcg/minute (doses calculated and rounded for an 80 kg patient based on weight-based dosing
Maximum Daily Dose Adults*	**Epinephrine:** • **Weight-based dosing:** maximum dose range for refractory shock: IV:0.5 to 2 mcg/kg/minute. • **Non-weight-based dosing:** maximum dose range for refractory shock: IV: 40 to 160 mcg/minute **Norepinephrine:** • **Weight-based dosing:** maximum dose range for refractory shock: IV: : 1 to 3.3 mcg/**kg**/minute. • **Non-weight-based dosing:** maximum dose range for refractory shock: IV: 80 to 250 mcg/minute
Dose (pediatrics)	**1- Epinephrine:** **Hypotension/shock, fluid-resistant:** Infants, Children, and Adolescents: Continuous IV or intraosseous infusion: 0.1 to 1 mcg/kg/minute; rates >0.3 mcg/kg/minute associated with vasopressor activity. **2- Norepinephrine:** **Hypotension/shock, fluid-resistant:** Infants, Children, and Adolescents: Continuous IV or intraosseous infusion: Initial: 0.05 to 0.1 mcg/kg/minute; titrate to desired effect; usual maximum dose: 2 mcg/kg/minute; higher doses have been reported in the literature.
Maximum Daily Dose Pediatrics*	**1- Epinephrine:** N/A

	2- **Norepinephrine:** maximum dose: 2 mcg/kg/minute
Adjustment	• Renal impairment No adjustment required • Hepatic impairment No adjustment requirement • Obesity For a continuous infusion, the ideal body weight is use • Pediatrics Same recommendations as for adults in terms of renal and hepatic impairment
Prescribing Edits*	MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by an intensivist (critical care doctor).	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Should be used after fluid therapy fails (if MAP goal was not reached).	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	• CV: bradycardia, cardiac arrhythmia, cardiomyopathy, peripheral vascular insufficiency • CNS: anxiety, transient headache • Dyspnea • Peripheral gangrene, peripheral ischemia
Drug Interactions (Contraindicated)	• Ergots derivates: ergot derivatives, counted as vasoconstrictive CYP3A4 substrates, may enhance the vasoconstricting effect of norepinephrine. Do not use this

	combination, especially in the case of regional anesthesia, that can potentially increase BP • Kratom: kratom can increase the side/toxic effect of norepinephrine. This combination is not advised. However, if used together, monitor for any increase in sympathomimetics (BP, heart rate), seizure, and other signs of toxicity • Lisuride: lisuride can increase the hypertensive action of norepinephrine. Do not concomitantly use these two drugs
Special populations	Obese patients, patients with cardiovascular instability (Refer 'Precautions' section)
Pregnancy	Due to worries about teratogenicity in fetuses, appropriate drugs shouldn't be withheld. Use of norepinephrine during the post-resuscitation phase is an option, but the fetus's exposure to vasoactive drugs should also be taken into account. Current Advanced Cardiovascular Life Support recommendations should be followed for dosages and indications.
Lactation	If norepinephrine is present in breast milk is unknown. When giving norepinephrine to nursing women, the manufacturer advises using care.
Contraindications	Hypotension from hypovolemia except as an emergency measure to maintain coronary and cerebral perfusion until volume could be replaced; mesenteric or peripheral vascular thrombosis unless it is a lifesaving procedure; during

	anesthesia with cyclopropane or halothane anesthesia.
Monitoring Requirements	Blood pressure (or mean arterial pressure), heart rate; cardiac output (as appropriate), intravascular volume status, pulmonary capillary wedge pressure (as appropriate); urine output, peripheral perfusion; monitor infusion site closely
Precautions	• Extravasation: Vesicant; make sure the needle or catheter is inserted correctly before and throughout the infusion. Avoid extravasation; if at all feasible, inject into a big vein. Don't inject into your leg veins. Watch the IV site carefully. If extravasation happens, use a small hypodermic needle to inject the region with diluted phentolamine (5 to 10 mg in 10 mL saline in adult patients). To avoid sloughing or necrosis, phentolamine should be given as soon as feasible after extravasation is noticed. • Before beginning therapy, patients with hypovolemia should be treated; despite having a normal blood pressure, they may still experience severe peripheral and visceral vasoconstriction, decreased renal perfusion and decreased urine output, tissue hypoxia, lactic acidosis, and reduced systemic blood flow. • This product could contain sodium metabisulfite. Patients with asthma or a sulfite allergy should be treated with caution since allergic responses, such as

	anaphylactic shock and severe asthmatic episodes, can happen. • Abrupt discontinuation: When ending therapy, gradually lower the infusion rate while increasing blood volume with IV fluids; severe hypotension may result from an abrupt withdrawal. • Appropriate use: Make sure there is enough circulation to reduce the need for vasoconstrictors. Avoid hypertension; keep an eye on your blood pressure and alter your infusion rate. Avoid using in individuals who have mesenteric or peripheral vascular thrombosis; doing so might worsen the ischemia and expand the infarct size.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

Regarding the HTA bodies' recommendations for the use of epinephrine or norepinephrine in burn cases, no information was found from the searches conducted by the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Scheme (PBS).

CONCLUSION STATEMENT – EPINEPHRINE/NOREPINEPHRINE

Epinephrine and norepinephrine are recommended in sepsis for their vasoconstrictor activity, as they can limit blood loss. No data has been published by HTA bodies on their use in the setting of burns. However, epinephrine and norepinephrine have been marketed for decades, with multiple generics available on the market, leading to a relatively low cost of treatment.

2.5 Anticholinergic Agents

2.5.1 Atropine Sulfate

Table 17. Atropine Sulfate Drug Information

SCIENTIFIC NAME ATROPINE SULFATE	
Trade Name(s) on Saudi Market	ATROPINE SULF.E.S® 50-100mcg/ml, ATROPINE SULPHATE® 1mg/1ml – 0.5mg-0.6mg, ATROPINE SULFATE®
SFDA Legal status	Prescription
SFDA	Registered, labeled indication
FDA	Registered (July 2001), labeled indication
EMA	Registered, labeled indication
MHRA (UK Market)	Registered, labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Anticholinergic
Drug Sub-Class	Antimuscarinic agent
ATC Code	A03BA01
Pharmacological Class (ASHP)	48:12.08 Anticholinergic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection Solution Solution for injection in pre-filled syringe
Route of Administration	Parenteral / IV / IM use
Dose (Adult) [DDD]*	**Organophosphate or carbamate insecticide or nerve agent poisoning:** **IV:** Mild to moderate symptoms: Initial: 1 to 2 mg bolus; repeat by doubling the dose every 3 to 5 minutes if previous dose did not induce a response. Maintain atropinization by administering repeat doses as needed for ≥2 to 12 hours based on recurrence of symptoms. After the

	desired response is achieved with bolus dosing, consider starting an IV continuous infusion for improved clinical outcomes (. Severe symptoms: Initial: 3 to 5 mg bolus (; repeat by doubling the dose every 3 to 5 minutes if previous dose did not induce a response (. Maintain atropinization by administering repeat doses as needed for ≥2 to 12 hours based on recurrence of symptoms (. After the desired response is achieved with bolus dosing, consider starting an IV continuous infusion for improved clinical outcomes. **IV continuous infusion:** After desired response is achieved with IV boluses, administer 10% to 20% of the total cumulative IV bolus dose as an IV continuous infusion per hour (e.g., if 18 mg given by IV bolus is required to achieve the desired response, start an IV continuous infusion of 1.8 mg per hour); adjust infusion rate as needed to maintain adequate response without causing atropine toxicity. **IM (AtroPen):** Mild symptoms (≥2 mild symptoms): Administer 2 mg as soon as an exposure is known or strongly suspected. If severe symptoms develop after the first dose, 2 additional doses should be repeated in rapid succession 10 minutes after the first dose; do not administer more than 3 doses. If profound anticholinergic effects occur in the absence of excessive bronchial secretions, further doses of atropine should be withheld. Severe symptoms (≥1 severe symptoms): Immediately administer **three** 2 mg doses in rapid succession.

	Muscarine-containing mushroom poisoning (off-label dose): IV: 1 to 2 mg; titrate and repeat as needed to reverse symptoms (i.e., titrate to achieve decreased bronchial secretions)
Maximum Daily Dose Adults*	2-3 mg
Dose (pediatrics)	**Organophosphate or carbamate insecticide or nerve agent poisoning:** **IV, IM, Intraosseous:** Infants and Children: Initial: 0.05 to 0.1 mg/kg; repeat every 3 to 5 minutes as needed, double the dose if previous dose does not induce atropinization. Maintain atropinization by administering repeat doses as needed for ≥2 to 12 hours based on recurrence of symptoms. Adolescents: Initial: 1 to 3 mg; repeat every 3 to 5 minutes as needed, doubling the dose if previous dose does not induce atropinization. Maintain atropinization by administering repeat doses as needed for ≥2 to 12 hours based on recurrence of symptoms. **Continuous IV infusion:** Infants, Children, and Adolescents: Following atropinization, administer 10% to 20% of the total loading dose required to induce atropinization as a continuous IV infusion per hour; adjust as needed to maintain adequate atropinization without atropine toxicity. **IM (AtroPen):** Infants, Children, and Adolescents: Number of doses

	dependent upon symptom severity: Weight-directed dosing: <7 kg (<15 lb): 0.25 mg/dose (yellow pen). 7 to 18 kg (15 to 40 lb): 0.5 mg/dose (blue pen). >18 to 41 kg (>40 to 90 lb): 1 mg/dose (dark red pen). >41 kg (>90 lb): 2 mg/dose (green pen). *Mild symptoms (≥2 mild symptoms):* Administer the weight-directed dose listed above as soon as an exposure is known or strongly suspected. If severe symptoms develop after the first dose, 2 additional doses should be repeated in rapid succession 10 minutes after the first dose; do not administer more than 3 doses. If profound anticholinergic effects occur in the absence of excessive bronchial secretions, further doses of atropine should be withheld. Mild symptoms of insecticide or nerve agent poisoning, as provided by manufacturer in the AtroPen product labeling to guide

	therapy, include: Blurred vision, bradycardia, breathing difficulties, chest tightness, coughing, drooling, miosis, muscular twitching, nausea, runny nose, salivation increased, stomach cramps, tachycardia, teary eyes, tremor, vomiting, or wheezing. *Severe symptoms (≥1 severe symptom):* Immediately administer **three** weight-directed doses in rapid succession. Severe symptoms of insecticide or nerve agent poisoning, as provided by manufacturer in the AtroPen product labeling to guide therapy, include: Breathing difficulties (severe), confused/strange behavior, defecation (involuntary), muscular twitching/generalized weakness (severe), respiratory secretions (severe), seizure, unconsciousness, urination (involuntary); **Note:** Infants may become

	drowsy or unconscious with muscle floppiness as opposed to muscle twitching.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment No adjustment required • Hepatic impairment No adjustment required • Interactions Concomitant drug use may expose to interactions – check before use • Pediatrics Weight-directed dosing. Same conditions for renal and hepatic impairment
Prescribing Edits*	MD, EU
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a physician experienced in the detection and management of mustard agent intoxications.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy):	
EU (Emergency Use Only): Administer as soon as an exposure is known or strongly suspected.	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	Anticholinergic symptoms (mydriasis, hyperthermia, tachycardia, cardiac arrhythmia, delayed gastric emptying) Ataxia Fever Headache Insomnia Dry mouth Anhidrosis

	Urticaria Urinary hesitancy Dry skin Blurred vision Cycloplegia Photophobia Anhidrosis Palpitation Dyspnea Paralytic ileus Pulmonary edema Nasal dryness Xerophthalmia Constipation May increase IOP in predisposed patients. May cause CNS disturbances (especially in pediatric patients)
Drug Interactions (Contraindicated)	• Aclidinium: aclidinium can increase the anticholinergic effect of Atropine. Do not concomitantly use these drugs. • Cimetropium; Cimetropium can increase the anticholinergic effect of Atropine. Do not concomitantly use these drugs. f these combinations cannot be avoided, monitor patients closely for evidence of anticholinergic-related toxicities • Eluxadoline: Eluxadoline can increase the anticholinergic effect of Atropine. Do not concomitantly use these drugs. • Glycopyrrolate (oral inhalation): glycopyrrolate can increase the anticholinergic effect of Atropine. Do not concomitantly use these drugs. f these combinations cannot be avoided, monitor

	patients closely for evidence of anticholinergic-related toxicities • Ipratropium (oral inhalation): ipratropium can increase the anticholinergic effect of Atropine. Do not concomitantly use these drugs. f these combinations cannot be avoided, monitor patients closely for evidence of anticholinergic-related toxicities • Levosulpiride: levosulpiride can increase the anticholinergic effect of Atropine. Do not concomitantly use these drugs. • Macimorelin: Atropine can decrease the diagnostic effect of Macimorelin. Avoid concomitant use of macimorelin and drugs that may blunt the growth hormone response to macimorelin • Oxatomide: Oxatomide can increase the anticholinergic effect of Atropine. Do not concomitantly use these drugs. • Potassium chloride / citrate: Atropine can increase the ulcerogenic effect of potassium chloride. Solid oral dosage forms of potassium chloride are contraindicated in patients with impaired gastric emptying (eg, due to the effects of drugs such as many anticholinergics). Patients on drugs with substantial anticholinergic effects should avoid using any solid oral dosage form of potassium chloride. Agents with greater anticholinergic effects (eg, systemic products) are likely of

	more concern than agents with lesser anticholinergic effects (eg, inhaled, ophthalmic, or topical products). Prescribing information for at least one systemic glycopyrrolate formulation lists use with solid oral dosage forms of potassium chloride as contraindicated. Liquid or effervescent potassium preparations are possible alternatives • Pramlintide: pramlintide can increase the anticholinergic effect of atropine, especially in the GI tract. Do not use these drugs together • Revefenacin: Atropine can increase the anticholinergic effect of revefenacin. Avoid concurrent use of revefenacin with other drugs that have anticholinergic properties. If such combinations cannot be avoided, monitor patients closely for evidence of anticholinergic-related toxicities • Tiotropium: Atropine can increase the anticholinergic effect of tiotropium. Avoid concurrent use of revefenacin with other drugs that have anticholinergic properties. If such combinations cannot be avoided, monitor patients closely for evidence of anticholinergic-related toxicities • Umeclidinium: umeclidinium can increase the anticholinergic effect of atropine. Avoid concurrent use of umeclidinium with any other drugs that have

	anticholinergic properties. If such combinations cannot be avoided, monitor patients closely for evidence of anticholinergic-related toxicities
Special populations	• Patients who have received heart transplants: Due to the transplanted heart's lack of vagal innervation, atropine therapy for bradycardia is likely to be unsuccessful. Atropine can be used cautiously since cholinergic reinnervation can happen over time (years), but some people may have paradoxical heart rate slowdown and high-degree AV block as soon as it is administered. • Pediatrics: Atropine's anticholinergic effects on children may make them more susceptible. Use with care in children with spastic paralysis.
Pregnancy	Antidotes should be supplied to pregnant women if there is a clear rationale for usage and should not be withheld due to concerns about teratogenicity. In general, antidotes should take into consideration the health and prognosis of the mother.
Lactation	The manufacturer advises taking into account the danger of baby exposure, the advantages of nursing for the child, and the advantages of treatment for the mother while deciding whether to breastfeed during therapy.
Contraindications	• Hypersensitivity to atropine or any component of the formulation; • GI obstruction

	• Glaucoma (known or suspected), • Pyloric stenosis or prostatic hypertrophy (except in doses typically used for preanesthesia).
Monitoring Requirements	• Heart rate, blood pressure, • Respiratory status, oxygenation secretions. • Maintain atropinization with repeated dosing as indicated by clinical status. • Crackles in lung bases, or continuation of cholinergic signs, may be signs of inadequate dosing. Pulmonary improvement may not parallel other signs of atropinization. • Monitor for signs and symptoms of atropine toxicity (eg, fever, muscle fasciculations, delirium); if toxicity occurs, discontinue atropine and monitor closely.
Precautions	• Hypersensitivity: Anaphylactic responses and other hypersensitivity events are possible. • Hyperthermia: Patients who are exposed to hot settings or intense activity may have hyperthermia or heat-related injuries because atropine inhibits perspiration. • Psychosis: This condition can develop in sensitive people or after using drugs in high dosages. • Arrhythmias: When treating type II second- or third-degree AV block (with or without a new broad QRS complex), avoid depending solely on atropine. Asystole or bradycardic PEA: Routine usage is unlikely to

	provide a therapeutic advantage and is no longer advised, despite the lack of evidence for any substantial negative effects. • Cardiovascular disease: Patients with myocardial ischemia, heart failure, tachyarrhythmias (including sinus tachycardia), and/or hypertension should use this medication with caution because treatment-related blood pressure increases and tachycardia can cause ischemia, trigger a MI, or increase arrhythmogenic potential. • Chronic lung disease: Patients who have this condition should take care since it might thicken bronchial secretions and lead to the production of potentially harmful viscid plugs. • Glaucoma: Patients with severe narrow-angle glaucoma should use cautiously since it might trigger acute glaucoma. • Patients with hepatic impairment should use atropine with caution; its effects may be extended in cases of severe hepatic impairment. • Hiatal hernia: Patients with a hiatal hernia and reflux esophagitis should use care. • Hyperthyroidism: Patients with hyperthyroidism should use with care. • Acetylcholinesterase inhibition side effects in myasthenia gravis: Use extremely cautiously or stay away from; may cause a myasthenic crisis.

