Injuries associated with electronic nicotine delivery systems: A systematic review

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BACKGROUND:	Since its introduction on the market in 2007, the number of reports on injuries caused by the overheating, ignition, or explosion of
	electronic nicotine delivery systems (ENDSs) has increased significantly. These injuries appear to have different causes, the most
	important one being lithium-ion battery overheating to the point of ignition or explosion.
METHODS:	A literature search for all relevant studies concerning ENDS-related traumatic injuries of all kinds was conducted, according to the
	Preferred Reporting Items for Systematic Reviews and Meta-analyses protocol. The search started with the first introduction of
	ENDSs in 2007 and ended February 2020. Articles included were reports on patients who sustained flame, chemical, or traumatic
	injuries of the skin, soft tissue, and/or bone, related to the use of ENDSs.
RESULTS:	This systematic review includes 180 patients from 41 case series and reports, published between 2016 and 2020. The mean age was
	30.8 years (range, 17–59 years) with an overall male predominance (168 of 180 patients, 93%). In most injuries, multiple anatom-
	ical sites were affected, with the thigh/lower limb being the most commonly injured area (77%) followed by the upper limb/hand
	(43%). Eighty-two patients (51%) required a surgical treatment, 70 patients (43%) were managed conservatively with dressings or
	ointments, and 9 patients (6%) underwent enzymatic debridement. Thirty-five percent of all patients underwent skin grafting.
CONCLUSION:	Injuries from overheating, ignition, or explosion of ENDSs are an emerging, underreported, and underresearched issue. There is a
	need for increased regulation of ENDSs and improved surveillance of related injuries. Both health care providers and consumers
	should be made aware of the risks and be advised about how to safely handle these devices. In contrast to other articles, this sys-
	tematic review includes all types of injuries related to ENDS overheating, ignition, and explosion. To our knowledge, this is the
	most extensive systematic review performed to date. (J Trauma Acute Care Surg. 2020;89: 783-791. Copyright © 2020 Wolters
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LEVEL OF EVIDENCE:	Review article, level III.
KEY WORDS:	Electronic nicotine delivery system; e-cigarette; battery; explosion; ignition.

he first electronic nicotine delivery system (ENDS) was an e-cigarette (EC) developed in 2003 by Hon Lik, a Chinese pharmacist. Electronic nicotine delivery systems are composed of a mouthpiece, a cartridge, a heating element, a microprocessor, and a battery.¹ They include electronic cigarettes (ECs or "cigalikes") and personal vaporizers. E-cigarettes imitate the look and feel of a traditional cigarette. They make use of disposable "e-liquid" cartridges (see further), and their small batteries can be either rechargeable or disposable. Vaporizers on the other hand, use larger and rechargeable batteries, combined with a tank to store e-liquid and a replaceable coil.² All these devices are designed to simulate the act of smoking, although with less of the toxic chemicals produced by burning tobacco.³ Some ENDSs are activated by inhalation, while other ones are manually activated by pressing a button. Once activated, the microprocessor turns on the heating element, a coil, in contact with a liquid solution (e-liquid), so to deliver vaporized e-liquid. The

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J Trauma Acute Care Surg Volume 89, Number 4 chemical composition of this e-liquid varies significantly between manufacturers: generally, it includes nicotine, propyl ethylene glycol, glycerol, and occasional impurities such as heavy metals, which are intrinsically cytotoxic.^{4,5} Since their commercialization in 2006, the popularity of ENDSs among young adults has increased considerably, even surpassing that of smoking tobacco products.^{6,7} According to recent studies, ENDSs encountered a great popular success with more than 2.5 million users in the United States⁸ and 7.5 million Europeans using an EC or vaping device.⁹

Electronic nicotine delivery systems are increasingly seen, by the general public, as a less harmful alternative to traditional methods of inhaled tobacco use.¹⁰ Some authors have addressed their potential as a tobacco replacement in the context of a public health harm reduction strategy,^{11,12} and several studies have investigated their potential as a smoking cessation aid.^{13,14} In 2015, an expert independent review concluded that ENDSs are significantly less harmful than tobacco.¹ However, a 2014 systematic review already stated that the long-term effects are unknown and that the general public is insufficiently informed about the known adverse health effects including the risk for traumatic and burn injuries.¹⁰ Furthermore, evidence establishing a link with smoking cessation is lacking, and there is growing evidence of these devices presenting new dangers.^{11,15,16} The potential toxicity of ENDS vapor and its potential for increasing tobacco use have also been addressed.^{17–21} In 2016,

