Advances in the treatment of burned children

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INTRODUCTION AND CONCEPT

Thanks to the implementation of evidence-based medicine and the creation of cross-disciplinary specific units, significant advances have been made in terms of sequelae and mortality rates in burned children over the last years[1].

EPIDEMIOLOGY

Data on burn epidemiology is variable and inconsistent. In order to standardize data collection, the WHO created the first global burn registry (www.who.int/violence_injury_prevention/burns/gbr) in 2018. All institutions can contribute online with their cases.

BURN PHYSIOPATHOLOGY

Local injury – with three concentric areas of coagulation, stasis, and hyperemia –, inflammatory acute systemic response – potentially with multifactorial shock and systemic inflammatory response syndrome –, and long-term metabolic response are present in all burns. In addition, immune system dysfunction predisposes to infections[2].

INITIAL ASSESSMENT AND TREATMENT OF CHILDREN WITH SEVERE BURNS

In children with severe burns, the ABCDE protocol[3] should be followed.

Potentially deadly injuries, regardless of skin injuries, should be immediately assessed and treated.

The patient should be taken away from the damaging source, and burns should be irrigated with moderately cold water for 20 minutes[4].

Burned patients are immunocompromised, which means prophylactic intubation is not indicated. However, if deemed necessary, intubation should be carried out at an early stage, before airway edema occurs.

In patients with suspected acute injury as a result of smoke inhalation, close clinical monitoring is required in the first 24 hours, since they may have severe pulmonary damage with few clinical and radiological signs.

BURN CLASSIFICATION

The factors determining burn severity include age – prognosis is worse in patients under 2 years of age –, presence of acute injury as a result of smoke inhalation and other severe injuries, burn extension, burn deepness, and burn location.

Burn extension determines short-term prognosis (survival).

Burn deepness and location determine long-term prognosis (sequelae and quality of life).

Deepness assessment

Even though clinical assessment by an expert remains the most widely used method to determine burn deepness, more accurate and objective methods have been developed. Doppler laser blood flow measurement in burned areas has been demonstrated as a very useful technique to accurately predict burn deepness and healing potential[5].

The main drawbacks of these devices lie in the fact they are very expensive and require patient cooperation, which limits their use in pediatrics. More recently, high-resolution thermographic cameras have been developed to analyze and correlate burn temperature with burn

DOI: 10.54847/cp.2022.03.12
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Date of submission: June 2022 *Date of acceptance:* June 2022

Table I. Hydroelectrolytic replacement calculation formulas in burned children.

	First 24 hours post-burn	*Composition*	*Administration instructions*	*24-48 hours post-burn*
Parkland	[4 ml (3 ml in <30 kg) x weight (kg) x %BBS] + baseline requirements (as per the Holliday-Segar method)	Ringer lactate Complement with 5% dextrose as required	50% of the volume in the first 8 hours post-burn, and the remaining 50% in the next 16 hours post-burn	½ of the requirements calculated for the burn + baseline requirements (as per the Holliday-Segar method) 5% dextrose, sodium, potassium, and albumin solutions to be considered according to serum levels
Galveston-Shriners	5,000 ml/m² BBS + baseline requirements (2,000 ml/m² TBS)	Ringer lactate Complement with 5% dextrose as required Add 12.5 g of albumin per liter after the first 12 hours post-burn	50% of the volume in the first 8 hours post-burn, and the remaining 50% in the next 16 hours post-burn	3,500 ml/m² BBS + baseline requirements (1,500 ml/m² TBS) Progressively reduce intravenous supply according to enteral supply 5% dextrose, sodium, potassium, and albumin solutions to be considered according to serum levels
Cincinnati-Shriners	4 ml x weight (kg) x %BBS + baseline requirements (1,500 ml/m² TBS)	Ringer lactate (add 50 meq/l of sodium bicarbonate in young children) Add 5% dextrose as required	50% of the volume in the first 8 hours post-burn (0-8 hours)	5% dextrose, sodium, potassium, and albumin solutions to be considered according to serum levels
		Ringer lactate Add 5% dextrose as required	25% of the volume in the second 8 hours post-burn (8-16 hours)	
		Ringer lactate (add 12.5 g of albumin per liter in young children) Add 5% dextrose as required	25% of the volume in the third 8 hours post-burn (16-24 hours)	

BBS = burned body surface; TBS = total body surface. Total body surface is calculated according to normal weight and size diagrams.

deepness, which represents an appealing alternative as they are easy to use.