	• Neuropathy: Patients with autonomic neuropathy should use care. • Pyloric stenosis: Patients with partial pyloric stenosis should exercise care since it might result in a full pyloric blockage. • Renal impairment: Patients with renal impairment should use atropine with caution since its effects may last longer in cases of severe renal impairment. • Urinary retention: Patients who have urinary obstruction should exercise care since urine retention may result. • Benzyl alcohol and derivatives: Some dosage forms may contain sodium benzoate/benzoic acid, which is a metabolite of benzyl alcohol and has been linked to a potentially fatal toxicity in neonates (referred to as "gasping syndrome"); avoid or use dosage forms containing benzyl alcohol derivative with caution in neonates. See the labeling provided by the manufacturer. • Suitable use: toxicity from anticholinesterase: The muscarinic but not the nicotinic effects of anticholinesterase poisoning are reversed by atropine. Confirmatory laboratory testing shouldn't be used as an excuse to postpone administration. When giving more injections as needed, pay special attention to the consequences. The occurrence of these side effects is not a sign

	that medication is working; atropine poisoning has come from the incorrect use of mydriasis as a sign of effective treatment. The ideal measure of success is the cessation of bronchial secretions. Patients with organophosphorus pesticide or nerve agent poisoning may need further therapy with a cholinesterase reactivator (such as pralidoxime). Medical staff should always take precautions to protect themselves from unintentional contamination, and treatment should always involve thorough evacuation and decontamination measures. Antidotal administration is solely meant for initial treatment; further, more in-depth medical attention is needed after administration. People shouldn't just rely on antidotes since they may still need additional supportive treatments, such mechanical breathing.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of burn treatment options in austere conditions by the following agencies/institutes/authorities: Canadian Agency for Drugs and Technologies in Health (CADTH) for atropine sulfate.

Table 18. Atropine Sulfate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Atropine Sulfate	CADTH	Regarding the clinical efficacy of atropine at different dosages for organophosphate poisoning in a pre-hospital context, no pertinent research could be found. There were no evidence-based recommendations found for treating organophosphate poisoning in a prehospital context[13].

Conclusion statement – ATROPINE SULFATE

Atropine is recommended in the case of Mustard agent intoxication because it might reverse its effects but needs to be used early in treatment procedure. According to CADTH, there are still no guidelines for treating this kind of intoxication before hospitalization.

2.6 Anticoagulants

2.6.1 Enoxaparin Sodium

Table 19. Enoxaparin Sodium Drug Information

SCIENTIFIC NAME ENOXAPARIN SODIUM	
Trade Name(s) on Saudi Market	CLEXANE® prefilled syringe 20-40-60-80mg, INHIXA®, ENOXAPARIN BOS®, ENDOSA® prefilled syringe 2000-4000-6000-8000 UI, ENOXA®, FARINOX® solution for injection 20-40-60-80mg, COGUPERIN® 20-40-60-80mg
SFDA Legal status	Prescription
SFDA	Registered, labeled indication
FDA	Registered (December 1998), labeled indication
EMA	Registered (September 2016), labeled indication
MHRA (UK Market)	Registered, labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Anticoagulants

Drug Sub-Class	Low molecular weight heparin (LMWH)
ATC Code	B01AB05
Pharmacological Class (ASHP)	20:12.04.16 Heparins
DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled syringe, solution for injection
Route of Administration	IV / Subcutaneous use
Dose (Adult) [DDD]*	***Medical patients with acute illness at moderate and high risk for venous thromboembolism:*** **SUBQ:** 40 mg once daily; continue for length of hospital stay or until patient is fully ambulatory and risk of venous thromboembolism (VTE) has diminished. Extended prophylaxis beyond acute hospital stay is not routinely recommended. ***Trauma, moderate to high risk (off-label use):*** Time of initiation is a balance between the benefits of VTE prevention and risk for bleeding. In most trauma patients, initiate within 24 to 48 hours of hospital admission provided hemostasis has been achieved and risk for bleeding is low. Prophylaxis may be delayed in some subgroups, such as those with traumatic brain injury, active bleeding, coagulopathy, spinal cord injury, spine surgery, or solid organ injury, but can be started within 72 hours in most situations. **Patients ≤65 years of age, ≥50 kg, and CrCl >60 mL/minute:** *Non–weight-based dosing*: **SUBQ:** 40 mg every 12 hours; consider dose adjustment based on anti-factor Xa level, targeting a peak level of 0.2 to 0.4 units/mL or a trough level of 0.1 to 0.2 units/ml.

	Weight-based dosing: **SUBQ:** 0.5 mg/kg every 12 hours; consider dose adjustment based on anti-factor Xa level, targeting a peak level of 0.2 to 0.4 units/mL or a trough level of 0.1 to 0.2 units/mL. **Patients >65 years of age, <50 kg, CrCl 30 to 60 mL/minute, traumatic brain injury, or spine trauma: SUBQ:** 30 mg every 12 hours; consider dose adjustment based on anti-factor Xa level, targeting a peak level of 0.2 to 0.4 units/mL or a trough level of 0.1 to 0.2 units/mL.
Maximum Daily Dose Adults*	300 mg q12h
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment No adjustment required only in the trauma patient's category where injection can be cut in half daily. In dialysis, enoxaparin should be avoided as it might accumulate • Hepatic impairment No adjustment required • Obesity Class 3 obesity: Clinical debate exists on the appropriateness of either a fixed-dose regimen or a weight-based dosing technique, but both are feasible. • Elderly Blood loss is more common with dosages of 1.5 mg/kg/day or 1 mg/kg every 12 hours, and older patients also experience more significant adverse effects and bleeding from injections. Older patients, especially those under 45 kg, should get careful attention. It could be necessary to modify or change the dosage.

	• Pediatrics little information available: You may think about adjusting your dosage to reach your desired anti-factor Xa level of 0.1 to 0.3 units/mL 4 to 6 hours after your dose. Dose given according to kid's weight. Renal and hepatic impairment adjustments should rely on adults recommendations
Prescribing Edits*	AGE, MD
AGE (Age Edit): Not to be used as prophylaxis in pediatrics.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a specialty physician.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	• Major hemorrhage • Spinal hematoma or epidural intracranial hemorrhage • Thrombocytopenia (HIT) and thrombosis in heparin-induced thrombocytopenia (HITT) • Anemia • Peripheral edema • Ecchymoses, alopecia, maculopapular rash • Nausea • Hematuria, intracranial/retroperitoneal/intraocular hemorrhage • Increase in ASAT/ALAT plasma levels, hyperkalemia, hyperlipidemia, hyperTG, hepatotoxicity • Local bleeding at injection site

	• Anaphylactic shock, angioedema, delayed-hypersensitivity reaction
Drug Interactions (Contraindicated)	• Apixaban: Apixaban can increase the anticoagulant effect of enoxaparin. Do not use this combination. Some limited combined use may be indicated during periods of transition from apixaban to a vitamin K antagonist. • Dabigatran etexilate: Dabigatran can increase the anticoagulant effect of enoxaparin. Do not use this combination. Some limited combined use with warfarin may be indicated during periods of transition from dabigatran to warfarin. • Defibrotide: defibrotide can increase the anticoagulant effect of enoxaparin. Do not concomitantly use these drugs. • Edoxaban: Edoxaban can increase the anticoagulant effect of enoxaparin. Do not use this combination. Some limited combined use may be indicated during periods of transition from one anticoagulant to another. • Hemin: Hemin can increase the anticoagulant effect of enoxaparin. Do not concomitantly use these drugs • Mifepristone: The way this possible interaction is handled varies depending on whether mifepristone is being taken to end an intrauterine pregnancy or to treat hyperglycemia in Cushing syndrome patients. Mifepristone can increase the

	adverse /toxic effects of enoxaparin. This combination is contraindicated if mifepristone is used to terminate pregnancy. If used to treat hyperglycemia due to Cushing syndrome, enoxaparin should be used with caution and patients should be monitored for signs and symptoms of bleeding. • Omacetaxine: enoxaparin can increase the side / toxic effects of omacetaxine. Avoid concurrent use of anticoagulants with omacetaxine in patients with a platelet count of less than 50,000/uL. Use caution with any concurrent use, even in patients with higher platelet counts. Monitor patients closely for evidence of bleeding. • Rivaroxaban: Enoxaparin can increase the anticoagulant effect of rivaroxaban. Avoid concurrent use of rivaroxaban with other anticoagulants whenever possible, other than during transition periods, due to the possible increased risk for bleeding. • Urokinase: Urokinase can increase the anticoagulant effect of enoxaparin. Avoid systemic urokinase in patients receiving (or who have recently received) anticoagulants. UK product labeling specifically lists this as a contraindication. In patients who have recently received heparin, verify that aPTT is twice control values or less before urokinase initiation. Continuation of heparin

	may be considered in patients receiving hemodialysis. • Vorapaxar: Vorapaxar can increase the side / toxic effects of enoxaparin. Do not concomitantly use these drugs.
Special populations	• Elderly In senior individuals, use with caution since delayed elimination is possible. A change in dosage may be necessary (for example, skipping the IV bolus and administering a lower therapeutic dose to patients with acute STEMI who are under 75 years old). • Low weight patients In women under 45kg and in males above 57kg, the risk of bleeding may be raised • Elective surgery / procedure The last dosage should be given to patients receiving therapeutic dose enoxaparin as bridging anticoagulation at least 24 hours before the operation or surgery. The morning of the day before surgery, give 1 dosage to individuals who are on a twice-daily regimen. The morning of the day before surgery, give 50% of the prescribed dose to individuals who are on a once-daily regimen. Restart treatment within 24 hours of the operation or surgery if the risk of bleeding is manageable.
Pregnancy	**Pregnant trauma patients:** *Patients >90 kg:* **SUBQ:** 40 mg every 12 hours; dose adjustment based on anti-factor Xa level is recommended, targeting a peak level of 0.2 to 0.4 units/mL or a trough level of 0.1 to 0.2 units/mL. *Patients ≤90 kg:* **SUBQ:** 30 mg every 12 hours; dose adjustment based on anti-

	factor Xa level is recommended, targeting a peak level of 0.2 to 0.4 units/mL or a trough level of 0.1 to 0.2 units/mL. Drug-treated pregnant women should be closely observed for signs of bleeding or excessive anticoagulation. Pregnant women should be informed of the possible risk to the baby and mother if treatment is given while pregnant since hemorrhage can happen anywhere and can result in the death of the mother or the fetus.
Lactation	Whether treatment is excreted in human milk is unknown; There is little information on the impact of enoxaparin or metabolites on breastfed children or milk supply, and passage of enoxaparin or metabolites in milk in lactating rats is quite limited. Along with the mother's clinical requirement for medication and any potential negative effects on the breastfed infant from drugs or from an underlying maternal ailment, the developmental and health benefits of nursing should be taken into consideration. Unknown excretion in breast milk during lactation; not advised
Contraindications	Known hypersensitivity to enoxaparin, heparin, pork products, or any ingredient of the product (including benzyl alcohol in multiple-dose vials); history of immune mediated heparin-induced thrombocytopenia (HIT) in the past 100 days or in the presence of circulating antibodies; active major bleeding, use of multiple-dose vials in newborns or premature neonates; acute or subacute bacterial endocarditis; major blood clotting disorders; active

	gastric or duodenal ulcer; hemorrhagic cerebrovascular accident (except if there are systemic emboli); severe uncontrolled hypertension; diabetic or hemorrhagic retinopathy; other conditions or diseases involving an increased risk of hemorrhage; injuries to and operations on the brain, spinal cord, eyes, and ears; spinal/epidural anesthesia when repeated dosing of enoxaparin (1 mg/kg every 12 hours or 1.5 mg/kg daily) is required, due to increased risk of bleeding.
Monitoring Requirements	• Anti-factor Xa levels can be used to track the effects of an anticoagulant in individuals with impaired renal function. • Monitoring of PT and/or aPTT is not required, but other measurements such as serum creatinine, anti-factor Xa levels, and fecal occult blood should be taken at baseline and during treatment. Although it is not necessary, routine anti-factor Xa activity monitoring has been used in individuals with obesity and/or renal disease. • If anti-factor Xa monitoring is available for patients weighing more than 144 kg, modifying the dose based on anti-factor Xa activity is advised; if anti-factor Xa monitoring is not possible, reducing the dose if bleeding occurs. Keep a watchful eye out for thrombosis symptoms or indicators in obese patients. • In pregnant women receiving therapeutic dosages of enoxaparin or when receiving

	enoxaparin to avoid thromboembolism with artificial heart valves, it is advised to monitor anti-factor Xa activity. • During or immediately after a lumbar puncture or neuraxial anesthesia (such as epidural anesthesia/analgesia or spinal anesthesia/analgesia), patients who are taking anticoagulants should be closely monitored for signs and symptoms of neurological impairment, such as midline back pain, sensory and motor deficits, and bowel and/or bladder dysfunction.
Precautions	• Hyperkalemia: Rarely, hyperkalemia can be brought on by decreasing the synthesis of aldosterone. happens more frequently in individuals who have a higher risk of developing hyperkalemia (risk factors include renal disease, concurrent use of potassium-sparing diuretics or potassium supplements, and bodily tissue hematomas). • Thrombocytopenia: In patients with a history of HIT, use with the utmost caution or avoid. Use in individuals with a history of HIT only if more than 100 days have passed since the previous episode and there are no circulating antibodies (HIT may still occur in these patients; weigh the risks and benefits before using and only after considering non-heparin alternative therapies). If platelets are below 100,000/mm3 and/or thrombosis

	occurs, stop therapy and look into alternate options. • Renal impairment: Patients with renal impairment should use this medication with care; dose adjustments may be necessary. It is advised that young patients with renal impairment undergo more regular monitoring. • Benzyl alcohol and derivatives: Pregnant patients should not take some dose forms because they may contain benzyl alcohol. Large doses of benzyl alcohol (99 mg/kg/day) in newborns have been linked to a possibly deadly toxicity (referred to as "gasping syndrome").Use care when administering dose forms containing benzyl alcohol to newborns. See the labeling provided by the manufacturer. • Administration: Avoid intramuscular administration. • Switching to different products: Not to be used in place of heparin or any other low-molecular-weight heparins (unit for unit). • Neuraxial anesthesia: Delay catheter insertion or removal for at least 12 hours after low-dose enoxaparin administration and at least 24 hours after high-dose enoxaparin administration; risk of neuraxial hematoma may still persist at these time intervals as anti-factor Xa levels are still detectable. In order to provide patients receiving twice-daily high-dosage enoxaparin more time before catheter insertion or

	removal, the second dose should be deferred. Prior to starting enoxaparin, indwelling catheters should be taken out. Withhold enoxaparin for at least 4 hours after catheter removal. Only when there is sufficient hemostasis and no sooner than 12 or 24 hours following the installation of the needle or catheter, respectively, may prophylactic or therapeutic dosages of enoxaparin be administered. In individuals with CrCl less than 30 mL/minute, you might want to double these intervals.
Black Box Warning	Patients anticoagulated with low-molecular-weight heparin (LMWH) or heparinoids who undergo neuraxial (epidural/spinal) anesthesia or spinal puncture may develop epidural or spinal hematomas. The paralysis brought on by these hematomas may be long-lasting or permanent. Patients should be closely observed for any indications of neurologic impairment, such as tingling, numbness, or weakening of the muscles. If neurologic compromise is noticed, immediate medical attention is required. Prior to performing neuraxial interventions on patients who are or will be on an anticoagulant for thromboprophylaxis, doctors should weigh the advantages against the risks. **Factors increasing risk of epidural or spinal hematomas**:

	• Catheters for epidural indwelling. • Concurrent use of other medications that impact hemostasis (NSAIDs, platelet inhibitors, and other anticoagulants, for example). • Epidural or spinal punctures that were painful or repeated in the past. • History of spinal surgery or deformity. **Enoxaparin dosage should be administered at the right time for catheter insertion or removal.** • It is unknown when it is best to administer enoxaparin and do neuraxial operations. • A minimum of 12 hours should pass following the administration of preventive dosages, such as those used to prevent DVT, before inserting or removing a spinal catheter. • For patients taking greater therapeutic dosages (such as enoxaparin 1 mg/kg BID or 1.5 mg/kg qDay), longer waits (24 hr) are reasonable to take into account. • Enoxaparin post-procedure doses should typically be administered no earlier than 4 hours following catheter removal.
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of DVT prophylaxis options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health

(CADTH), Haute Autorité de Santé (HAS) and Pharmaceutical Benefits Scheme (PBS) as applicable. The recommendations are for enoxaparin sodium.