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Madsen et al.²² published a case report suggesting that ENDSs can induce inflammation and mimic responses found in metastatic cancer. One year later, Fracol et al.²³ found EC vapor to be cytotoxic to endothelial cells, independently of nicotine content. Moreover, several authors have described a recently identified (2019) lung disease linked to ENDS use: e-cigarette or vaping product use–associated lung injury.^{19–21}

As previously mentioned, the power source of ENDSs usually is a battery that can be recharged or replaced. Rechargeable lithium-ion batteries are by far the most commonly used batteries in these devices, which are susceptible of overheating, igniting, and/or exploding.²⁴ This may occur through a phenomenon known as "thermal runaway," when a lithium-ion battery short-circuits because of overheating, exposure to moisture, excessive or improper charging, excessive external heat, direct contact with metallic objects, or physical damage to the battery.²⁵ Thermal runaway is an uncontrollable exothermic reaction among the anode, cathode, and flammable electrolytes within the battery itself. This happens when increases in temperature and pressure cause the battery to rupture and potentially ignite and/or explode, possibly causing an array of injuries.²⁶ In recent years, the number of reports worldwide on injuries due to overheating, ignition, and/or explosion of these devices has increased exponentially. Between 2015 and 2017, there were an estimated 2035 ENDS explosion and burn injuries presenting to US emergency departments (95% confidence interval, 1107–2964). This is more than 40 times the number of injuries reported by the Food and Drug Administration from 2009 to 2015.²⁷ Corey et al.²⁸ estimated the incidence of ENDS-related burn injuries in the United States in 2016 to be around 1,007 (95% confidence interval, 357–1657). Numerous case studies have shown that, in addition to the thigh, the genitalia, hands, or face is often injured as well. In addition to burns, different maxillofacial fractures have also been described.¹⁸

The aim of this study was to provide an overview of all relevant studies concerning ENDS-related traumatic injuries of all kinds: burn injuries (flame and chemical) and traumatic injuries of the skin, soft tissue, and/or bone (e.g., fractures), to estimate the implications on immediate management with a particular focus on surgical versus conservative treatment.

PATIENTS AND METHODS

This systematic review was prospectively registered in PROSPERO.

The reporting of this systematic review with the key words *e-cigarette, ENDS, battery, explosion, ignition, lithium,* and *burn* was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocol (Fig. 1).²⁹ Before the literature search, a study protocol was formulated. The literature search itself started with the introduction of ENDSs in 2006 and ran until February 2020. PubMed, Web of Science, Google Scholar, Scopus, Embase, and Cochrane Library database searches were performed, based on the inclusion and exclusion criteria defined by the study team (Table 1). The initial search resulted in 1,637 articles. Articles included were reports (case reports, meta-analyses, randomized controlled trials, reviews, and systematic reviews) on patients (age, 0–99 years) who sustained flame, chemical, or traumatic injuries

of the skin, soft tissue, and/or bone caused by, or in the context of, using ENDSs. Non-English articles and publications with insufficient information were excluded from this systematic review. Nonmedical reports such as news articles or institutional reports were excluded as well. To extend our literature search, the bibliographies of the articles we selected were also screened for missed publications.

RESULTS

A total of 41 articles met the inclusion criteria (Table 2). Our search yielded 18 case reports and 23 case series, adding up to a total of 180 cases, published between 2016 and 2020 in a variety of medical journals.^{7,8,18,25,30–66} The incidents took place in the United States, the United Kingdom, Canada, Germany, France, Belgium, and Malaysia. To our knowledge, this is the most extensive review on this topic, as all kinds of traumatic injuries were included in contrast to other systematic reviews limited to burn injuries.^{1,67}

In this systematic review, the mean age was 30.8 years (range, 17-59 years) with most patients being male (168 of 180 patients or 93%). In 94% of patients, burn wounds were present and needed treatment. In the majority of cases (62%), ENDSs (or an isolated battery) overheated, ignited, and/or exploded in pants pockets. In 10% of cases, the devices caused injuries while being used, and in another 10% while being handheld without being activated. Seventy-seven percent of patients sustained injuries to the lower limb (mostly thigh), 43% to the upper limb (mostly hand), and 10% to the genitalia, and 8% suffered injuries to the face. The average TBSA was 4.72% (range, 0%–16%) with the most frequent burn depth being a combination of partial thickness and full thickness burns, followed by partial thickness burns alone. Overall, 43% of patients were treated conservatively, 51% required surgery, and 6% underwent enzymatic debridement for their deep partial and/or full-thickness burns. Thirty-five percent of all patients underwent skin grafting.