Extension assessment

In the last years, various computer programs have been developed to calculate burn extension in a more accurate fashion. They have only been used in clinical trials so far, since they are complex and too slow for daily clinical practice. However, in the future, they could prove useful in the field of telemedicine.

TREATMENT

Hydroelectrolytic replacement

Burns involving less than 15% of the TBS may be treated with oral rehydration only. When the BBS exceeds 15%, intravenous hydroelectrolytic replacement is required to prevent a potential shock.

Table I features the three most frequent specific pediatric formulas for fluid therapy calculation in burned children. None of them has been demonstrated to be superior[6], which means they can be used interchangeably according to each institution's experience and preferences. However, Parkland's formula is more intuitive for rapid calculation.

Hourly diuresis remains the main marker allowing for hydroelectrolytic replacement monitoring. Transpulmonary thermodilution has also been proposed, but no essays have been carried out in pediatric burned patients yet.

In order to standardize criteria and calculation of hydroelectrolytic replacement volume at any given time, decision-making support software has been developed to offer recommendations to healthcare professionals. Fully

automated closed-circuit systems have also been developed to permanently adjust fluid infusion based on a computer algorithm.

Hypercatabolic response

Various pharmacological strategies to suppress or reduce hypermetabolism – which is frequent in burned patients – have been demonstrated to be effective[8].

- Insulin: Strict glucose control is critical. The objective is to maintain mean glucose levels <110-140 mg/dl.
- Propranolol: This is the most effective anti-catabolic therapy for burn treatment, since it antagonizes the excess of circulating catecholamines. It is indicated in patients with a BBS >20%, and it should be maintained for at least 1 year.
- Growth hormone: Recombinant human growth hormone (RHGH) exogenous administration in burned children with a BBS >40% accelerates healing and reduces hospital stay. RHGH use in the acute phase is highly controversial, but if administered in the long term during the chronic phase – the first 12 months post-burn –, it is seemingly correlated with fewer complications and remains effective. Combined use with propranolol has also demonstrated to be beneficial.
- Oxandrolone: This testosterone analogue – testosterone levels are down in these patients – has a lower androgenic effect. Oxandrolone use in patients with a BBS >30% has demonstrated to be beneficial both in the short- and in the long-term (12-24 months post-burn)[9].
- Other anabolic agents still under development include metformin, IGF-1 combined with IGFBP-3, GLP-1, and PPAR-γ agonists.

Nutrition

Nutritional supply should be initiated as soon as possible, in the first hours. Whenever possible, the administration route of choice should be the enteral route, which is preferred to the parenteral one[10].

In patients with burns in less than 15-20% of the TBS, fractional oral feeding is feasible. In patients with a larger BBS, continuous enteral feeding should be applied – via a nasogastric or a transpyloric tube, and in patients with a BBS >50%, through gastrostomy –, since it allows for better nutrient absorption and utilization. Full enteral feeding formulas with normal calorie and high protein levels should be used. Formulas complemented with arginine and/or glutamine are preferred, since skin losses are increased in burned patients. In addition, A, D, E, C, and K vitamin supplements, folic acid, copper, iron, selenium, and zinc should be supplied, since they have been demonstrated to accelerate the healing process.

Analgesia, sedation, and anxiolysis

Analgesia is necessary in all cases[11], since burns are some of the most painful injuries. Patients with moderate or severe burns often require morphine, while combined analgesics and sedatives are usually administered for dressing changes and wound care. For anxiety control and post-traumatic stress disorder prevention and treatment, opioids, long half-life benzodiazepines (diazepam, lorazepam), and more recently, amitriptyline – a tricyclic antidepressant – have demonstrated to be effective.

Antibiotic therapy

Infections are the main cause of morbidity and mortality in burned patients. Burns are first colonized by gram-positive cocci (*Streptococcus and Staphylococcus aureus*), and then by gram-negative bacteria (*Pseudomonas, Acinetobacter*) and even fungi.

However, prophylactic antibiotics are contraindicated, since they make prognosis worse as they select multi-resistant germs. They should only be used for perioperative prophylaxis and documented infections[12].

Surgical debridement

Hydrosurgery proves useful for superficial and intermediate dermal burns. It uses the Venturi effect generated by a high-pressure saline solution jet to raise necrotic tissues so that they are aspirated by the vacuum. This system has certain advantages vs. traditional mechanical debridement, since it allows for greater accessibility in difficult areas. However, the fact it is a small device may extend the procedure in time, thus increasing the risk of hypothermia[13].