Table 20. Enoxaparin Sodium HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Enoxaparin Sodium	NICE	Pharmacological venous thromboembolism (VTE) prophylaxis should be started as soon as feasible and within 14 hours of hospital admission for patients aged 16 and older who are determined to need it. The majority of patients admitted to hospitals have VTE risk evaluations, but the results are not always quickly implemented, delaying pharmacological prophylaxis and raising the risk of hospital-acquired thrombosis. For medical, surgical, and trauma patients, ensuring that prophylaxis is begun as soon as feasible and within 14 hours of hospital admission will lower the risk of VTE[14] . On admission, administer intermittent pneumatic compression as part of a mechanical VTE prophylaxis to patients who have sustained significant or moderate trauma. Continue until the person's movement is no longer noticeably limited in comparison to what is expected or usual for them. In patients who have experienced severe or substantial trauma, reevaluate the risk of VTE and bleeding anytime their clinical status changes and, ideally, every day. When the risk of VTE surpasses the danger of bleeding, consider pharmaceutical VTE prevention as soon as feasible following the risk assessment for patients who have experienced significant or major trauma. Continue for at least seven days[15].
	PBS	July 2020 Enoxapo® received the approval for prevention and treatment of DVT. Enoxapo was TGA registered on 10 February 2020 for the same indications for which Clexane Safety-Lock is TGA-registered: • Prevention of thromboembolic disorders of venous origin in patients undergoing orthopedic and general surgery. • Prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness.

		• Prevention of thrombosis in extra-corporeal circulation during hemodialysis. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2020-07/files/enoxaparin-psd-july-2020.pdf.
	HAS	Received approval on November 4th 2015, and covers several indications including prophylaxis: 1)Prophylactic treatment of venous thromboembolism in high-risk surgery moderate and high, particularly in orthopedic or general surgery, including surgical oncology. 2)Prophylactic treatment of venous thromboembolism in patients affected an acute medical condition (such as acute heart failure, respiratory failure, severe infections or rheumatic diseases) and whose mobility is reduced, at increased risk of venous thromboembolism. 3)Prevention of thrombus formation in the extracorporeal circulation circuit during hemodialysis[16].
	CADTH	In September 2021, the CADTH issued a report concerning the use of enoxaparin biosimilars like Inhira, citing its approval as an alternative to Clexane in the prevention and treatment of VTE, and so it says indirectly that enoxaparin is already approved for that indication[42].

Conclusion statement – ENOXAPARIN SODIUM

Enoxaparin sodium is recommended as a prophylaxis agent of DVT in patients at moderate to high-risk. In addition, it has been advised as an alternative if heparine is contraindicated for certain patients.

According to PBS and HAS, this drug can also be used in DVT prevention under surgery, and a possible agent for DVT prophylaxis under hemodialysis. Furthermore, as reported by CADTH, certain biosimilars can be used as alternatives to the original brand.

2.7 Beta Adrenergic Agonists

2.7.1 Dobutamine

This beta-adrenergic has been proposed as an inotropic stabilizer in sepsis.

Table 21. Dobutamine Drug Information

SCIENTIFIC NAME DOBUTAMINE	
Trade Name(s) on Saudi Market	Dobutamine HCL ® 250mg/20ml vial, Dobutamine JPI® 250mg/20ml, Cardutrex®
SFDA Legal status	Prescription
SFDA	Registered, labeled indication
FDA	Registered (July 1978), labeled indication
EMA	Registered
MHRA (UK Market)	Registered, labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Catecholamines
Drug Sub-Class	Inotropic agent
ATC Code	C01CA07
Pharmacological Class (ASHP)	24:04.08 Cardiotonic Agents
DRUG INFORMATION	
Dosage Form	Solution for injection Solution for infusion Concentrate for solution for infusion
Route of Administration	IV use
Dose (Adult) [DDD]*	Inotropic support (Off-label): Continuous infusion IV: Initial: 2 to 5 mcg/kg/minute; titrate based on clinical end point (eg, BP, end-organ perfusion); usual dosage range: 2 to 10 mcg/kg/minute; however, doses as low as 0.5 mcg/kg/min have been used in less severe cardiac decompensation
Maximum Daily Dose Adults*	20mcg/kg/min
Dose (pediatrics)	N/A

Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment No adjustment required • Hepatic impairment No adjustment required • Obesity Use of ideal body weight for initial weight-based dosing, then titrate to hemodynamic effect and clinical response • Pediatrics For hemodynamic support, doses are reduced compared to adults, and no changes are required in the case of renal or hepatic impairment • Interactions Drug interactions may occur if concomitant therapy is used – check before use
Prescribing Edits*	AGE, MD, ST
AGE (Age Edit): Not to be used in pediatrics for inotropic support.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by an intensivist (critical care unit physician).	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): In patients with shock (e.g., sepsis) who fail to meet hemodynamic goals with vasopressor therapy (e.g., norepinephrine), dobutamine may be added to vasopressor therapy if there is continued hypoperfusion despite volume resuscitation.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	• Cardiovascular: Increased heart rate, increased systolic blood pressure, ventricular premature contractions, angina pectoris,

	chest pain, palpitations, Hypotension, ventricular ectopy • Central nervous system: Headache • Gastrointestinal: Nausea • Respiratory: Dyspnea • Endocrine & metabolic: Decreased serum potassium • Cardiomyopathy (stress), eosinophilia, hypersensitivity reaction, localized phlebitis - > <1%, postmarketing, and/or case reports
Drug Interactions (Contraindicated)	• Kratom: the latter can increase the adverse/toxic effects of dobutamine (sympathomimetic) – avoid use
Special populations	Elderly: vigilant use, start at lower end of the dosage range
Pregnancy	Category B When other choices are available, dobutamine should not be utilized as a diagnostic tool for stress testing during pregnancy. The medications used to treat cardiac arrest in pregnant women are the same as those used in non-pregnant women. Due to worries about teratogenicity in fetuses, appropriate drugs shouldn't be withheld. Utilizing dobutamine during the post-resuscitation period is a possibility, but the fetus's exposure to inotropic support should also be taken into account.
Lactation	It is unknown if the medication is excreted in breast milk – avoid use
Contraindications	• Hypersensitivity to dobutamine or sulfites (some contain sodium metabisulfite), or any ingredient of the product;

	• Hypertrophic cardiomyopathy with outflow tract obstruction (formerly known as idiopathic hypertrophic subaortic stenosis). • Pheochromocytoma • Stress testing: Patients with recent (<2 to 4 days) myocardial infarction, unstable angina, severe aortic stenosis, atrial tachyarrhythmias with uncontrolled ventricular response, prior history of ventricular tachycardia, uncontrolled hypertension (>200/110 mm Hg), and aortic dissection or large aortic aneurysm
Monitoring Requirements	BP, heart rate, ECG, hemodynamic parameters as appropriate (eg, CVP, RAP, MAP, CI, PCWP, SVR, $ScvO_2$ or SvO_2); intravascular volume status; kidney function; urine output.
Precautions	**Arrhythmias**: Ventricular arrhythmias, such as supraventricular and nonsustained ventricular tachycardia, have been documented. Patients with decompensated heart failure should be constantly monitored for arrhythmias; abrupt cardiac death has been reported. Before beginning treatment for atrial fibrillation or flutter, make sure the ventricular rate is under control since this might speed up the response time. **BP effects**: A rise in blood pressure is more frequently seen because of increased cardiac output, although at higher dosages, hypotension secondary to vasodilation may occur. **Heart failure complications**: Long-term usage in patients with New York Heart Association Classes III/IV heart failure

	has been associated with an increased risk of hospitalization and mortality. **Tachycardia**: May result in increases in heart rate that are dose related. **Ventricular ectopy**: Dependent on dosage, may worsen ventricular ectopy. **Aortic stenosis**: When there is a mechanical blockage, such as significant aortic stenosis, treatment is ineffective. **Electrolyte imbalance**: To reduce the risk of arrhythmias, correct electrolyte abnormalities, particularly hypokalemia or hypomagnesemia, before use and throughout therapy. **Hypovolemia**: To improve hemodynamics, if necessary, address hypovolemia initially. Use with care in individuals who have ongoing myocardial ischemia or a recent myocardial infarction; this condition can increase myocardial oxygen demand. **Monoamine oxidase inhibitors**: When used together with monoamine oxidase inhibitors in individuals, prolonged hypertension may occur. It's possible for a product to include sodium sulfite.
Black Box Warning	-N/A
REMS*	-N/A

Conclusion statement – DOBUTAMINE

Dobutamine is only recommended for the management of inotropic instability during sepsis. However, no data from HTA bodies were found to support the recommendation of dobutamine use.

2.8 Betablockers

2.8.1 Propranolol

Table 22. Propranolol Drug Information

SCIENTIFIC NAME PROPRANOLOL	
Trade Name(s) on Saudi Market	INDICARDIN® 10-40mg tablet, INDERAL® 10-40-80mg tablet and 1mg/ml, PROTENSE® 40mg/5ml oral solution
SFDA Legal status	Prescription
SFDA	Registered, Not indicated
FDA	Registered (November 1967), Not indicated
EMA	Registered, not indicated
MHRA (UK Market)	Registered, not indicated
PMDA	Registered (May 2016), not indicated
Indication (ICD-10)	T30
Drug Class	Beta-blocker
Drug Sub-Class	Non-selective
ATC Code	C07AA05
Pharmacological Class (ASHP)	12:16.08.04 Non-selective beta-Adrenergic Blocking Agents
DRUG INFORMATION	
Dosage Form	Tablet Solution Oral solution
Route of Administration	Oral / IV use
Dose (Adult) [DDD]*	**Burns, moderate to severe (hypermetabolism modulation) (adjunctive agent) (off-label use):** **Oral:** Initial: 10 to 20 mg 3 to 4 times daily; titrate as tolerated to a heart rate decrease of 15% to 20% from baseline. Generally, start within the first ~7 days following injury, after the patient is hemodynamically stable.

Maximum Daily Dose Adults*	Usual total daily dosage range: 0.5 to 2 mg/kg/day in 3 to 6 equally divided doses
Dose (pediatrics)	Initiate at 1mg/kg/day divided into 4 doses Reassess daily until target HR achieved. May increase to max of 4mg/kg/day divided into 4 doses[43].
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment No adjustment necessary, but to use with caution in high grade insufficiency, s decreased hepatic extraction has been reported and patients may be more prone to adverse effects when initiating therapy. No adjustment required in dialysis • Hepatic impairment No adjustment required, but to use with vigilance since hepatic insufficiency increases exposure to the medication. • Elderly IV: Use caution; initiate at lower end of the dosing range. Oral: Refer to adult dosing; consider lower initial doses and titrate to response. • Pediatrics Propranolol not recommended in burn management. No adjustment required, however to use with caution since renal and hepatic impairment increase exposure to medication • Interactions Drug interactions may exist if concomitant drugs are used – check interactions
Prescribing Edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	

G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a physician specialized in the management of burns.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	• Bradyarrhythmia: first-degree / second-degree / complete atrioventricular block • Bronchospasm, bronchiolitis • CNS: fatigue, insomnia, vivid dreams, memory impairment, sexual disorder • Masking and potentiation of hypoglycemia • Withdrawal syndrome: tachycardia. Hypertension, exacerbation of angina pectoris, acute myocardial infarction • Cold extremity • GI: abdominal pain, constipation, decreased appetite
Drug Interactions (Contraindicated)	• Beta2-agonists: Propranolol can decrease the bronchodilatory activity of beta2-agonists. Do not use combination. If used concomitantly, monitor closely for diminished bronchodilatory effects of the beta2-agonist. Canadian metaproterenol labeling states coadministration with beta-blockers is contraindicated. • Bromperidol: the latter can decrease the hypotensive activity of propranolol. In addition,

	propranolol can increase the hypotensive effect of bromperidol. Avoid concomitant use. • Etofylline: Propranolol can decrease the therapeutic effect of etofylline. Avoid combination • Fexinidazole: Propranolol, a bradycardia-causing agent, can increase the arrhythmogenic activity of fexinidazole. Avoid concurrent use. If patients are, or need to be, treated with drugs known to induce bradycardia, either do not initiate therapy with fexinidazole until such drugs are eliminated from the body (allow a washout period of 5 half-lives for such other drugs), or do not start such drugs until fexinidazole is eliminated from the body (allow a washout period of 7 days after the last fexinidazole dose). • Fezolinetant: Propranolol, a CYP1A2 weak inhibitor can enhance the plasma levels of Fezolinetant. Concomitant use is contraindicated. • Rivastigmine: the latter can increase the bradycardic activity of propranolol. Concomitant use is forbidden due to the increased risk of syncope. • Thioridazine: Propranolol can enhance the plasma levels of Thioridazine. Concomitant use is contraindicated. • White Birch Allergen Extract: Propranolol can increase the adverse/toxic effect of White Birch Allergen Extract.

	Specifically, beta-blockers may reduce the effectiveness of beta-agonists that may be required to treat systemic reactions to white birch allergen extract. Avoid combination
Special populations	• Cardiovascular concerns should be taken into account when treating infantile hemangiomas; monitor heart rate and blood pressure after starting or increasing propranolol dosage; stop treatment if severe (heart rate 80 bpm) or symptomatic bradycardia or hypotension (systolic blood pressure 50 mm Hg) occur. • Hypoglycemia: Can hide symptoms and/or increase hypoglycemia. To reduce the risk of hypoglycemia, administer during or after a meal. Withhold the dosage from babies or kids who aren't eating often or who are throwing up; stop the therapy and get help right away if hypoglycemia develops. • Breathing problems: Can result in bronchospasm. Discontinue treatment in babies or kids who have a lower respiratory infection with wheezing or dyspnea. • Smokers: Cigarette smoking may lower propranolol plasma levels by accelerating metabolism. Patients ought to be told not to smoke.
Pregnancy	Beta-blockers may raise the risk of bradycardia, hypoglycemia, hypotension, and respiratory depression in the newborn if used during the third

	trimester of pregnancy. Newborns should be watched after and treated with care. Fetal development should be tracked throughout pregnancy if a beta-blocker is required, and the infant should be checked for bradycardia, hypoglycemia, and respiratory depression for 48 hours following birth. For managing hypermetabolic pregnant thyrotoxicosis symptoms, propranolol is advised.
Lactation	An newborn who consumed breast milk containing propranolol had bradycardia. When taken at regular dosages, propranolol may generally be safe to use during nursing. Babies that are breastfed need to be watched for bradycardia, cyanosis, and hypoglycemia.
Contraindications	• Hypersensitivity to propranolol, beta-blockers, or any ingredient of the product; • Uncompensated heart failure (unless the failure is due to tachyarrhythmias being treated with propranolol); cardiogenic shock; severe sinus bradycardia, sick sinus syndrome, or heart block greater than first-degree (except in patients with a functioning artificial pacemaker); bronchial asthma. • Bronchospasm; COPD, Asthma right ventricular failure secondary to pulmonary hypertension; • Allergic rhinitis during pollen season; • Patients prone to hypoglycemia; • Hypotension (BP parameters not specified in labeling);

	• Metabolic acidosis; • Vasospastic angina (also referred to as Prinzmetal angina or variant angina); severe peripheral arterial circulatory disturbance; • Untreated pheochromocytoma; • Hereditary problems of galactose intolerance, glucose-galactose malabsorption, or congenital lactase deficiency • Hemangeol: Premature infants with corrected age <5 weeks; infants weighing <2 kg; heart rate <80 bpm; BP <50/30 mm Hg; pheochromocytoma; history of bronchospasm. Infants weighing <2.5 kg; breastfed infants if mother is treated with medicines contraindicated with propranolol; heart rate <100 bpm or BP <65/45 mm Hg (<3 months of age), heart rate <90 bpm or BP <70/50 mm Hg (3 to <6 months of age), heart rate <80 bpm or BP <80/55 mm Hg (6 to 12 months of age).
Monitoring Requirements	• Acute cardiac treatment: ECG, heart rate, and blood pressure. • Hypertension: Blood pressure, heart rate. • Mental alertness; signs and symptoms of bronchospasm in patients with existing bronchospastic disease; serum glucose (in patients with diabetes). • Proliferating infantile hemangioma (Hemangeol): Monitor heart rate and blood pressure for 2 hours after initiation or dose increases.