In current literature, hospitalization and wound healing as well as data on long-term follow-up are rarely reported. Twenty-eight authors addressed (one of) these topics, in a very limited fashion, reporting a median hospital stay of 5.9 days (range, 0-18 days), an average 95% wound healing time of 21.9 days (range, 14–61 days), and a mean follow-up of 107 days (range, 1–15 months).

Thus far, no official guidelines have been published on the management of these injuries, and different treatment options are still being investigated.

As a first step toward creating guidelines, different classifications have been put forward to provide guidance for the adequate management of these types of injuries.

In 2017, Patterson et al.⁵³ presented a classification based on the distinct injury patterns seen in their study. A numerical classification was created, establishing a distinction between direct and indirect injuries.

Direct injury:

• Type 1: Hand injuries while ENDSs were being held or kept in the patient's pocket. Severe hand burns can result in the patient's inability to work or care for himself/herself if the functionalities of their hands are lost.⁶⁸

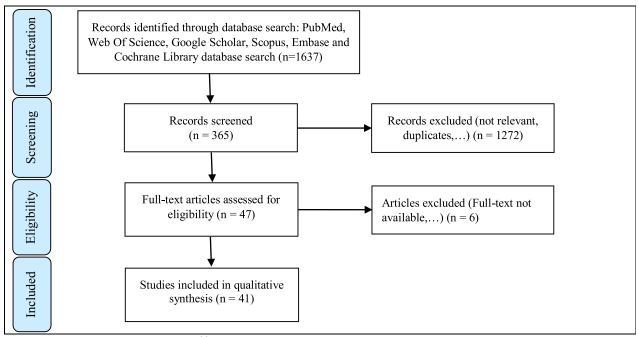


Figure 1. Flow diagram of search strategy.²⁹

• Type 2: Face injury while ENDSs were being held or used. These injuries may cause concern for upper airway injury and may warrant an admission for airway observation. They are unlikely to need autografting, since it is often a flash burn. The face heals well because of abundant blood supply and high density of skin adnexa for reepithelialization. 69

• Type 3: Waist/groin injuries. These injuries are seen when the EC explodes/ignites while being stored in the individual's

TABLE 1. Literature Search Strategy

Search Strategy	Relevant/Total No. Articles
PubMed: ("electronic nicotine delivery systems" [MeSH Terms] OR ("electronic" [All Fields] AND "nicotine" [All Fields] AND "delivery" [All Fields] AND "systems" [All Fields]) OR "electronic nicotine delivery systems" [All Fields] OR "e cigarette" [All Fields]) AND ("explosions" [MeSH Terms] OR "explosions" [All Fields] OR "explosions" [All Fields])	38/49
PubMed: ("electronic nicotine delivery systems" [MeSH Terms] OR ("electronic" [All Fields] AND "nicotine" [All Fields] AND "delivery" [All Fields] AND "systems" [All Fields]) OR "electronic nicotine delivery systems" [All Fields] OR "e cigarette" [All Fields]) AND ("burns" [MeSH Terms] OR "burns" [All Fields] OR "burn" [All Fields])	36/114
PubMed: ENDS [All Fields] AND ("explosions" [MeSH Terms] OR "explosions" [All Fields] OR "explosion" [All Fields])	4/33
PubMed: ("lithium" [MeSH Terms] OR "lithium" [All Fields]) AND battery [All Fields] AND ("burns" [MeSH Terms] OR "burns" [All Fields] OR "burn" [All Fields])	15/37
PubMed: ("lithium" [MeSH Terms] OR "lithium" [All Fields]) AND battery [All Fields] AND ("explosions" [MeSH Terms] OR "explosions" [All Fields])	16/41
Web of Science: TS = (E-cigarette and explosion); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = 2007–2020	22/31
Web of Science: TS = (e-cigarette and burn) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = 2007–2020	29/93
Web of Science: TS = (lithium battery and explosion); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = 2007–2020	32/275
Web of Science: TS = (Lithium battery and burn); Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = 2007–2020	19/160
Google Scholar: "E-cigarette AND ENDS AND burn AND explosion," range 2007–2020	55/581
Embase: 'electronic cigarette':ti AND 'explosion':ti AND [2007-2020]/py	5/5
Embase: 'electronic cigarette':ti AND 'burn':ti AND [2007-2020]/py	3/7
Cochrane: electronic cigarette AND burn in Title Abstract Keyword — with Cochrane Library publication date Between Jan 2007 and Mar 2020 (Word variations have been searched)	0/14
Scopus: TITLE-ABS-KEY ("electronic cigarettes" AND explosion) AND PUBYEAR > 2006	45/56
Scopus: TITLE-ABS-KEY ("electronic cigarettes" AND burn) AND PUBYEAR > 2006	46/141
Total	365/1,636