In patients with deep burns, the necrotic tissue may be removed before the graft is implanted. Meanwhile, a temporary covering method – either a biosynthetic dressing or skin from a cadaveric donor – may be used[14].

This is the most widely endorsed approach in patients with large burns, since early debridement reduces systemic inflammatory response and bacterial colonization. Therefore, it should be carried out in the first 72 hours – if so permitted by patient condition. From that moment on, hyperemia will occur, which means escharectomy bleeding will be greater. The most effective hemostasis is skin covering, either with the patient's skin or a donor's, since it locally activates the intrinsic coagulation pathway through tissue thromboplastin.

It should be noted that from day 10, there is a higher risk of developing hypertrophic scars if epithelialization has not been completed. Risk increases up to 80% from day 21 without epithelialization.

Escharotomy

Circular burns may compromise distal perfusion, thus causing respiratory insufficiency or intra-abdominal compartment syndrome. Diagnosis is primarily clinical, but some tests, such as Doppler ultrasound flow measurement, intra-compartment pressure measurement, and distal O_2 saturation, are useful, too.

In all these situations, incisions on the eschar are necessary to improve perfusion. It is an urgent procedure,

but there are some free 6-12 hours – the time it takes for edema to emerge.

In the long-term, escharotomy has a poor cosmetic prognosis and causes retractions and hypertrophic scars. However, this should not dissuade physicians from conducting it if required.

In 2012, a local chemical treatment for injury debridement in burned patients was made available. It consists of a bromelain-enriched (Nexobrid®) proteolytic enzyme concentrate.

It is available as lyophilized powder to be manually mixed with a gel at the time of application.

It selectively acts on thermally injured collagen, while respecting healthy tissues. However, vaseline should be applied around the injury to prevent the active principle from running away to the healthy area, which would cause its effect to be lost. The drug should be in contact with the burned area for 4 hours, during which the whole area is covered in a sterile plastic for occlusion purposes.

Given that application is painful and patient cooperation is required – the patient should not move for 4 hours –, the procedure is carried out under sedation in nearly 100% of pediatric cases.

In adult patients, it has dramatically changed treatment of burned patients in the acute phase.

Regarding potential side-effects, such as bed bleeding or allergies, they have not been documented in pediatric patients yet, since the clinical trial is still in progress. However, anaphylactic reactions have been noted in patients allergic to pineapple[15].

Silver sulfadiazine should not be used in the areas to be treated at baseline, since the pseudo-eschar created blocks its action.

Nexobrid® has dramatically changed treatment in these patients. Intermediate burn areas in pediatric patients used to be left untouched for various days so that epithelialization-prone areas were spontaneously established, and areas eligible for graft treatment were delimited.

Thanks to this treatment, what used to take various days to be exposed is now visible on the first day. Following removal, the areas that will require a graft on the next days are immediately visible. The other areas are treated with biosynthetic dressings according to the conventional technique.

Enzymatic debridement's ability to normalize intra-compartment pressure in circular burns is to be highlighted, since it makes escharotomy unnecessary. It should be noted that escharotomy – even when required – offers poor cosmetic results in the long term, and it sometimes causes functional sequelae requiring a new surgical treatment.

Temporary covering

There is a wide array of covering materials available, from the traditional nitrofurazone or silver sulfadiazine (Biobrane®) ointments – which remain very useful in selected cases in spite of being old – to the current hydrofiber dressings with Ag or Suprathel®[16].

Suprathel® is a copolymer made up of 70% of lactic acid which is available as an elastic, microporous, absorbing membrane. Its acid pH inhibits bacterial growth and stimulates angiogenesis. It is available as an adaptable, elastic dressing that self-adheres to the area and requires no staples. It does not require frequent wound care either – every 5 to 6 days, while raising external layers only –, which avoids painful or uncomfortable episodes for the patient.

DEFINITIVE TREATMENT

Skin grafts

Partial skin grafts are those taken at certain levels of the papillary dermis only.

The donor area will heal from the pluripotent cells in the adnexa, and it will be fully epithelialized in 5-7 days.

Various resources are available to reduce bleeding during escharectomy. In the limbs, ischemia proves useful, and in other areas, subcutaneous adrenalin injection – a dilution of 0.5 mg of adrenalin in 500 ml of PSS is prepared, with a maximum dose of 25 ml/kg –is feasible.

When there are not enough donor areas available, graft meshing will be used. Traditional meshing may be conducted in various sizes – 1:1.5, 1:2, 1:3, and 1:6.