Precautions	**Anaphylactic reactions**: Patients using beta-blockers may become more susceptible to repeated challenges; use cautious if there is a history of severe anaphylaxis to allergens. Treatment for anaphylaxis in people using beta-blockers, such as epinephrine, may be ineffective or have unwanted side effects. **Heart failure**: Propranolol has not been proven to be effective in treating compensated heart failure; use with caution in patients and keep an eye out for a worsening of the disease. **Patients with hepatic impairment** should use this medication with care; dose adjustments may be necessary. **Myasthenia gravis**: Patients with myasthenia gravis should use care. **Raynaud disease and peripheral vascular disease**: Patients with these conditions may experience arterial insufficiency symptoms earlier or more severely. Use with care and keep an eye out for arterial blockage advancement. **Pheochromocytoma** (untreated): Before using any beta-blocker, adequate alpha-blockade is necessary. **Psoriasis**: Although a cause-and-effect relationship has not been conclusively demonstrated, beta-blocker usage has been linked to the onset or worsening of psoriasis. **Renal impairment**: When starting medication in individuals with extensive renal impairment, use with caution as the risk of adverse effects may rise due to reduced hepatic extraction and higher propranolol concentrations. **Thyroid disease**: Can conceal tachycardia and other hyperthyroidism

	symptoms. Carefully manage and monitor if thyrotoxicosis is suspected; sudden withdrawal may worsen hyperthyroidism symptoms or cause a thyroid storm. Test results for thyroid function may change. **Vasospastic angina**: Since unopposed alpha-1 adrenergic receptors induce coronary vasoconstriction and might exacerbate anginal symptoms, beta-blockers lacking alpha-1 adrenergic receptor blocking action should be avoided in individuals with vasospastic angina.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

No available data was found from the searched HTA bodies, such as the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Scheme (PBS) regarding their recommendations for the use of propranolol in burn-related hypermetabolism.

Conclusion statement – PROPRANOLOL

Propranolol is advised as a modulator in post-burn hypermetabolism in children. It has been proved to reduce heart rate, cardiac work, and post-burn hepatomegaly. Another effect is its beneficial immune modulation. However, no data from HTA bodies were found to support the recommendation of propranolol use in hemodynamic management.

2.9 Antineoplastic Agents

2.9.1 Bleomycin

This well-known antineoplastic drug has been mentioned as a potential therapeutic agent in certain types of skin scars wound healing.

Table 23. Bleomycin Drug Information

SCIENTIFIC NAME BLEOMYICIN	
Trade Name(s) on Saudi Market	Bleocin® 15mg vial
SFDA Legal status	Prescription
SFDA	Registered, Not indicated
FDA	Registered (June 1996), Not indicated
EMA	Not registered
MHRA (UK Market)	Registered, not indicated
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Bleomycins
Drug Sub-Class	Glycopeptide antibiotic
ATC Code	L01DC01
DRUG INFORMATION	
Dosage Form	Solution
Route of Administration	IV use
Dose (Adult) [DDD]*	**Resistant keloid lesions:** injected into the mid-lesion in depth, 0.2-0.4 ml/cm2 (maximum volume per session 3.5 ml). The interval between injections was 4 weeks, and the total number of treatment sessions depended on the cosmetic outcome of each lesion[44].
Maximum Daily Dose Adults*	Cumulative lifetime dose (**IV**): 400 units.
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment The dosage should be adjusted according to the Creatinine Clearance of the patient, and so quantity

	administered decreases. In hemodialysis, dose should be reduced to half the original. • Hepatic impairment No adjustment required • Pediatrics Similar recommendations as for renal and hepatic impairment in adults. If concomitant therapy needs to be administered, interactions must be checked. • Obesity Fixed doses are used, so independent of body weight. • Toxicity (adults & pediatrics) If pulmonary changes are notices, Bleomycin should be discontinued until proven not incriminated. If pulmonary diffusion capacity for carbon monoxide <30% to 35% of baseline Bleomycin should be discontinued. If pulmonary diffusion capacity for carbon monoxide corrected for hemoglobin content decrease of more than 25% during therapy, Bleomycin should be stopped to limit further pulmonary toxicity.
Prescribing Edits*	MD, QL
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a specialty physician.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): Cumulative lifetime dose **(IV)**: 400 units.	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	

Main Adverse Drug Reactions (Most common)	Mucocutaneous toxicity including rash, erythema, hyperpigmentation, urticaria (>50%) Febrile reactions, acute (25-50%) Mucositis (30%), Stomatitis (30%) Interstitial pneumonitis (10%), Pulmonary fibrosis (10%) Anorexia, Weight loss, Rales Tachypnea Alopecia (1-10%) Fatal pulmonary fibrosis (1%) Confusion Shivering Anphylactoid reactions Onycholysis Pruritus, Skin thickening Scleroderma Post marketing, and/or case reports: Angioedema, bone marrow depression (rare), cerebrovascular accident, cerebral arteritis, chest pain, coronary artery disease, hepatotoxicity, hyperpigmentation (flagellate), ischemic heart disease, malaise, myocardial infarction, nausea, nephrotoxicity, pericarditis, Raynaud's phenomenon, scleroderma (scleroderma-like skin changes), Stevens-Johnson syndrome, thrombotic thrombocytopenic purpura, toxic epidermal necrolysis, vomiting
Drug Interactions (Contraindicated)	Brentuximab Vedotin: The latter can increase the adverse/toxic effect of Bleomycin. The risk of pulmonary toxicity is particularly increased.
Special populations	A greater frequency of pulmonary toxicity is seen in children who are younger at the time of therapy, with cumulative doses below 400 units/m2

	(when paired with chest irradiation), and have renal impairment.
Reproduction	Patients under Bleomycin should avoid becoming pregnant
Pregnancy	In general, if chemotherapy is indicated, it should be avoided in the first trimester and there should be a 3-week time period between the last chemotherapy dose and anticipated delivery, and chemotherapy should not be administered beyond week 33 of gestation. (animal studies suggest teratogenic effects)
Lactation	Not known whether the drug is excreted in human milk; because many drugs are excreted in human milk and because of potential for serious adverse reactions in nursing infants, recommended that nursing be discontinued by women receiving bleomycin therapy
Contraindications	Hypersensitivity or idiosyncratic reaction to Bleomycin or any other ingredient in the product
Monitoring Requirements	• Pulmonary function tests, including total lung volume, forced vital capacity, diffusion capacity for carbon monoxide; vital capacity, total lung capacity and pulmonary capillary blood volume may be better indicators of changes induced by bleomycin; • Forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1], and diffusing capacity of the lungs for carbon monoxide [DLCO]) were performed prior to treatment, before each chemotherapy cycle, and then repeated at 1 year, 3 years, and 5 years during follow up for testicular cancer patients receiving bleomycin;

	• Chest x-ray • Renal function • Liver function • Monitor for signs/symptoms of hypersensitivity; temperature initially; check body weight at regular intervals. • HBV screening with hepatitis B surface antigen, hepatitis B core antibody, total Ig or IgG, and antibody to hepatitis B surface antigen prior to beginning (or at the beginning of) systemic anticancer therapy; do not delay treatment for screening/results.
Precautions	• Hepatotoxicity: May result in toxicity of the liver. • Idiosyncratic response: In 1% of lymphoma patients who had bleomycin treatment, a severe idiosyncratic reaction characterized by hypotension, mental disorientation, fever, chills, and wheezing (similar to anaphylaxis) has been documented. Careful monitoring is necessary following these dosages since adverse responses typically happen after the first or second dose. • The most serious toxicity is pulmonary fibrosis, which often begins as pneumonitis but can occasionally proceed to pulmonary fibrosis. Patients who are older or who have had more than 400 units of radiation during their lifetime are at a higher risk. Smoking, having received radiation therapy in the past, and getting oxygen at the same time (particularly high inspired oxygen doses) are other potential risk factors. Withhold therapy and look into if there were any drug-related alterations to the lungs. In a study of patients with

	testicular cancer receiving bleomycin as part of the BEP regimen, pulmonary function testing (including forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], and diffusing capacity of the lungs for carbon monoxide [DLCO]) was performed prior to treatment, before each chemotherapy cycle, and then repeated at 1 year, 3 years, and 5 years during follow up; if the carbon monoxide diffusing capacity corrected for hemoglobin content decreased more than 25% during therapy (compared with baseline), bleomycin was discontinued to avoid further pulmonary toxicity. • Renal toxicity: May cause renal toxicity. • O2 during surgery: Patients who have received bleomycin should be treated with caution since there is an increased risk of pulmonary toxicity associated to bleomycin. • Patients with creatinine clearance values of < 50 mL/min should be treated with caution and their renal function should carefully monitored during the administration; lower doses of bleomycin may be required in these patients than those with normal renal function
Black Box Warning	**Experienced physician:** It is recommended that bleomycin be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

	Pulmonary toxicity: Pulmonary fibrosis is the most severe toxicity associated with bleomycin. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and in those receiving more than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses. **Idiosyncratic reaction:** A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin.
REMS*	N/A

Health Technology Assessment (HTA)

A thorough review of various HTA bodies including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Scheme (PBS) yielded no result for the use of bleomycin in burns.

Conclusion statement – BLEOMYCIN

This drug, only cited by the international guidelines, is currently advised in hypertrophic resistant lesions and keloid diathesis, without detailing its mechanism of action. However, no data from HTA bodies were found to support the recommendation of bleomycin use in burns.

2.10 Calcium Channel Blockers

2.10.1 Verapamil

This well-known antihypertensive drug has been mentioned as a potential therapeutic agent in certain skin scar healing.

Table 24. Verapamil Drug Information

SCIENTIFIC NAME VERAPAMIL	
Trade Name(s) on Saudi Market	ISOPTIN® S.R. / RETARD / AMP / TABLET
SFDA Legal status	Prescription
SFDA	Registered, Not indicated
FDA	Registered (October 1998), Not indicated
EMA	Not registered
MHRA (UK Market)	Registered, not indicated
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Anti-hypertensive agent; Calcium Channel Blocker (CCB), Nondihydropyridin
Drug Sub-Class	Antianginal agent, Antiarrhythmic agent, Class IV, antihypertensive
ATC Code	C08DA01
Pharmacological Class (ASHP)	24:08.12.92 Calcium-Channel Blocking Agents, Miscellaneous
DRUG INFORMATION	
Dosage Form	Prolonged-release tablet Solution for injection Tablet
Route of Administration	Oral use / IV use
Dose (Adult) [DDD]*	**Treatment of keloids and hypertrophic scars:** IV: 0.5mg/cm. Treatments were continued for a maximum of six sessions or till complete flattening of the scar, whichever came earlier, then patients followed for 3months regarding recurrence of lesions and side effects[45].

Maximum Daily Dose Adults*	480 mg
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Kidney impairment No adjustment necessary • Hepatic impairment Oral: In cirrhosis, reduce dose to 20% of normal and monitor ECG. Extended release: Administer 30% of the normal dose in severe hepatic impairment. Extended release (delayed-onset/PM formulation): Initial: 100 mg once daily at bedtime. Injection: There are no dosage adjustments provided in the manufacturer's labeling; use with caution and consider additional ECG monitoring in severe impairment. In cirrhosis, reduce dose to 50% of normal and monitor ECG. Repeated injections in patients with hepatic failure may lead to accumulation. If repeated injections are essential, monitor BP and PR interval closely and use smaller doses. • Elderly Adjustments needed in hypertension indication • Pediatrics Dose adjusted according to adults' recommendations
Prescribing Edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a specialty physician.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	

EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	• Acute decompensated HF with pulmonary edema, hypotension • Bradyarrhythmia: first-, second-, third-degree atrioventricular block or sinus bradycardia • Increase in hepatic enzymes (ASAT/ALAT/AP), and serum bilirubin jaundice • Ventricular fibrillation • Headache, depression, seizure, vertigo, muscle fatigue, rotary nystagmus, respiratory failure, psoriasis • Dermatologic, endocrine & metabolic, GI symptoms and other
Drug Interactions (Contraindicated)	• Aprepitant: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Aprepitant. Do not use this combination (contraindicated) • Asunaprevir: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Asunaprevir. Do not use this combination (contraindicated) • Bilastine: Verapamilm a P-gp/ABCB1 inhibitor can elevate the plasma levels of Bilastine. This combination should be avoided especially in patients with modern to severe renal insufficiency. • Bosutinib: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Busotinib. Do not use this combination (contraindicated)

	• Bromperidol: The latter can decrease the hypotensive effect of Verapamil. In addition, Verapamil can increase the hypotensive effect of Bromperidol. This combination is contraindicated. • Budesonide (topical): Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Budesonide. Do not use this combination (contraindicated) • Dantrolene: the latter can increase the hyperkalemia induced by Verapamil, and also the negative inotropic effect of Verapamil. This combination is contraindicated in the treatment of malignant hyperthermia. • Disopyramide: Verapamil can increase the adverse/toxic effect of Disopyramide. Of particular concern is the potential for profound depression of myocardial contractility. Concurrent use of disopyramide within 48 hours prior to or 24 hours after verapamil should be avoided. Both agents can significantly depress myocardial contractility. • Dofetilide: Verapamil can enhance the plasma levels of Dofetilide. And so, this combination is forbidden. • Domperidone: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Domperidone. Do not use this combination (contraindicated) • Doxorubicin: Verapamil, a P-gp/ABCB1 inhibitor can elevate the plasma levels of Doxorubicin. This combination should be avoided

	• Elacestrant: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Elacestrant. Do not use this combination (contraindicated) • Eletriptan: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Eletriptan. The latter should not be used within 72h of treatment with Verapamil. • Fexinidazole: Verapamil, a bradycardia-causing agent, can increase the arrhythmogenic effect of Fexinidazole. Avoid concomitant use of fexinidazole with bradycardia-causing agents. If patients are, or need to be, treated with drugs known to induce bradycardia, either do not initiate therapy with fexinidazole until such drugs are eliminated from the body (allow a washout period of 5 half-lives for such other drugs), or do not start such drugs until fexinidazole is eliminated from the body (allow a washout period of 7 days after the last fexinidazole dose). • Fezolinetant: Verapamil, a CYP1A2 weak inhibitor, can elevate the plasma levels of Fezolinetant. Do not use this combination (contraindicated) • Flibanserin: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Flibanserin. Do not use this combination (contraindicated). If initiating flibanserin following Verapamil use, start 2 weeks after the last dose of Verapamil. If initiating Verapamil following flibanserin use, start

	Verapamil 2 days after the last dose of flibanserin. • Fosaprepitant: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Fosaprepitant. Do not use this combination (contraindicated) • Fusidic acid (systemic): Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Fusidic acid. Do not use this combination (contraindicated) • Infigratinib: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Infigratinib. Do not use this combination (contraindicated) • Ivabradine: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Ivabradine. Do not use this combination (contraindicated) • Lemborexant: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Lemborexant. Do not use this combination (contraindicated) • Lomitapide: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Lomitapide. Do not use this combination (contraindicated) • Lonafarnib: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Lonafarnib. Do not use this combination (contraindicated) • Methysergide: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Methysergide. Do

	not use this combination (contraindicated) • Neratinib: Verapamil, a P-gp/ABCB1 inhibitor can elevate the plasma levels of Neratinib. This combination should be avoided • Nisoldipine: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Nisoldipine. Do not use this combination (contraindicated) • Orelabrutinib: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Orelabrutinib. Do not use this combination (contraindicated) • Pacritinib: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Pacritinib. Do not use this combination (contraindicated) • Pazopanib: Verapamil, a P-gp/ABCB1 inhibitor can elevate the plasma levels of Pazopanib. This combination should be avoided • Pimozide: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Pimozide. Do not use this combination (contraindicated) • Sertindole: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Sertindole. Do not use this combination (contraindicated) • Simeprevir: Verapamil, a CYP3A4 moderate inhibitor, can elevate the plasma levels of Simeprevir. Do not use this combination (contraindicated)

	• Sirolimus: Verapamil, a P-gp/ABCB1 inhibitor can elevate the plasma levels of Sirolimus. This combination should be avoided • Topotecan: Verapamil, a P-gp/ABCB1 inhibitor can elevate the plasma levels of Topotecan. This combination should be avoided in patients using the oral route. If the IV route is administered, monitor closely for increased topotecan toxicity if combined with Verapamil. • Vincristine: Verapamil, a P-gp/ABCB1 inhibitor can elevate the plasma levels of Vincristine. This combination should be avoided (liposomal formulation)
Special populations	Avoid IV usage for supraventricular tachycardia in newborns and young babies owing to severe apnea, bradycardia, hypotensive responses, and cardiac arrest; Use IV with caution in older kids as cardiac depression and hypotension are possible side effects.
Pregnancy	Category C
Lactation	Distributed in milk; nursing infant doses range from <0.01% to 0.1% of mother's dose; manufacturer suggests refraining from nursing
Contraindications	• Oral / IV use: hypersensitivity to verapamil or any component of the formulation; severe left ventricular dysfunction; hypotension (systolic pressure <90 mm Hg) or cardiogenic shock; sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker); second- or third-degree atrioventricular (AV) block (except in patients with a functioning artificial ventricular pacemaker); atrial flutter or

	fibrillation and an accessory pathway. Complicated myocardial infarction (MI) (ventricular failure manifested by pulmonary congestion); severe congestive heart failure and/or severe left ventricular dysfunction (eg, ejection fraction <40%) unless secondary to a supraventricular tachycardia amendable to oral verapamil; marked bradycardia; concurrent use of ivabradine or flibanserin; concurrent use with beta-blockers in patients with poor ventricular function and in the treatment of hypertension; concurrent use of grapefruit juice; breastfeeding. • Drug interactions
Monitoring Requirements	• Blood Pressure • Heart Rate • Liver function • Kidney function
Precautions	Use has been linked to increased anterograde conduction down the accessory pathway, which can result in ventricular fibrillation, in patients with an accessory pathway (such as those with Wolff-Parkinson-White syndrome) or preexcitation syndrome during an episode of atrial fibrillation or flutter. **Arrhythmia**: Severe hypotension is likely to happen after injection in individuals with broad complex tachycardias unless the etiology is confirmed to be supraventricular. **Attenuated neuromuscular transmission**: Patients with attenuated neuromuscular transmission (Duchenne muscular dystrophy, myasthenia gravis), should be treated

	cautiously and may need a dose reduction. **Hepatic impairment**: In patients with hepatic impairment, use with caution; dosage reduction may be necessary; in cases of severe impairment, monitor hemodynamics and perhaps an ECG. Verapamil IV injections should not be repeated in individuals who have severe liver failure. **Increased intracranial pressure**: When IV verapamil is administered to patients who have supratentorial tumors during the induction of anesthesia, the intracranial pressure increases; use with caution in these patients. **Left ventricular dysfunction**: Due to lack of benefit and/or poorer outcomes with calcium channel blockers generally, avoid usage in individuals with heart failure. **Renal impairment**: Use with caution in individuals who have renal impairment; in cases of severe impairment, monitor hemodynamics and perhaps ECG. Potential toxic dose in patients <6yo: 15mg/kg
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

No available data was found from the searched HTA bodies, such as the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Scheme (PBS) regarding their recommendations for the use of verapamil in burns.