TABLE 2. Summary of Ca	Summary of Case Reports and Series on EC Burns	S		
Authors	Location of Ignition/Explosion	Involved Body Areas	%TBSA/Depth	Intervention
2016, Shastry and Langdorf ⁷	In hand	Thorax, abdomen	Unknown/PT	Conservative
2016, Colaianni et al. ³⁰	Pants pocket (2) In mouth during use	LL (3), UL (1), genitalia (1) Face and intraoral (1)	Unknown in all three cases/FT + PT (2), facial lacerations and tooth fracture (1)	Surgical (2) Conservative (1)
2016, Walsh et al. ³¹	Pants pocket	IL	1.5% TBSA/MDB	Conservative
2016, Kumetz et al. 32	In mouth during use Pants pocket	Intraoral LL, UL	Unknown/unknown 4%/Mixed PT and FT	Surgical Conservative
2016, Archambeau et al. ⁸	In mouth during use	Face	<1%/Unknown	Surgical
2016, Sheckter et al. ³³	Pants pocket (3)	TT (3)	Mean TBSA: 8%/PT and FT	Surgical with grafting (2) Conservative
2016, Herlin et al. ³⁴	Pants pocket (2)	LL (2)	Mean TBSA: 4%/mixed PT and FT	Surgical with grafting (2)
2016, Kite et al. ³⁵	In mouth during use In hand	Intraoral UL, thorax	<1%/Intraoral mucosa laceration chipped and missing maxillary teeth 3%/DPT, FT, soft tissue loss night palm	Surgical (2)
2016, Nicoll et al. ³⁶	Pants pocket (2)	UL (2), LL (2)	Mean TBSA: 3.5%/SPT and SB	Surgical (2) with grafting (1)
2016, Paley et al. 37	In mouth during use In hand	Face, intraoral, UL Face, UL	0%/SB, loss of 2 incisors, corneal defects bilateral Unknown/unknown, bilateral cornea burns	Surgical Conservative
2016, Khairudin et al. ³⁸	In hand	Face, eye	0%/Eyelid and conjunctival laceration and burns	Surgical
2016, Jiwani et al. ³⁹	Pants pocket (8), in lap (1) In mouth during use (1)	LL (8), UL (5), genitalia Face, thorax, abdomen	Mean TBSA 5.95% (range, 1–27.3)/PT (4), mixed PT and FT (5), FT (1)	Conservative (5) Surgical (5) with grafting (4)
2016, Norii et al. ⁴⁰	In mouth during use	Intraoral	0%/PT, pharynx and mucosa lacerations, fractures of first and second vertebrae, fracture incisors bilateral.	Surgical
2016, Roger et al. ⁴¹	In mouth during use	Abdomen, face, intraoral	No details	Surgical
2016, Harrison and Hicklin ⁴²	In mouth during use	Intraoral	Unknown/intraoral trauma	Surgical
2016, Bohr et al. ⁴³	Pants pocket	ILL	8%/PT	Surgical with grafting
2016, Cason et al. ⁴⁴	In mouth during use	Face, thorax, eye, UL	Unknown/inhalation, fracture palate + nose + hand, teeth dislocation, soft palate defect, corneal lesion	Surgical
2016, Hassan et al. ⁴⁵	Pants pocket (6)	LL, genitalia (6)	Between 2% and 5% TBSA/mixed PT and FT	Surgical with grafting (6)
2016, Moore et al. ⁴⁶	In mouth during use	Face, intraoral, UL	0%/SB, teeth fractures	Conservative
2017, Brooks et al. ⁴⁷	In mouth during use	Intraoral, face	0%/Fracture maxilla + nose + teeth, tooth avulsions, intraoral and facial lacerations	Surgical
2017, Bauman et al. ⁴⁸	Pants pocket (3)	LL (3)	Mean TBSA: 7.3%/DPT and FT (2), SPT (1)	Surgical (3) with grafting (2)
2017, Harshman et al. ⁴⁹	Pants pocket (2)	LL (2), UL (1)	Mean TBSA: 6.5%mixed PT and FT (2)	Surgical with grafting (2)
2017, Foran et al. ⁵⁰	In hand	UL	<1% SPT, high-pressure injection e-liquid	Surgical
2017, Arnaout et al. ⁵¹	In charger Pants pocket (2)	LL (3), UL (2), genitalia (1)	Mean TBSA: 3%/SB (1), SPT (1), MDB (1)	Conservative (3)
2017, Treitl et al. ⁵²	Pants pocket (3)	LL (3), genitalia and UL (1)	Mean TBSA: 7.3%/PT and FT (2), PT (1)	Conservative (1), enzymatic (1), surgical with graffing (1)
2017, Patterson et al. ⁵³	Pants pocket In mouth during use	UL, LL, genitalia Face, eye	1% TBSA/PT 0.5% TBSA/SPT, lip laceration, comea abrasion	Surgical Conservative