Larger meshings offer worse cosmetic and functional results.

Meek's meshing technique transforms the laminar graft into a series of small quadrangular grafts overlaid on a special paper lattice. Separation between fragments can be adjusted, with fragments being orderly laid for secondary healing[17]. It covers greater areas than traditional meshing, but it is more arduous. In addition, secondary epithelialization areas are larger, which means long-term results are worse.

The scalp as a donor area has a series of advantages. Children have larger head sizes – relatively speaking –, which means greater skin pieces can be obtained. In addition, if the graft is adequately taken, the donor area will be hidden by hair growth. Previous infiltration with saline solution is necessary to achieve a tangential area where the dermatome can be leaned on, which allows adrenalin to be diluted, and bleeding to be reduced.

Direct covering by means of an autograft can be considered in the acute phase post-burn, but this option is rarely used, since short-term results are worse. Therefore, it is only applied to small extensions or well-delimited areas, or in the presence of social factors which demand treatment is carried out in the shortest time possible.

Keratinocyte culture

It is indicated in patients where there is great disproportion between the surface to be covered and the availability of skin to be grafted[18].

A healthy skin biopsy is carried out at the same time the first debridement is performed in the operating room. The relevant areas are then covered with cadaveric donor skin.

Keratinocyte culture will be ready in 3-4 weeks, which are sufficient for the donor skin to be successfully implanted without reaching the rejection phase caused by immune response.

It is provided by the laboratory in the form of a gel layer overlaid on a support textile layer, and the whole is covered with special preservation fluid.

Culture layers will be placed on the bed resulting from the excision of the epidermis and part of the dermis of the donor skin with dermatome, or directly in areas where donor skin has not been successfully implanted, once the superficial layer of the granulation tissue has been removed.

Covering or treating the area with topical or antiseptic antibiotics is contraindicated, since they would have a negative impact on cell proliferation. From day 7, small epithelial islets will emerge when removing bandage. On the following days, they will progressively grow and merge until full healing is achieved.

Keratinocyte culture covering offers worse long-term cosmetic and functional results than autologous grafts, but it is a rescue option in patients with large burns and without enough donor areas.

TREATMENT OF PATIENTS WITH SEQUELAE

Even if epithelization is achieved from the borders of the injury, the likelihood of healing disorders increases from day 10-12.

Reconstruction surgery techniques include**:**

Scar removal and primary closure

Simple scar excision with primary closure should only be carried out if there is no border tension.

Skin grafts

Total skin grafts are technically the ideal skin solution to cover a defect in the sequela phase. Owing to the fact they are little available, they are typically used in small areas, such as the hands, the fingers, the eyelids, or the perioral region[19].

Dermal substitutes

Artificial dermal substitutes create a 3D pattern so that fibroblasts are laid in an orderly manner. Therefore, the optimal arrangement of collagen fibers reduces retractions and offers a better result. In addition, they allow for a certain filling effect, which mitigates the consequences of subcutaneous tissue loss following cicatricial retraction freeing.

There are various dermal substitutes available on the market, such as Matriderm®, Alloderm®, Integra®..., all of which are based on acellular matrixes. Alloderm® is made from human skin, whereas Matriderm® and Integra® are of bovine origin[20].

Artificial dermis (Integra®) is a type I purified collagen compound from bovine tendons. It is arranged in the form of a 3D net and combined with glycosaminoglycan – chondroitin sulfate. The first provides elasticity, whereas the second inhibits the emergence of myofibroblasts. Following placement on the bed, patient fibroblast colonization will be carried out, and a thin autograft will be subsequently performed following removal of the silicone layer, which will expose the whole epidermal layer[21].

The total colonization and artificial dermis vascularization process takes a mean of 3 weeks, but in the absence of complications, it should be extended for an extra 1-2 weeks so that vascularization is more complete, and successful cutaneous autograft implantation is more likely.

In the weeks prior to graft implantation, occlusive wound care with silver or nitrofurazone dressings should be carried out, while avoiding iodized antiseptics in young children, if possible.

Integra® fixation with vacuum therapy protects the area from bacterial contamination and improves vascularization from the surgical bed. In these cases, in order to transfer the vacuum to the surgical bed, small windows should be created in the artificial dermis, or a meshed device should be used.

Tissue expanders

Tissue expanders help distend the healthy skin available next to any given cicatricial area, and allow it to cover the defect with advancement or rotational flaps made of expanded skin at the time of excision.