Conclusion statement – VERAPAMIL

This drug, only cited by the international guidelines, is advised for young hypertrophic and keloid scarring, without detailing its mechanism of action.

However, no data from HTA bodies were found to support the recommendation of verapamil use in burns.

2.11 Calcium Salts

2.11.1 Calcium Gluconate

Dosages expressed in terms of the calcium gluconate salt are based on a solution concentration of 100 mg/mL (10%) containing 0.465 mEq (9.3 mg) elemental calcium per mL, except where noted. Profound and precipitous hypocalcemia may occur after exposure to higher hydrofluoric acid concentrations to even a small surface area. Additional treatment measures may be required (e.g., magnesium)

Table 25. Calcium Gluconate Drug Information

SCIENTIFIC NAME CALCIUM GLUCONATE	
Trade Name(s) on Saudi Market	CALCIUM GLUCONATE® 10% - 1%
SFDA Legal status	Prescription
SFDA	Registered, labeled indication
FDA	Registered (June 2017), Not indicated
EMA	Not registered
MHRA (UK Market)	Registered, labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Calcium salt
Drug Sub-Class	N/A
ATC Code	A12AA03
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for injection Solution Solution for infusion
Route of Administration	IV use
Dose (Adult) [DDD]*	**IV:** 2 g immediately or as soon as possible after exposure (before serum calcium level is known). Monitor serum calcium level: if serum calcium level is not within normal range, then give an

	additional 1 g, followed by 4 g over 1 hour, as needed, to maintain serum calcium levels. **IV (Bier block technique) (off-label route):** Add 1.5 g (15 **mL** of a 10% solution) to 35 mL of NS and infuse over 2 minutes using a Bier block technique.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment In patients with chronic renal disease who are asymptomatic or who have stable hypocalcemia with only minor symptoms (such paresthesia), IV calcium should not be administered as the first course of treatment. Start with the lowest dose possible because buildup with renal disease may develop and future doses may need to be adjusted based on blood calcium values • Hepatic impairment No first dosage modification is required; serum calcium values should be used to determine subsequent doses. Equally quick rises in ionized concentrations are seen in patients undergoing liver transplantation in the anhepatic stage, indicating that calcium gluconate does not require hepatic metabolism for the release of ionized calcium. • Pediatrics In this indication, IV route is not recommended in pediatric patients • Interactions Concomitant drug therapy may expose to interactions – check before use
Prescribing Edits*	MD, EU
AGE (Age Edit): N/A	

CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a specialty physician (intensivist).	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): Administer immediately after exposure.	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	• Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, decreased blood pressure, syncope, vasodilation • Central nervous system: Anxiety, feeling hot • Gastrointestinal: Unusual taste (chalky) • Neuromuscular & skeletal: Tingling sensation
Drug Interactions (Contraindicated)	• Baloxavir marboxil: calcium gluconate can decrease the plasma levels of baloxavir marbozil. Avoid coadministration of baloxavir marboxil with polyvalent cation-containing products (eg, aluminum, calcium, iron, magnesium, selenium, zinc). The duration of dose separation required to minimize this interaction has not been investigated or established. • Calcium acetate: calcium gluconate can increase the adverse/toxic effect of calcium acetate. Concurrent use of other calcium salts with calcium acetate should be avoided. This combination is particularly dangerous in patients with other risk

	factors for hypercalcemia, such as those with end-stage renal disease. • Levonadifloxacin: calcium gluconate can diminish the plasma levels of levonadifloxacin. Avoid any concomitant use of oral levonadifloxacin with calcium salts, even if administration of the individual agents were to be separated by several hours. • Unithiol: Unithiol can diminish the therapeutic effect of calcium gluconate. Do not concomitantly use these drugs.
Special populations	N/A
Pregnancy	Patients who are pregnant and women who are not pregnant both need calcium. There isn't much information available on antidotes used during pregnancy. Antidotes should be supplied to pregnant patients if there is a clear rationale for usage and should not be withheld due to concerns about teratogenicity. In general, antidotes should take into consideration the health and prognosis of the mother.
Lactation	The manufacturer advises taking into account the danger of baby exposure, the advantages of nursing for the child, and the advantages of treatment for the mother while deciding whether to breastfeed during therapy.
Contraindications	Hypercalcemia; concomitant use of IV calcium gluconate with ceftriaxone in neonates (≤28 days of age).
Monitoring Requirements	• Serum calcium every 4 to 6 hours (during intermittent infusion), every 1 to 4 hours (during continuous

	infusion), or every 4 hours in patients with renal impairment; • albumin, phosphate, and magnesium; • vitals and ECG when appropriate. • Monitor infusion site.
Precautions	• Extravasation: Parenteral calcium is a vesicant; make sure the catheter or needle is in the right place before and throughout the infusion. Avoid extravasation; the consequences might be disastrous (for example, extensive tissue necrosis). Keep an eye on the IV site. • GI effects: Oral calcium supplements (particularly carbonate salt) may cause constipation, bloating, and gas. • Hyperphosphatemia: Use with caution in individuals with severe hyperphosphatemia as high phosphorus and calcium levels may cause calcium-phosphate precipitation in the pulmonary artery system and soft tissue. • Hypokalemia: Patients with severe hypokalemia should use this medication with care since sudden increases in blood calcium levels might cause potentially fatal cardiac arrhythmias. • Hypomagnesemia: Since hypomagnesemia frequently results in hypocalcemia, treating hypocalcemia in individuals who also have hypomagnesemia may be challenging. If the initial therapy for hypocalcemia is ineffective, check blood magnesium levels and treat hypomagnesemia (if required).

	• Calcium-containing kidney stones: Exercise caution when giving calcium supplements to individuals who have a history of kidney stones. • Renal impairment: Patients with chronic renal failure should use this medication with caution to prevent hypercalcemia; regular monitoring of blood calcium and phosphorus levels is required. • Aluminum: The parenteral product may include aluminum; excessive dosages, extended usage, or renal impairment may result in dangerous aluminum concentrations. Due to immature renal function and aluminum ingestion from other parenteral routes, premature newborns are more at risk. CNS and bone toxicity are linked to parenteral aluminum intake of >4 to 5 mcg/kg/day; tissue loading may occur at lower levels. See the labeling provided by the manufacturer. • Appropriate product selection: Calcium comes in a variety of salt forms. When ordering and giving calcium, the salt form must be carefully considered. If the wrong salt is chosen or substituted without the necessary dose adjustment, significant over- or under-dosing may follow. • IV administration: Unless the patient is experiencing cardiac arrest, avoid very fast IV administration (do not exceed 200 mg/minute for adults and 100 mg/minute for pediatric patients). This can lead to vasodilation, hypotension,

	bradycardia, arrhythmias, syncope, and cardiac arrest. • Oral administration: Vitamin D and calcium taken orally will improve calcium absorption. • Topical administration: Keep out of the eyes; do not administer orally. • Tartrazine: Some goods may contain tartrazine, which in some people might lead to allergic reactions.
Black Box Warning	N/A
REMS*	N/A

Conclusion Statement – CALCIUM GLUCONATE

IV calcium gluconate is recommended as an antidote due to hydrogen fluoride intoxication and burns in austere conditions. However, no data from HTA bodies were found to support the recommendation of calcium gluconate use.

2.12 Fluids

2.12.1 Lactated Ringer

The principal use of crystalloids, particularly lactated ringers, is their capacity to fill vessels and so act as an IV resuscitation fluid. Depending on the situation and the patient, specific quantities are administered.

Table 26. Lactated Ringer Drug Information

SCIENTIFIC NAME LACTATED RINGER	
Trade Name(s) on Saudi Market	Compound sodium lactate infusion®, Lactated Ringers®, Lactated Ringers injection®
SFDA Legal status	Prescription
SFDA	Registered, labeled indication
FDA	Registered (august 2020), labeled indication
EMA	Not registered
MHRA (UK Market)	Not registered
PMDA	Not registered

Indication (ICD-10)	T30
Drug Class	Electrolyte supplement
Drug Sub-Class	N/A
ATC Code	B05XA31 B05BB01
Pharmacological Class (ASHP)	40:36 Irrigating Solutions
DRUG INFORMATION	
Dosage Form	Solution Solution for injection
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	Fluid resuscitation (off-label): IV for a minimum of 30ml/kg needs to be administered within 3h post shock or hypoperfusion. Need to administer vasopressors in parallel to stabilize MAP to >65mmHg. Some patients may require a more rapid administration or a bigger volume
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Septic shock: Infants, Children, and Adolescents: IV:** 10 or 20 mL/kg; reassess often and repeat as needed
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Pediatrics In septic shock IV 10 or 20ml/kg • Drug interactions
Prescribing Edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by an intensivist (critical care physician).	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	

SAFETY	
Main Adverse Drug Reactions (Most common)	• Hypersensitivity: non immune anaphylaxis, hypersensitivity reaction • Fever • Injection site infections • Phlebitis, thrombosis • Extravasation, hypervolemia
Drug Interactions (Contraindicated)	N/A
Special populations	Pediatrics: use with vigilance in neonates and infants less than 6m of age
Pregnancy	Category C, use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done.
Lactation	Use with vigilance
Contraindications	• Injection: Hypersensitivity to sodium lactate or any ingredient of the product; concomitant use with ceftriaxone in neonates (≤28 days). • Irrigation: Parenteral administration; irrigation during electrosurgical procedures. • Lactic acidosis • Hypernatremia or fluid retention • CHF, shock, respiratory alkalosis or other conditions that increase lactate • Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.
Monitoring Requirements	• Serum sodium, potassium, chloride, calcium, bicarbonate concentrations • Acid-base balance • Osmolarity; I & O, weight • Monitor infusion site.
Precautions	• Alkalosis: Administer with extreme vigilance, if at all, to patients with

	alkalosis or at risk for alkalosis. Lactate is metabolized to bicarbonate and may worsen metabolic alkalosis. • Cardiovascular: Vigilant use in patients with cardiovascular disease or insufficiency. Use with caution in patients with heart failure. • Diabetes: Use with caution in patients with DM2; lactate is a substrate for gluconeogenesis. • Fluid overload: May occur, resulting in dilution of serum electrolyte concentrations, overhydration, congested states, pulmonary edema, or acid-base imbalance. Use with extreme caution, if at all, in patients with hypervolemia, overhydration, edema, or conditions that may cause sodium and/or fluid overload. • Hepatic dysfunction Use with extreme vigilance, if at all, in patients with severe hepatic impairment because of impaired lactate metabolism. • Hypercalcemia: Use with caution in patients with hypercalcemia or conditions predisposing to hypercalcemia (eg severe kidney impairment, granulomatous diseases associated with increased calcitriol synthesis such as sarcoidosis or renal calculi). • Hyperkalemia: Use with extreme caution, if at all, in patients with hyperkalemia or conditions predisposing to hyperkalemia (eg, severe kidney impairment, adrenocortical insufficiency, acute dehydration, extensive tissue injury or burns).

	• Significant hypokalemia may manifest • Hypersensitivity reactions: May occur. Discontinue infusion immediately if signs/symptoms of a hypersensitivity reaction develop. • Kidney dysfunction: Use with extreme caution, if at all, in patients with severe renal insufficiency. May cause potassium and/or sodium retention. • Injection: Not for the treatment of lactic acidosis or severe metabolic acidosis, or the correction of severe acidotic states. LR is insufficient to produce a useful effect in case of severe potassium deficiency and should not be used for this purpose. Should not be administered simultaneously with citrate anticoagulated/preserved blood through the same administration set because of the likelihood of coagulation. Should not be administered rapidly or overdosed. • Irrigation: Use with caution when used for continuous irrigation or in body cavities; possible absorption and circulatory overload may occur.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of burn treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE) for Lactated Ringer.

Table 27. Lactated Ringer HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Lactated Ringer	NICE	If patients require IV fluid resuscitation, provide crystalloids with sodium concentrations between 130 and 154 mmol/l with a 500 ml bolus over less than 15 minutes. Tetrastarch should not be used for fluid resuscitation[20].

Conclusion statement – LACTATED RINGER

Crystalloid solution Ringer is recommended as a fluid resuscitation agent in the case of severe burns to limit hypovolemic shock and its consequences.

2.12.2 Human Albumin

Table 28. Human Albumin Drug Information

SCIENTIFIC NAME HUMAN ALBUMIN	
Trade Name(s) on Saudi Market	PLASBUMIN® 20% solution for IV injection, UMAN ALBUMIN® 20% solution for infusion, ZENALB-20® sterile liquid, ALBUTEIN® soln. for injection, HUMAN ALBUMIN® 5%, HUMAN ALBUMIN 50G-I and 200G-I TAKEDA®, HUMAN ALBUMIN 20% ® +infusion set, HUMAN ALBUMIN® 5%-20%, HUMAN ALBUMIN GRIFOLS® 20% IV injection, ALBUREX®, FLEXBUMIN 200gm/L ® solution for infusion
SFDA Legal status	Prescription
SFDA	Registered, labeled indication
FDA	Registered (October 2005), labeled indication
EMA	Registered, labeled indication
MHRA (UK Market)	Registered, labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Blood factors
Drug Sub-Class	Protein based therapies

ATC Code	B05AA01
Pharmacological Class (ASHP)	16:00 Blood Derivatives
DRUG INFORMATION	
Dosage Form	Suspension for injection Solution Solution for infusion
Route of Administration	IV use
Dose (Adult) [DDD]*	Hypovolemia: It is often preferable to use 5% albumin to replenish lost volume. If hemodynamic stability is not obtained after the initial dose of 12.5 to 25 g (250 to 500 mL), repeat the IV dose as necessary after 15 to 30 minutes. Note: In patients with sepsis or septic shock, consider whether high quantities of crystalloid treatment are ineffective. Individual responses should be taken into account while adjusting the volume given and the pace of infusion.
Maximum Daily Dose Adults*	5%, 25%: Typically, not recommended to exceed 1 to 2 mL/minute in patients without shock.
Dose (pediatrics)	**Hypovolemia, plasma volume expansion, including hypovolemic shock:** Infants, Children, and Adolescents: 5% albumin: IV: 0.5 to 1 g/kg/dose (10 to 20 mL/kg/dose) over 5 to 10 minutes. Note: Usual adult dose: 12.5 to 25 g/dose (250 to 500 mL/dose). May repeat after 15 to 30 minutes if response is not adequate.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment No adjustment required, vigilant use • Hepatic impairment No adjustment required, vigilant use • Pediatrics

	In hypovolemia management, 5% albumin is also used, and doses vary between 0.5 to 1g/kg/dose over 5 to 10min. Same adult requirements for renal and hepatic impairment.
Prescribing Edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by an intensivist (critical care physician).	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	• Cardiovascular: Flushing, heart failure, hypotension, tachycardia, acute myocardial infarction, atrial fibrillation • Dermatologic : Pruritus, skin rash, urticaria • Gastrointestinal : Nausea, vomiting, dysgeusia, sialorrhea • Nervous system: Chills, rigors, headache • Respiratory: Bronchospasm, dyspnea, pulmonary edema • Anaphylactic shock, hypersensitivity reaction • Hyperchloremic metabolic acidosis
Drug Interactions (Contraindicated)	There are no known significant interactions.
Special populations	Patients who must follow a sodium limit should use this medication with care. Albumin 5% and 25% solutions, which are regarded as isotonic with plasma,

	had sodium concentrations of 130 to 160 mEq/L.
Pregnancy	Products made from pooled human plasma are manufactured with albumin, an endogenous protein. When nonprotein colloids are contraindicated, use in pregnant individuals may be investigated.
Lactation	The manufacturer advises taking into account the danger of baby exposure, the advantages of nursing for the child, and the advantages of treatment for the mother while deciding whether to breastfeed during therapy.
Contraindications	• Hypersensitivity to albumin or any ingredient of the product; • Severe anemia, • Heart failure; patients at risk of volume overload (eg, patients with kidney insufficiency, severe anemia, stabilized chronic anemia, or heart failure); dilution with sterile water for injection (may cause hemolysis or acute kidney failure).
Monitoring Requirements	• Electrolytes, • Hemoglobin/hematocrit, • Urine output regularly; • Monitor hemodynamic parameters, BP, heart rate, volume status, and signs and symptoms of pulmonary edema, central venous pressure, pulmonary artery occlusion pressure.
Precautions	• Hypersensitivity: Anaphylactic or severe allergic response might happen. In the event that allergic or anaphylactic responses are detected, stop using the medication right away and handle properly. • Abnormal coagulation: Significant replacement amounts may cause

	abnormal coagulation. Observe and, if necessary, replenish blood ingredients. • Electrolyte imbalance: Electrolyte imbalance can be caused by high replacement volumes. Replace or maintain electrolytes as needed by keeping an eye on them. • Hemodynamic effects: All patients should have their hemodynamic parameters continuously monitored since they might experience cardiac or respiratory failure, renal failure, or an increase in intracranial pressure. • Heart failure, pulmonary edema, hypertension, hemorrhagic diathesis, cirrhosis, and esophageal varices are a few diseases where hypervolemia and its repercussions or hemodilution may raise the risk of severe effects. Adjust the rate of administration in accordance with the solution concentration and hemodynamic state; use fast infusions to closely monitor. When a patient has a history of cardiovascular illness, fast infusions should be avoided since they might lead to pulmonary edema and volume overload. At the first indications of cardiovascular overload, such as headache, dyspnea, jugular venous distention, rales, or abnormally high levels of systemic or central venous blood pressure, stop the medication. Every patient has to be kept an eye out for hypervolemia symptoms including pulmonary edema. track your blood pressure. • Critical illness: Patients with traumatic brain damage shouldn't

	get resuscitation since there is a higher fatality rate in this demographic. • Hepatic impairment: Patients who have this condition should use caution since a high protein intake might aggravate or even cause encephalopathy. • Use with caution in people who have renal impairment since a protein load can cause azotemia. Patients using albumin solution for chronic renal insufficiency may be at risk for aluminum buildup and possible toxicities (such as hypercalcemia, vitamin D-refractory osteodystrophy, anemia, and severe progressive encephalopathy). • Aluminum: The parenteral product may include aluminum; excessive dosages, chronic usage, or renal failure may result in dangerous aluminum concentrations. Due to immature renal function and aluminum ingestion from other parenteral routes, premature newborns are more at risk. CNS and bone toxicity are linked to parenteral aluminum intake of >4 to 5 mcg/kg/day; tissue loading may occur at lower levels. See the labeling provided by the manufacturer. • Dilution: Avoid dilution of 5% albumin for injection with sterile water as this may cause hemolysis and/or renal failure. • Human plasma: A substance made from human plasma that may include infectious agents that might spread illness. The danger is decreased by screening donors and

	testing, inactivating, or removing certain viruses. It is important to report any infections considered to be spread by this medication. • Certain formulations may contain latex rubber, potassium and/or sodium • Due to the potential of intraventricular hemorrhage (from the fast growth of the intravascular volume), use the 25% concentration in newborns with the utmost caution; infuse gently. When 5% human albumin is occasionally unavailable, 5% solutions can occasionally be made by diluting 25% human albumin with NS or with D5W (if sodium load is a concern); however, avoid diluting albumin solutions with sterile water as this can cause hypotonic-associated hemolysis, which can be fatal.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of fluid resuscitation induced by burns treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE) for human albumin.

Table 29. Human Albumin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Human Albumin	NICE	Consider human albumin solution 4% to 5% for fluid resuscitation only in patients with severe sepsis[20].

Conclusion statement – HUMAN ALBUMIN

Human albumin has been recommended in patients with extremely severe burns, meaning that more than 30% of their body surface is burned. Colloids have the potential to increase oncotic pressure, which would reduce fluid loss and the quantity of crystalloids needed in the first phase of treating severe burns. Therefore,

by lowering issues related to fluid overload, such as acute respiratory distress syndrome, congestive acute renal damage, and abdominal compartment syndrome, colloid injection may improve prognosis. Furthermore, human albumin could have anti-inflammatory and antioxidant qualities.

According to NICE, this solution can also be used as a fluid resuscitation agent in patients with severe sepsis.

2.13 Vaccines

Tetanus prophylaxis

Tetanus prophylaxis should be provided as soon as feasible after a wound but should still be given to individuals who show up late for treatment. This is due to the incubation period's wide range; the majority of instances take place within 8 days, but it can also last up to 21 days. Human tetanus immune globulin administration longer than a week or so after the injury is likely to be of limited value for individuals who have previously had tetanus vaccinations but are out of date. Td or Tdap should be administered simultaneously, and human tetanus immune globulin should be given up to 21 days after the injury for individuals who are believed to be entirely unvaccinated.

Table 30. Tetanus Prophylaxis Administration Depending on the Wound and Patient's Status

Previous doses of tetanus toxoid	Clean and mild wound injury		Other types of wounds	
	Vaccine containing Tetanus Toxoid	Humanized tetanus immunoglobulins	Vaccine containing Tetanus Toxoid	Humanized tetanus immunoglobulins
< 3 doses or unknown	Administer	Don’t administer	Administer	Administer
≥ 3 doses	Administer only if last dose given ≥ 10y ago	Don’t administer	Administer only if last dose taken ≥ 5y ago	Don’t administer

DT, DTP/DTwP, DTaP, Td, Tdap, or TT (no longer available in the United States) are all possible dosage forms for tetanus toxoid.

For instance, but not restricted to, wounds that have been punctured, avulsed, or have been damaged by projectiles, crushing, burns, or frostbite.

The optimal vaccine formulation is determined by the patient's age and immunization history:

- DTaP, 7 years old.
- Tdap for under immunized youngsters between the ages of 7 and 11 who have never had it before. Tdap should be given again to children who had it when they were 7 to 9 years old when they are 11 to 12 years old.
- 11 years: For those patients in this age range who have not previously received Tdap, a single dose of Tdap is recommended over Td; otherwise, Td or Tdap may be provided without preference. Each pregnancy should include Tdap for expectant mothers.

250 units intramuscularly at a separate location from the tetanus toxoid; if human tetanus immune globulin is not available, intravenous immune globulin should be given. Regardless of their prior tetanus vaccination history, those with infected wounds who have HIV infection or severe immunodeficiency should additionally get human tetanus immune globulin.

The vaccination series should be finished if required.

Booster dosages used more frequently than every five years are unnecessary and may exacerbate side effects[46].

2.13.1 Tetanus Vaccine

Table 31. Tetanus Vaccine Drug Information

SCIENTIFIC NAME TETANUS VACCINE	
Trade Name(s) on Saudi Market	TETAVAX® 40 I.U INJ., TRIPACEL® VACCINE, ARAPENTA® Injection, INFANRIX HEXA® VACCINE, STABLIX® 0.5 ML SUSPENSION FOR INJECTION Vials. ADACEL® 0.5 ml suspension for injection, BOOSTRIX® VACCINE, HEXAXIM® vaccine, NIMENRIX®, TETRAXIM®, Pentaxim®, Stablix® 0.5 ml Ampules, Tedalix®
SFDA Legal status	Prescription
SFDA	Registered, labeled indication

FDA	Registered (December 1991), labeled indication
EMA	Registered (July 2005)
MHRA (UK Market)	Registered
PMDA	Registered, Not indicated
Indication (ICD-10)	T30
Drug Class	Vaccine
Drug Sub-Class	Toxoid vaccine
ATC Code	J07AM01 / 51 J01CA J07CA11 J07CA09 / 02 / 06 J07AJ52 J07AH08
Pharmacological Class (ASHP)	80:00 Antitoxins, Immune Globulins, Toxoids, and Vaccines
DRUG INFORMATION	
Dosage Form	Suspension for injection Solution for injection Powder and suspension for injection Suspension Powder and solvent for solution for injection
Route of Administration	Intramuscular use
Dose (Adult) [DDD]*	See table 32
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	See table 32
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Renal impairment No adjustment required • Hepatic impairment No adjustment required • Pediatrics Refer table 7. No adjustment required in renal or hepatic impairment
Prescribing Edits*	AGE, PE

AGE (Age Edit): Children younger than 7 years of age receive DTaP or DT, while older children and adults receive Tdap and Td.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): Administer as recommended according to the history of tetanus immunization doses.	
SAFETY	
Main Adverse Drug Reactions (Most common)	Frequency not defined: • Malaise • Rash • Arthus reaction • Nausea • Hypotension • Fever • Guillain-Barre syndrome • EEG disturbances
Drug Interactions (Contraindicated)	Elivaldogene autotemcel: Elivaldogene autotemcel can increase the side / toxic effect of vaccines. Administration of vaccines is not recommended in the 6 weeks before myeloablative conditioning, and until hematologic recovery after elivaldogene autotemcel treatment. Childhood vaccines should be administered prior to myeloablative conditioning when possible.
Special populations	Pediatrics and altered immunocompetence (refer Precautions section)
Pregnancy	Category C: use with caution if benefits outweigh risks
Lactation	Not known if excreted in breast milk

Contraindications	• Hypersensitivity to tetanus toxoid or any other ingredient in the product • Delay if acute / febrile illness • Progressive neurologic disorders • History of transient thrombocytopenia following an earlier immunization against diphtheria and/or tetanus
Monitoring Requirements	• Hypersensitivity and syncope for 15min following administration • If seizure-like activity associated with syncope occurs, maintain patient in supine or Trendelenburg position to reestablish adequate cerebral perfusion.
Precautions	• Adults: DT toxoids preferred • For passive immunization, use Tetanus Immune Globulin (TIG). • Adsorbed to aluminum for greater immunogenicity • Need 3 doses for primary immunization • Alternative is fluid toxoid for use if hypersensitive to aluminum • Need four 0.5 mL doses for primary immunization • Children <7 years ➢ Not recommended, use instead: ➢ Diphtheria, Tetanus toxoids, and Acellular Pertussis vaccine (DTaP), or ➢ Diphtheria, Tetanus toxoids, and Pertussis vaccine (DTP), or ➢ Diphtheria and Tetanus Toxoids (DT) • Anaphylactoid shock • Arthus-type hypersensitivity Patients with a history of severe local reaction (Arthus-type) following a previous diphtheria toxoid or tetanus toxoid-containing vaccine dose should not be given further routine or

	emergency doses of Td unless ≥10 years since most recent dose, even if using for wound management with wounds that are not clean or minor; these patients generally have high serum antitoxin levels • Shoulder injury related to vaccine: if performed too high on the arm can cause shoulder bursitis and tendinopathy. Use proper techniques for administration • Syncope: has been reported; procedures should be in place to avoid injuries from falling and to restore cerebral perfusion if syncope occurs • Acute illness: Depending on the severity of the symptoms and the underlying cause of the illness, it is decided whether to provide or postpone vaccination in cases of recent or ongoing febrile illness. Patients with moderate or severe acute illnesses (fever included) should postpone immunization; those with mild acute illnesses shouldn't. • Bleeding disorders: Use with caution in patients with bleeding problems (particularly those with thrombocytopenia); bleeding or hematomas may develop after IM delivery; if the patient is receiving antihemophilia or any comparable medication, IM injection might be planned soon after such therapy is provided. • Guillain-Barre syndrome: Use with caution if Guillain-Barré syndrome occurred within 6 weeks of prior tetanus toxoid-containing vaccine

	• Anticoagulant therapy: use with caution, bleeding/hematoma may occur • Altered immunocompetence: Postpone vaccination during periods of severe immunosuppression (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy [including high-dose corticosteroids]) if appropriate; may have a reduced response to vaccination. • Some products may contain latex, thimerosal, aluminum, neomycin, polymyxin B, polysorbate 80.
Black Box Warning	N/A
REMS*	N/A

Conclusion Statement – TETANUS VACCINE

Vaccination by tetanus toxoid is considered one of the initial steps of wound care management. And so, according to the patient's vaccination status, it is advised to administer the vaccine and / or immunoglobulins to limit possible infection and its consequences. However, no data from HTA bodies were found to support the recommendation of tetanus vaccine use.

2.14 Other Drugs

This section outlines the drugs that can be used for the management of burns but that are currently **not SFDA registered**.

2.14.1 Hydrocodone

Hydrocodone was approved by the FDA in 1943 (initial approval) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate[47].

US Boxed warnings:

- Addiction, abuse, and misuse
- Opioid analgesic risk evaluation and mitigation strategy (REMS)
- Life-threatening respiratory depression

- Accidental ingestion
- Neonatal opioid withdrawal syndrome
- Cytochrome P450 3A4 Interaction
- Risks from concomitant use with benzodiazepines or other CNS depressants
- Interaction with alcohol (capsule, extended release, 12-hour)

2.14.2 Butorphanol

Butorphanol received its initial approval by the FDA in 1978 for pain management[48].

Regarding the HTA bodies' recommendations for the use of butorphanol in burn-related pain cases, no information was found from the searches conducted by the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Scheme (PBS).

2.14.3 Nalbuphine

Nalbuphine was initially approved by the FDA on 19/03/1998 for the relief of moderate to severe pain[49].

Special alerts:

The FDA has issued a drug safety communication to announce safety-related updates to the prescribing information for immediate-release (IR) and extended-release (ER)/long-acting (LA) opioid analgesics, including updates to Boxed Warnings, Indications and Usage, Dosage and Administration, Warnings and Precautions, and the Medication Guide. These safety labeling changes are intended to provide clarity on appropriate patient populations for opioid treatment, appropriate dosage and administration, and updated information on the risks associated with opioid use. The required safety labeling changes include stating:

- the risk of overdose increases as the dosage increases for all opioid pain medicines;
- IR opioids should not be used for an extended period of time unless a patient's pain remains severe enough to require them and alternative treatment options continue to be inadequate;
- many acute pain conditions treated in the outpatient setting require no more than a few days of an opioid pain medicine;

- it is recommended to reserve ER/LA opioid pain medicines for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate; and
- a warning about opioid-induced hyperalgesia (OIH), including information on differentiating OIH symptoms from those of opioid tolerance and withdrawal.

US Boxed warnings:

- Life-threatening respiratory depression
- Risks from concomitant use with benzodiazepines or other CNS depressants

2.14.4 Bacitracin

Bacitracin is a topical antibiotic ointment widely used by both medical professionals and the general public to treat minor skin injuries, including cuts, scrapes, and burns.

In 1948, the United States Food and Drug Administration (FDA) granted approval for the short-term prevention and treatment of both acute and chronic localized skin infections using bacitracin[50].

2.14.5 Cerium Nitrate

Cerium nitrate (CN) in combination with silver sulfadiazine (SSD) cream has been utilized or promoted in numerous countries for several decades, with burn surgeons praising its advantages in various publications. However, it is important to note that CN+SSD cream is not universally employed and does not have approval from the U.S. Food and Drug Administration (FDA)[51].

The use of cerium nitrate was mentioned in International Society for Burn Injuries (ISBI) Practice Guidelines for Burn Care (2016, 2018) as an option for the management of full thickness burns when early surgical excision and wound closure cannot be performed[11].

2.14.6 Topical Honey

Honey-based devices approved by the FDA are recommended for treating various wound types, including wounds with low to moderate-to-heavy exudate, diabetic foot ulcers, leg ulcers, pressure ulcers, burns, traumatic wounds, surgical wounds, chronic wounds, or colonized acute wounds, among other specified indications[52].

The use of topical honey was mentioned in International Society for Burn Injuries (ISBI) Practice Guidelines for Burn Care (2016, 2018) as an option for the management of superficial partial thickness burns[11].