The inflating process of tissue expanders takes approximately 3 months. They are particularly useful to remove alopecia areas and cervical retractions[22].

If the inflating process is too quick, or if the cicatricial skin adjacent to the pouch is also expanded, ulcerations may occur, with the resulting exposure of prosthetic material, which causes partial or total failure.

Skin flaps

This technique is rarely used in pediatric patients[23].

They may be indicated when there is a direct injury in bone, articular, or tendinous areas, with exposure. However, the great tissue regeneration capacity they have and the cosmetic and functional damage caused by the donor area of the flap should be taken into account – otherwise, disproportionate sequelae considering the extension of the area covered may be found in adulthood.

However, local advancement or rotational flaps remain frequent in patients with burn sequelae. In linear cicatricial retractions, in the hands, in the canthi, in the mouth, etc., basic plasty techniques (z-plasty, w-plasty, etc.) are also common (Fig. 1).

Figure 1. Z-plasty axillary retraction reconstruction, and secondary redundant arm skin remodeling.

1. Hypertrophic scars

Hypertrophic scars are characterized by excessive production of cicatricial tissue. Contrarily to keloids, they do not exceed the limits of the primary injury. Apart from causing itching and pain, hypertrophic scars in articular areas also bring about functional limitations[24].

Intralesional corticoid injection has been demonstrated as a useful technique for the treatment of these injuries. It has a multiple action mechanism – on the one hand, it inactivates TGF-b1 and activates collagenase, and on the other hand, it has an anti-inflammatory and vasoconstrictor effect. Triamcinolone is typically used, and it is usually carried out under sedation.

Pressotherapy is useful for the treatment of hypertrophic scars, since it causes capillary collapse as a result of pressure[25].

A thick silicone plate below the garment may also prove useful thanks to combined pressure and contact with the silicone.

On the face, using a customized thermoplastic mask is the only way of applying uniform pressure. In the manufacturing process, the whole face undergoes a surface scanner, which takes a few seconds and is carried out with the patient awake.

Placing a silicone layer with an occlusive effect increases hydration at the stratum corneum of the skin. Increased collagenase activity secondary to a slight rise in temperature has also been described.

In the last years, laser treatment has emerged as a new therapeutic option in the management of scars, with very positive results[26]:

- Pulsed dye laser: it is primarily absorbed by oxyhemoglobin, which means hypervascularized tissue is the main target of it. It is useful in the treatment of immature and reddish scars. It reduces erythema and itching, with a moderate effect on hypertrophy.
- Fractional CO_2 laser: it has been demonstrated to be effective for the treatment of hypertrophic and keloid scars, and to improve itching, erythema, pigmentation disorders, and neuropathic pain – which may also be the case with some scars. It also seems efficacious for the treatment of atrophic scars. Additionally, it allows drugs, such as corticoids, to be administered within the injury.

Decision on which laser is to be used should be made on a case-by-case basis. Combining various types – if required – is also feasible.

The laser is usually applied under sedation or general anesthesia in pediatric patients, since it is painful and requires patient cooperation.

2. Retractions

Scar contraction is a normal process that may cause functional limitations. Retraction primarily occurs in the flexor aspect of joints. Through physical therapy, splinting, and postural measures, retraction occurrence will be modified and reduced. In young children, ligament laxity makes retraction occurrence more likely in all articular aspects, and it may cause dislocations.

Special locations:

a. The **cervical region** is a complex area in the treatment of cicatricial retractions. How to best avoid retractions – implanting total skin grafts, conducting skin flaps with expanded skin, dividing the platysma muscle, using artificial dermis, etc. – remains an issue of discussion. Good early rehabilitation treatment is key. It should consist of silicone collars, extension splints, and physical therapy, along with adequate scar treatment by means of silicone patches, local hydration, laser, etc.

b. Tissue expanders are key to treat areas with cicatricial alopecia in the **scalp**.

It should be noted that some deep and intermediate scalp burns will end up causing cicatricial alopecia even if skin grafts have not been required. Indeed, hair follicles are damaged by the burn itself or surrounded by cicatricial fibrous tissue. This will cause areas of

Figure 2. Intra-operative image of scalp expanders, and alopecic area excision result.