2.14.7 Mafenide Acetate

On June 5, 1998, the Food and Drug Administration (FDA) approved NDA 019832 for SULFAMYLON® (Mafenide Acetate, USP) Powder for 5% Topical Solution, under the Agency's accelerated approval regulations. It was approved for "for use as an adjunctive topical antimicrobial agent to control bacterial infection when used under moist dressings over meshed autografts on excised burn wounds"[53].

However, on Nov 30,2022, The Food and Drug Administration (FDA) is withdrawing approval of new drug application (NDA) 019832 for SULFAMYLON® (Mafenide Acetate, USP) Powder for 5% Topical Solution, held by Mylan Institutional, Inc., a Viatris company (Mylan).

The use of mafenide acetate was mentioned in International Society for Burn Injuries (ISBI) Practice Guidelines for Burn Care (2016, 2018) as an option for the management of deep or infected burns and deep burns of the ear[11].

2.14.8 Acetic Acid

Acetic acid is not approved by the FDA for topical wound irrigation[54].

The use of acetic acid was recommended by the International Society for Burn Injuries (ISBI) Practice Guidelines for Burn Care (2016, 2018) as an option for the management of chronic, heavily colonized, and infected wounds[11].

2.14.9 Iodine

Most OTC drugs are not reviewed and approved by the FDA; however, they may be marketed if they comply with applicable regulations and policies. FDA has not evaluated whether this product complies.

The British Burn Association (BBA) recommends the use of povidone-iodine solution for the management of cold burns (frostbites).

The International Society for Burn Injuries (ISBI) Practice Guidelines for Burn Care (2016, 2018) recommends the use of iodine for graft donor site with minimal to moderate exudate and for partial thickness burn with moderate to high exudate.

2.14.10 Lorazepam

On September 30, 1977, FDA approved Ativan (lorazepam) oral tablet for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms.

The American Burn Association (ABA) Guidelines (2017, 2020) recommends the use of lorazepam to reduce anxiety and prevent hallucinations in patients using ketamine.

2.14.11 Vaseline

Most OTC drugs are not reviewed and approved by FDA; however, they may be marketed if they comply with applicable regulations and policies. FDA has not evaluated whether this product complies[55].

The Société Française d'Anesthésie et de Réanimation (SFAR) Management of Severe Thermal Burns in the Acute Phase in Adults and Children (2020) recommends the use of fatty substance (such as Vaseline) as a non-pharmacological approach to pain management since it causes chilling to the limited injured surfaces and helps with the management of the burns.

No available data was found from the searched HTA bodies, such as the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Scheme (PBS) regarding their recommendations for the use of Vaseline in burns.

2.14.12 Cetrimide

This drug has not been found by the FDA to be safe and effective, and this labeling has not been approved by the FDA[56].

The World Health Organization (WHO) Burn Management Guidelines (2020) recommends that the wound should be cleaned with 0.25% chlorhexidine solution, 0.1% **cetrimide** solution or another mild water-based antiseptic.

2.14.13 Dakin's Solution

This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA[57].

The use of Dakin's solution was mentioned in International Society for Burn Injuries (ISBI) Practice Guidelines for Burn Care (2016, 2018) as an option for the management of chronic, heavily colonized, and infected wounds[11].

2.14.14 Triamcinolone Acetonide

This topical corticosteroid has been mentioned as a good option is specific types of skin scars.

SCIENTIFIC NAME TRIAMCINOLONE ACETONIDE	
FDA	Registered (June 2008), Not indicated
EMA	Not registered
MHRA (UK Market)	Registered, labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Corticosteroid
Drug Sub-Class	Glucocorticoid
ATC Code	D07CB01
Pharmacological Class (ASHP)	84:06.08 Corticosteroids
DRUG INFORMATION	
Dosage Form	Ointment Cream
Route of Administration	Topical
Dose (Adult) [DDD]*	Apply thin film to affected areas BID/QID
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	• Kidney and hepatic impairment No adjustment necessary • Pediatric population Dosage should be based on severity of disease and patient response; use smallest amount for shortest period of time to avoid HPA axis suppression. Therapy should be discontinued when control is achieved. As for adults, no adjustment needed in kidney and/or hepatic impairment • Drug interactions

	Several interactions exist with corticosteroids, and so caution is needed.
Prescribing Edits*	MD
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a specialty physician.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
Maximum Daily Dose Adults*	Not mentioned
SAFETY	
Main Adverse Drug Reactions (Most common)	• Dermatologic: Acneiform eruption, allergic contact dermatitis, atrophic striae, desquamation, folliculitis, hypertrichosis, hypopigmentation, local dryness, maceration of the skin, miliaria, perioral dermatitis, skin atrophy, skin blister • Endocrine & metabolic: Cushing syndrome, glycosuria, HPA-axis suppression, hyperglycemia • Gastrointestinal: Oral mucosa changes (paste; atrophy or maceration) • Infection: Secondary infection • Local: Application site burning, application site irritation, application site pruritus
Drug Interactions (Contraindicated)	Aldesleukin: Triamcinolone may decrease the antineoplastic effect of aldesleukin (AVOID COMBINATION)
Special populations	• Older adult: Topical corticosteroids should be used with caution in the elderly and at the smallest effective dose for the shortest time feasible

	due to the possibility of side effects associated with systemic absorption. • Children may absorb proportionately more after topical administration and may be more vulnerable to systemic consequences. In children using topical corticosteroids, HPA axis suppression, cerebral hypertension, and Cushing syndrome have all been documented. The rate of growth in young individuals should be frequently checked since prolonged usage may slow it down.
Pregnancy	Category C, here may be an increased risk of low birth-weight infants following maternal use of potent or very potent topical products, especially in high doses, although this risk is likely to be low. Topical corticosteroids may be used to treat atopic dermatitis in pregnant individuals when first-line therapies such emollients are ineffective. Topical corticosteroids are categorized according to their potency, which is influenced by both the medicine and its formulation (such as a cream, gel, or salt form). It is generally advised to use the least powerful substance during pregnancy in moderation. Strong to very strong topical corticosteroids should only be used as an alternate therapy in very small doses when under obstetrical care. Mild to moderate potency corticosteroids are preferable. Pregnant women should take caution when applying topical corticosteroids to areas prone to striae development (such as the belly, breasts, and thighs) and places with high percutaneous

	absorption (such as the armpit, skin folds, or vulva).
Lactation	Although it is unknown if enough triamcinolone is absorbed after topical application to create measurable levels in breast milk, systemic corticosteroids are known to be present in breast milk. Topical corticosteroids are often regarded as suitable for treatment in patients who are nursing, notwithstanding the manufacturer's cautionary advice. Avoid using topical corticosteroids to the region around the nipple and areola until nursing has ended; when a high-potency topical corticosteroid was given to the nipple of a breastfed newborn, hypertension was seen. Apply topical corticosteroids as soon as possible after weaning, then wipe the nipples before the next meal if necessary.
Contraindications	• Hypersensitivity to triamcinolone or other ingredient of the product • Underlying fungal, bacterial, or viral infection • Ophthalmic use
Monitoring Requirements	Skin atrophy; HPA axis suppression.
Precautions	**Hypothalamic-pituitary-adrenal (HPA) axis suppression**: May result in hypercortisolism or suppression of the HPA axis, especially in young children or patients taking high dosages for extended periods of time, and so interferes with growth and development. Adrenal crisis may result from inhibition of the HPA axis. **Immunosuppression**: If a dermatological infection continues despite receiving proper antimicrobial

	therapy, stop using the medication. Prolonged usage may lead to fungal or bacterial superinfection. **Sensitization**: Local sensitization (redness, irritation) has been linked to topical usage; stop using if sensitivity is noticed. Use medium to very high potency for <2 weeks to reduce local and systemic side effects. Use low potency for chronic therapy. Avoid medium to very high potency on face, folds, and groin because can increase steroid absorption. Use lower potency for children (ie, increase BSA/kg, therefore increase systemic absorption) Topical corticosteroids may be absorbed via the skin to cause systemic effects. Symptoms of Cushing syndrome, hyperglycemia, or glycosuria may be brought on by absorption. Use of occlusive dressings, application to skin that has been nipped off, or application to vast surface regions all promote absorption. **Polysorbate 80**: Some dosage forms may contain polysorbate 80 (also known as Tweens). Hypersensitivity reactions, usually a delayed reaction, have been reported following exposure to pharmaceutical products containing polysorbate 80 in certain individuals. Thrombocytopenia, ascites, pulmonary deterioration, and renal and hepatic failure have been reported in premature neonates after receiving parenteral products containing polysorbate 80. **Appropriate use**: For external use only; avoid contact with eyes. Do not use occlusive dressings on weeping or exudative lesions and general caution

	with occlusive dressings should be observed; discontinue if skin irritation or contact dermatitis should occur; do not use in patients with decreased skin circulation. **High-potency products**: Avoid the use of high-potency steroids on the face. Some dosage forms may contain propylene glycol; toxicities have been reported in children and adults, including hyperosmolality, lactic acidosis, seizures, and respiratory depression; large doses of propylene glycol delivered orally, intravenously (e.g., >3,000 mg/day), or topically in neonates have been associated with potentially fatal toxicities that can include metabolic acidosis, seizures, renal failure, and CNS depression.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

A thorough review of various HTA bodies including the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Scheme (PBS) yielded no result for the use of triamcinolone acetonide in burns.

Conclusion statement – TRIAMCINOLONE ACETONIDE

This drug, only cited by the international guidelines, is recommended for young hypertrophic and keloid scarring, as it improves inflammation and increases collagen degradation. Another type of lesions, the old ones can be managed concurrently with microneedles. However, no data from HTA bodies were found to support the recommendation of topical triamcinolone acetonide use in burns.

2.14.15 Petroleum Derivates

These products are usually used as emollient to be applied on wounds to refresh and accelerate healing.

SCIENTIFIC NAME PETROLEUM DERIVATES	
FDA	Not Registered, off-label (OTC)
EMA	Not registered
MHRA (UK Market)	The white petrolatum is not registered. Other petroleum derivates are registered, with labeled indication
PMDA	Not registered
Indication (ICD-10)	T30
Drug Class	Moisturizer
Drug Sub-Class	N/A
ATC Code	N/A
	N/A
DRUG INFORMATION	
Dosage Form	Ointment
Route of Administration	Topical
Dose (Adult) [DDD]*	Application after cleaning every 24-48h or as directed. Can be applied after skin removal, on skin graft. In first and 2nd degree burns (including sun burns) apply in a thick 0.25-0.5-inch layer until the skin no longer absorbs the product. If pain persist apply more until pain ceases. Continue to apply until complete healing. Need to be applied during any physical therapy treatments
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	N/A
Prescribing Edits*	N/A
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	

MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common)	Potential for hypersensitivity
Drug Interactions (Contraindicated)	N/A
Special populations	N/A
Pregnancy	Category A, generally acceptable
Lactation	No proof to be injected in breast milk, safe for use
Contraindications	Hypersensitivity
Monitoring Requirements	-N/A
Precautions	• For external use only • Is not filled with sunscreen, and so the latter needs to be applied alone
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

No available data was found from the searched HTA bodies, such as the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Health Care (IQWIG), and the Pharmaceutical Benefits Scheme (PBS) regarding their recommendations for the use of petroleum derivates in burns.

Conclusion statement – PETROLEUM DERIVATES

These topical petroleum-based ointments are recommended in initial therapy procedure to be applied on wounds under dressings, as emollients, to limit pain and hydrate the wound. These products are usually safe, with no special attention or monitoring needed. However, no data from HTA bodies were found to support the recommendation of topical petroleum derivates use in burns.

Section 3.0 Key Recommendations Synthesis

Burns are classified degrees depending on the wound's aspect and sensation. Other than the skin, human are subjects to other types of burns and complications, especially in austere conditions, due to radiations, electricity, intoxications…[36]

Despite the different degrees of skin burns, patient will experience the same skeleton of initial treatment with few specifications and modifications needed for particular types of wounds and patients (hands, pediatric, elderly), and special attention is needed to identify the patient category in need of immediate hospitalization[3,4].

In austere conditions, it is important to determine the etiology of the burn to be able to tailor a treatment[36].

Everyone can be exposed to burns, but some are more vulnerable than others.

Several tools have been developed to assess the severity of burns and to initiate IV hemodynamic resuscitation.

Management of Burns

The objectives in the management of burns are as follows:

- Detect patients in need of immediate hospitalization before it's too late
- Limiting damage in tissues by initiating appropriate therapy
- Monitor wounds for any infection and healing improvement
- Reducing risks of potential complications due to burns (burn shock…)[3,4,11]

Management options for burns

Wounds treatment options include:

- Initial therapy as a first line therapy that consists of:
  - Exposing the wound
  - Cool it with water
  - Clean it with chlorhexidine gluconate essentially
  - Apply topical silver sulfadiazine to limit the development of infections
  - Cover with dressing
  - Administer analgesics for the pain if needed[4]
- Maintenance therapy:
  - Check on the wound and monitor for healing improvement
  - Change dressing regularly and apply topical antibiotics
  - Other topicals like emollients and humectant can be used.
  - Physiotherapy and other body therapies as a rehabilitation procedure to restore muscular and neurological functions[11].

Other types of burns include:

- Radiation
- Electricity
- Intoxication by gas
- And so treatment can require the use of antidotes and other drugs[5,36,37]

Management options of burn-related conditions

Burn-related conditions can develop further to exposure, like DVT (enoxaparin), psychiatric disorders (anxiolytics and antidepressants), pain and sedation (ketamine, fentanyl, morphine, oxycodone, methadone, hydrocodone, butorphanol, nalbuphine, dexmedetomidine, gabapentin/pregabalin, acetaminophen, propofol, lidocaine), sepsis (antibiotics) and burn shock (IV fluid resuscitation – Lactated Ringer) … these conditions can be treated with medication following an algorithm[6,11,20,23].

Health Technology Assessment

NICE: recognized the effectiveness of lactated Ringer as an IV fluid resuscitation agent based on the few results that they have. It also accorded the use of human albumin in resuscitation, and enoxaparin and chlorhexidine in DVT and wound cleaning respectively[14,15,18,20].

HAS: granted marketing authorization of FLAMMAZINE, a cream containing silver sulfadiazine as an important component of initial treatment to prevent infections. Recommended also the use of enoxaparin in DVT prophylaxis and chlorhexidine in wound cleaning[16,22].

PBS and IQWIG: did not recommend any of the listed medications.

CADTH: approved the use of enoxaparin biosimilars in DVT prophylaxis, the use of chlorhexidine in wound cleaning, but did not advise atropine in the setting of organophosphate intoxication settings[13,42].