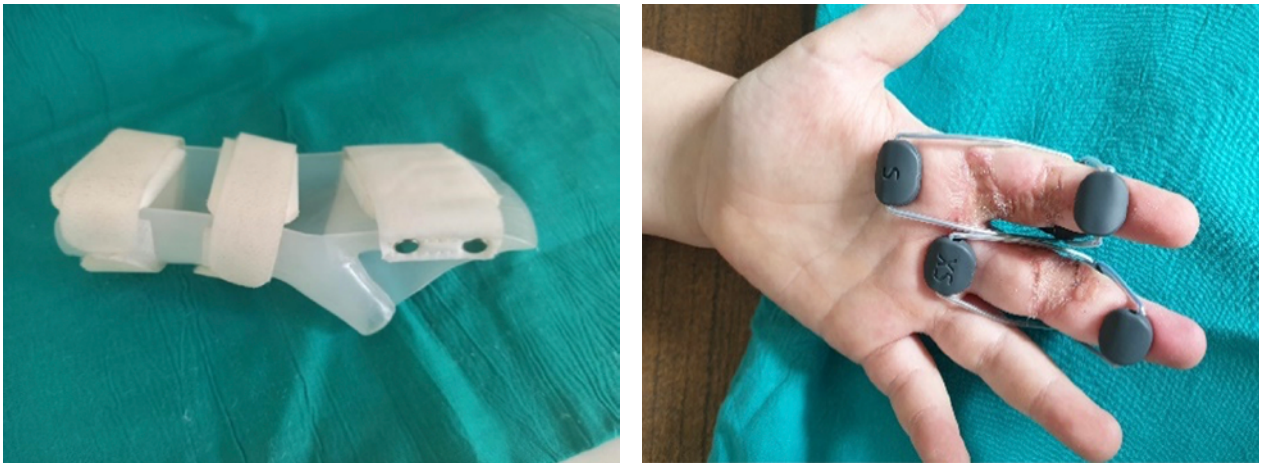

Figure 3. Palm extension splint in a 3-year-old child, and active splints to prevent retractions following skin graft.

alopecia or sparse hair to emerge, which is esthetically unacceptable (Fig. 2).

In the scalp, expanders cause external erosion, which is sometimes very remarkable and leaves the diploe exposed. This is not an issue per se, except for the flattened appearance it will have following removal, which will self-remodel.

c. Breast area: In girls, the initial debridement of thoracic burns involving the pectoral region should be highly conservative, since the areola and the nipple should be preserved. It should be noted that an acceptable result from a cosmetic and functional point of view may not be so in the future, when puberty development starts.

d. Hands: The growth-scar combination in this location may cause severe mobility limitations in children. Cicatricial sequela rehabilitation in the hands is key. It usually combines pressotherapy, splinting, and physical therapy with at-home exercises led by parents themselves if adequately trained[27] (Fig. 3).

Figure 4. Clinodactyly secondary to at-home electrical burn with bone involvement.

Figure 5. Palm skin graft pigmentation, and z-plasties in retractions.

3. Musculoskeletal sequelae

The whole musculoskeletal system is exposed to long-term sequelae in patients with large burns.

Some other alterations directly depend on local disorders, such as dislocations and articular subluxations.

Amputations are not very frequent. They mostly occur at the level of the distal phalanges of the hands and the feet, in cases with third-degree burns, and more often in young children, where tissue loss occurs as a result of direct damage by the causal agent.

Sometimes, electric burns cause bone loss as a result of the direct injury. They frequently involve the metaphysis, which leads to clinodactyly and other bone growth related diversions, which are difficult to treat without resorting to more aggressive surgical techniques, such as osteotomy and arthrodesis (Fig. 4).

4. Pigmentation disorders

Residual hyperpigmentation on the scars or the grafts mostly occurs in dark skins, or in skins under solar exposure. Once established, this complication is difficult to manage, but laser treatment can partially alleviate it. Dermabrasion of the superficial epidermal layers using a burr or a hydrosurgery device may also be useful, with good immediate results but with frequent recurrences, which make it necessary to repeat the procedure a few months later (Fig. 5).

5. Rehabilitation

In patients with large burns, the rehabilitation and reconstruction procedures to be carried out in the long-term should be scheduled from the start. This is why burn units benefit from cross-disciplinary teams where nurses, rehabilitation experts, and physical and occupational therapy specialists play a key role. Psychosocial rehabilitation should not be neglected either, which means psychiatrists and psychologists should also be part of them.

In pediatric patients, it is widely acknowledged that normal life resumption occurs when children return to school.

Early rehabilitation includes splinting and passive and active mobilization, also in intubated patients. In the future, active exercise will allow not only for early motor recovery, but also for prevention or minimization of the much-feared retractions. In addition, physical activity improves metabolic response in these patients[28].

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