Overall, further evidence and improvements in cost-effectiveness are required for wider endorsement of therapies in burn patients.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of burns. These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

1. Jeschke MG, van Baar ME, Choudhry MA, Chung KK, Gibran NS, Logsetty S. Burn injury. *Nat Rev Dis Primers*. 2020;6(1):11. doi:10.1038/s41572-020-0145-5
2. Yakupu A, Zhang J, Dong W, Song F, Dong J, Lu S. The epidemiological characteristic and trends of burns globally. *BMC Public Health*. 2022;22(1):1596. doi:10.1186/s12889-022-13887-2
3. European Burns Association. European Practice Guidelines for Burn Care: Minimum Level of Burn Care Provision in Europe. 2017. Version 4. Available online: http://www/euroburn.org/wp-content/uploads/EBA-Guidelines-Version-4-2017.pdf . Published online 2017.
4. World Health Organization (WHO). Burn Management. Published online November 2020. https://cdn.who.int/media/docs/default-source/integrated-health-services-(ihs)/csy/surgical-care/imeesc-toolkit/best-practice-safety-protocols/burn-management.pdf?sfvrsn=90e35f3d_5
5. Romanowski KS, Carson J, Pape K, et al. American Burn Association Guidelines on the Management of Acute Pain in the Adult Burn Patient: A Review of the Literature, a Compilation of Expert Opinion and Next Steps. *Journal of Burn Care & Research*. 2020;41(6):1152-1164. doi:10.1093/jbcr/iraa120
6. Legrand M, Barraud D, Constant I, et al. Management of severe thermal burns in the acute phase in adults and children. *Anaesth Crit Care Pain Med*. 2020;39(2):253-267. doi:10.1016/j.accpm.2020.03.006
7. Suman A, Owen J. Update on the management of burns in paediatrics. *BJA Educ*. 2020;20(3):103-110. doi:10.1016/j.bjae.2019.12.002
8. British Burn Association, Kristina Stiles, Nicholas Goodwin. First Aid Clinical Practice Guidelines. Published online April 2018.
9. British Burn Association. BBA Clinical Practice Guideline for Management of Burn Blisters . Published online June 20, 2018.
10. E. Battaloglu, L. Greasly, J. Leon-Villapalos, A. Young, K. Porter. Faculty of Pre-Hospital Care & British Burn Association Expert Consensus Meeting: Management of Burns in Pre-Hospital Trauma Care. *fphc.rcsed.ac.uk/media/2621/burns-consensus-2019.pdf*. Published online 2019.
11. Allorto N, Atieh B, Bolgiani A, et al. ISBI Practice Guidelines for Burn Care, Part 2. *Burns*. 2018;44(7):1617-1706. doi:10.1016/j.burns.2018.09.012
12. Ahuja RB, Gibran N, Greenhalgh D, et al. ISBI Practice Guidelines for Burn Care. *Burns*. 2016;42(5):953-1021. doi:10.1016/j.burns.2016.05.013

13. CADTH. Atropine for Organophosphate Poisoning in the Pre-Hospital Setting: Clinical Effectiveness and Guidelines . Published online May 23, 2019.
14. NICE. Venous thromboembolism in adults . Published online August 19, 2021.
15. NICE. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. Published online August 13, 2019.
16. HAS. Enoxaparine : LOVENOX 12 000 UI (120mg) / 0.8ml, solution en seringue préremplie. *Comission de la Transparence* . Published online April 22, 2020.
17. HAS. Gluconate de chlorhexidine 2%, alcool isopropylique 70% CHLORAPREP, solution pour applicatioin cutanée. *Commission de la transparence*. Published online March 20, 2020.
18. NICE. Surgical site infection : prevention and treatment . *nice.org.uk/guidance/ng125/chapter/Recommendations#antiseptic-skin-preparation*. Published online August 19, 2020.
19. CADTH. Antimicrobial or Antiseptic Cleansers for Wounds . *Canadian Journal of Health Technologies* . 2023;3(6).
20. NICE. Intravenous fluid therapy in adults in hospital. *nice.org.uk/guidance/cg174/chapter/Recommendations#resuscitation-2*. Published online May 5, 2017.
21. NICE. Chronic wounds: advanced wound dressings and antimicrobial dressings. *NICE*. Published online March 30, 2016.
22. HAS. Silver sulfadiazine FLAMMAZINE cream. *HAS - Transparency Committee* . Published online April 21, 2021.
23. NICE. Chronic pain (primary and secondary) in over 16s: assessment pf all chronic pain and management of chronic primary pain . *nice.org.uk/guidance/ng193/chapter/recommendations*. Published online April 7, 2021.
24. CADTH, Kendra Brett, Melissa Severn. IV acetaminophen for acute pain in emergency departments . 2023;3.
25. HAS. DEXDOR 100 microgrammes/ml, solution à diluer pour perfusion. *HAS - Commission de la Transparence*. Published online December 5, 2012.
26. CADTH. Pain Management in the Emergency Department and Upon Discharge. *cadth.ca/sites/default/files/pdf/htis/2021/RB1542%20ER%20Pain%20Final.pdf*. Published online January 2021.

27. CADTH. Assessing and Managing Chronic Non-Cancer Pain. *cadth.ca/sites/default/files/attachments/2021-11/NB_eLearn_module_english.pdf*.

28. CADTH. Ketamine for Chronic Non-Cancer Pain: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines. Published online May 28, 2020.

29. CADTH. Pharmacological Interventions for Chronic Pain in Pediatric Patients : A Review of Guidelines. Published online May 5, 2020.

30. HAS. Chlorhydrate de morphine: RENAUDIN 10mg/ml solution injectable. *HAS*. Published online June 13, 2018.

31. HAS. Oxynorm 10mg/ml solution buvable . *Commission de la Transparence*. Published online June 13, 2018.

32. HAS. Propofol Lipuro 1% (10mg/ml), 2% (20mg/ml) et 5mg/ml. *HAS - Avis sur les medicaments*. Published online July 2023.

33. CADTH. Sedative Agents During Medical Procedures : Guidelines . *CADTH rapid response report: summary of abstracts*. Published online March 25, 2020.

34. CADTH. Antibiotic Solutions for Surgical Irrigation. Published online February 2022.

35. CADTH. Antipsychotic Drugs or Benzodiazepines for Rapid Tranquilization in Mental Health Facilities or Emergency Department Settings. *Canadian Journal of Health Technologies* . 2021;1(8).

36. Cancio LC, Sheridan RL, Dent R, et al. Guidelines for Burn Care Under Austere Conditions. *Journal of Burn Care & Research*. 2017;38(1):e482-e496. doi:10.1097/BCR.0000000000000367

37. Young AW, Graves C, Kowalske KJ, et al. Guideline for Burn Care Under Austere Conditions. *Journal of Burn Care & Research*. 2017;38(2):e497-e509. doi:10.1097/BCR.0000000000000369

38. British Burn Association. BBA Initial Management of Ocular Burns Clinical Practice Guideline. Published online December 12, 2018.

39. Peery AF, Shaukat A, Strate LL. AGA Clinical Practice Update on Medical Management of Colonic Diverticulitis: Expert Review. *Gastroenterology*. 2021;160(3):906-911.e1. doi:10.1053/j.gastro.2020.09.059

40. Has. *HAS-Direction de l'Evaluation Médicale, Economique et de Santé Publique COMMISSION DE LA TRANSPARENCE*.

41. HAS. Chlorhydrate de lidocaine, Lidocaine Aguettant 20mg/ml SANS CONSERVATEUR, solution injectable. *Commission de la Transparence*. Published online 2021.

42. CADTH. Biosimilar Enoxaparin for the Prevention of Treatment of Thrombosis and Cardiovascular conditions . Published online September 2021.

43. Vanderbilt University Medical Center. Pediatric Burn Hypermetabolic Protocol. Published online 2017.

44. Dinh Huu N, Nguyen Huu S, Le Thi X, et al. Successful Treatment of Intralesional Bleomycin in Keloids of Vietnamese Population. *Open Access Maced J Med Sci*. 2019;7(2):298-299. doi:10.3889/oamjms.2019.099

45. Abedini R, Sasani P, Mahmoudi HR, Nasimi M, Teymourpour A, Shadlou Z. Comparison of intralesional verapamil versus intralesional corticosteroids in treatment of keloids and hypertrophic scars: A randomized controlled trial. *Burns*. 2018;44(6):1482-1488. doi:10.1016/j.burns.2018.05.005

46. Louise Thwaites M. Tetanus. *UpToDate - graphics: Wound management and tetanus prophylaxis*. Published online September 2023.

47. Fda, Cder. *ZOHYDRO ER (HYDROCODONE BITARTRATE) Label*. www.fda.gov/medwatch.

48. National Institutes of Health. BUTORPHANOL. Accessed November 23, 2023. https://drugs.ncats.io/drug/QV897JC36D

49. fda, cder. *NUBAIN-(Nalbuphine Hydrochloride) Injection, for Intramuscular, Subcutaneous, or Intravenous Use NUBAIN® (Nalbuphine Hydrochloride) WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS Life-Threatening Respiratory Depression*.

50. *BACITRACIN-Bacitracin Ointment Padagis US LLC*. www.fda.gov/medwatch.

51. Deldar R, D'Arpa P, Moffatt L, Leung K, Shupp J. Cerium Nitrate Treatment in the Management of Burns. *Adv Wound Care (New Rochelle)*. 2022;11(8):443-454. doi:10.1089/wound.2020.1330

52. Scepankova H, Combarros-Fuertes P, Fresno JM, et al. Role of Honey in Advanced Wound Care. *Molecules*. 2021;26(16):4784. doi:10.3390/molecules26164784

53. Fleischer S. */ Notices the SUPPLEMENTARY INFORMATION Section for Electronic Access to the Draft Guidance Document. FOR FURTHER INFORMATION CONTACT*. Vol 87.; 2022. www.fda.gov/animal-veterinary/

54. WellRx. ACETIC ACID Monographs. Published 2023. Accessed November 21, 2023. https://www.wellrx.com/acetic%20acid/monographs/

55. National Institutes of Health. VASELINE PURE- petrolatum jelly . Accessed November 23, 2023. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=eb182cdf-985e-4039-b426-fcbaef1ef78d&type=display

56. National Institutes of Health. LABEL: DERMA WOUND-EAZ- cetrimide cream. 2023. Accessed November 23, 2023. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fea2b4d1-c524-60ee-e053-6294a90ae6fe&audience=consumer

57. National Institutes of Health. DAKINS FULL- sodium hypochlorite solution Century Pharmaceuticals, Inc. Published 2019. Accessed November 23, 2023. file:///C:/Users/tea/Downloads/20190208_3d72b72c-2949-4eb6-b64c-6c4aef0eddd9%20(1).pdf

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Adult and Pediatric Quantity Limit

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

Information available in the notes

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

Drug interactions

- A: No known interaction
- B: No action needed

• C: Monitor therapy

• D: Consider therapy modification

• X: Avoid combination

Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks

Appendix B. Level of Evidence Adopted

Levels of evidence	
1a	Systematic Review of Randomized Control Trials
1b	Individual Randomized Control Trials (with narrow Confidence Interval)
1c	All or none case-series
2a	Systematic review of cohort studies
2b	Individual cohort study (including low quality RCT; eg, <80% follow-up)
2c	Outcomes Research or Ecological studies
3a	Systematic review of case–control studies
3b	Individual Case–control Study
4	Case-series (and poor-quality cohort and case–control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”
Grades of recommendations	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Level of evidence and grades of recommendations adapted by the ABA

Level of Evidence	Type of evidence
Ia	Evidence from systematic reviews or meta-analysis of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one other type of quasi experimental study
III	Evidence from non-experimental descriptive studies such as comparative studies, correlation studies and case-control studies
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Grade of recommendation	Type of evidence
A	Based on hierarchy I evidence
B	Based on hierarchy II evidence or extrapolated from hierarchy I evidence
C	Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence
D	Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II or III evidence

Levels of evidence and grade of recommendation adopted by the faculty of pre-hospital care & British Burn Association Guidelines

Appendix C. PubMed Search Methodology Terms

The search Query created in PubMed is below:

Query	Sort By	Filters	Search Details	Results
(burns[MeSH Terms]) Filters: **Guideline, from 2013 - 2023** Sort by: **Most Recent** ("burns"[MeSH Terms]) AND ((guideline[Filter]) AND (2013:2023[pdat])) **Translations burns[MeSH Terms]:** "burns"[MeSH Terms]	Best Match	Guidelines	2013-2023	26

Appendix D. Treatment Algorithms

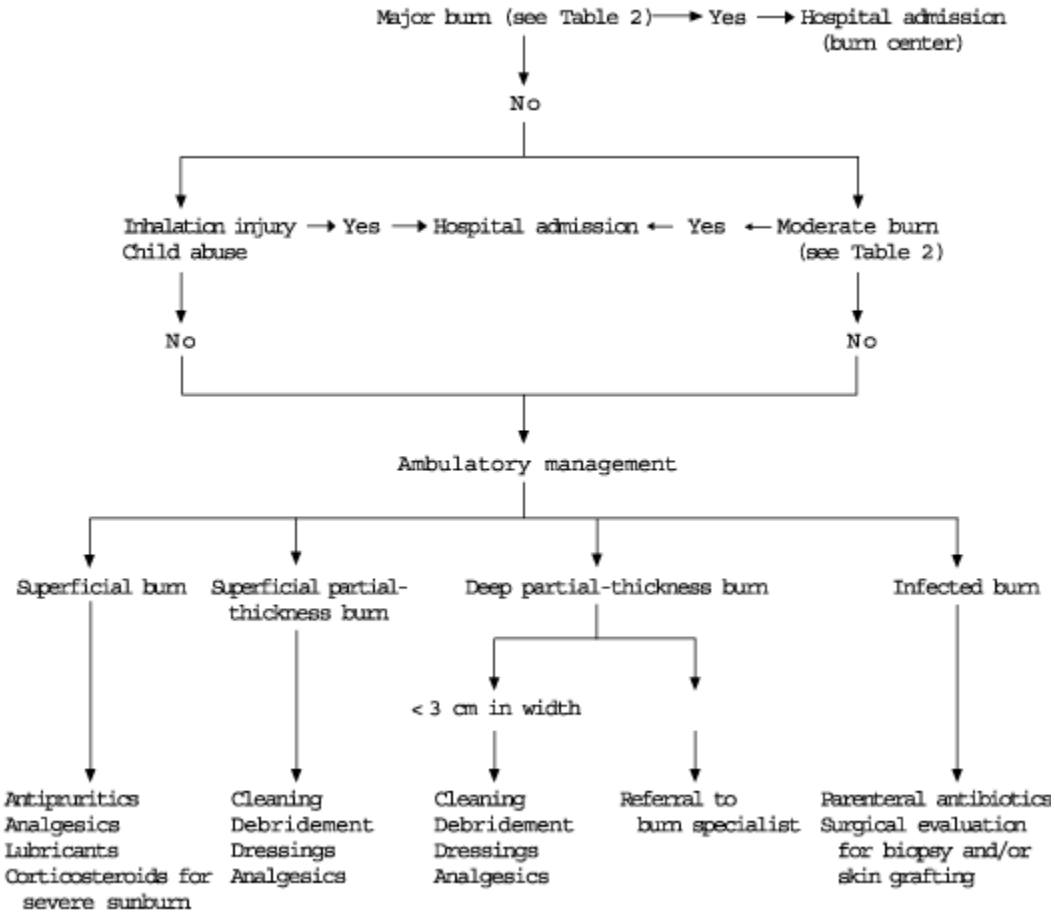


Figure 3. *Ambulatory management of burns*

Retrieved from https://www.aafp.org/pubs/afp/issues/2000/1101/p2015.html

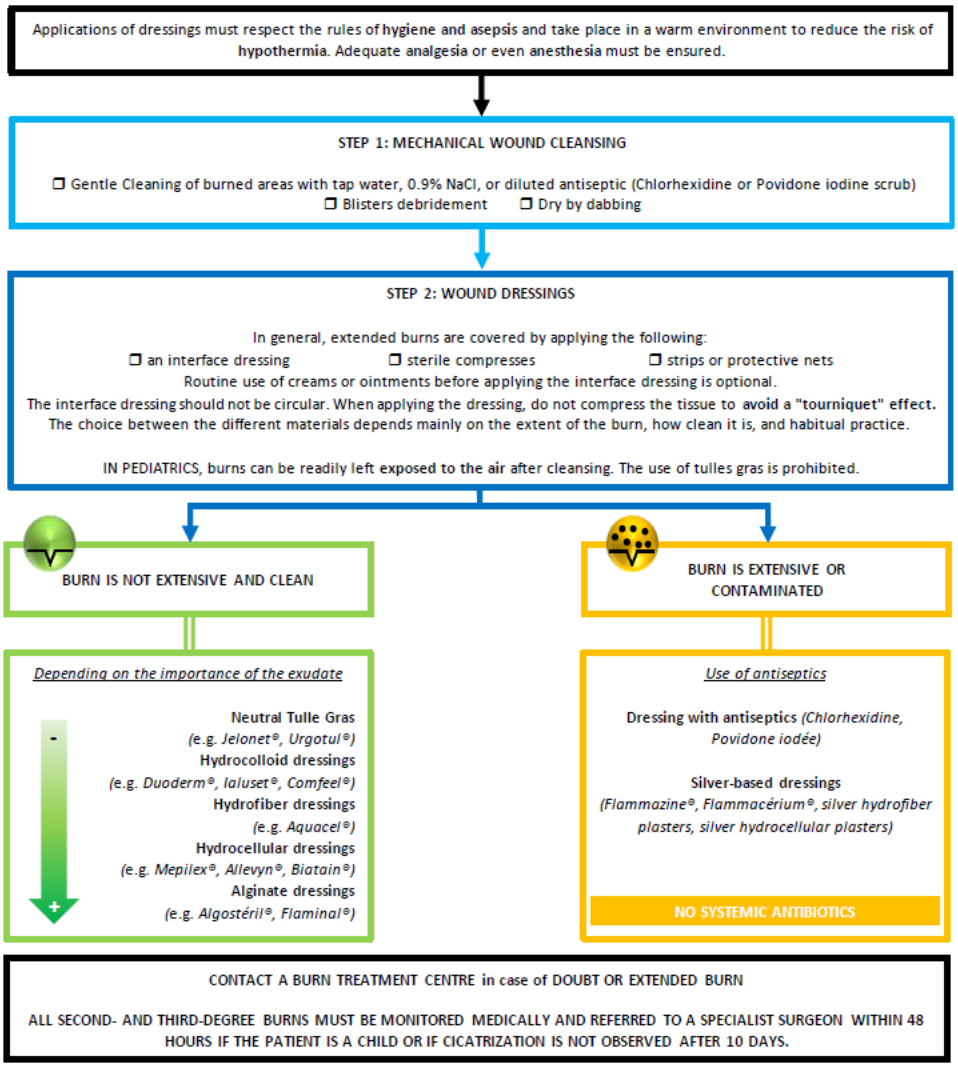


Figure 4. *Wound care and dressings. Retrieved from the SFAR 2020 guidelines.*