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Conservative (21) Surgical (9) with grafting (2)	Surgical Surgical Conservative	Conservative (2) Surgical with grafting (8)	Surgical Conservative (7) Surgical (3)	Conservative (6) Surgical with grafting (2)	Surgical (9) with grafting (8) Conservative (4)	Conservative (11) Surgical with grafting (3)	Conservative(1), Enzymatic (3) Surgical (3) with grafting (2)	Surgical with grafting	Enzymatic (3)	Enzymatic with grafting (2)	Conservative: 70 (43%) Surgery: 82 (51%) Enzymatic: 9 (6%) Skin graffing: 55 (35%)	depth burn.
Mean 4% TBSA (range, 1%-8% TBSA)/unknown	Skin laceration, facial fractures, pneumocephalus Unknown/mixed DPT and FT, blast injury 2% TBSA/PT	Mean TBSA 4.2% (range, 1–15.6)/unknown	Unknown/unknown Mean 3% TBSA/PT (5), mixed PT and FT (2), FT (3).	Mean 8% TBSA (range, 4%–16%)/PT (5), PT and FT (3)	Mean TBSA 4.7% (range, 1–10)/PT (6), PT and FT (7), FT (1)	Mean TBSA 3.6% (range <1–6)/PT (10), PT and FT (1), FT (3)	Mean 4% TBSA/mixed PT (2), SPT (3), unknown (1)	Unknown/unknown	Mean TBSA: 2.8%/mixed SPT and DPT (3)	9% TBSA/mixed SPT and DPT 9% TBSA/mixed SPT, DPT, FT	Mean TBSA: 4.73%	PT, partial thickness; SPT, superficial partial thickness; DPT, deep partial thickness; FT, full thickness; MDB, mixed depth burn.
LL (19), UL (16) Genitalia (4) Thorax (4)	Face UL Face, eyes, UL, LL	(9) 101 111 101	UL 11. (8) UL (5)	LL (7), UL (3), genitalia (2), thorax (1)	LL (14), UL (6) Genitalia (1)	LL (12), UL (8) Face (1)	LL (6) UL (3)	TI	LL (3), UL (1)	LL (21), OL (0) LL LL, UL	LL: 139 (77%) UL: 78 (43%) Genitalia: 18 (10%) Face: 14 (8%) Intraoral: 9 (5%) Thorax: 9 (5%) Eye: 4 (2%) Abdomen: 3 (2%)	partial thickness; SPT, superficial partial thickn
Pants pocket (17) In mouth during use (5) In hand (4), unknown (4)	In hand In hand In mouth during use	Pants pocket (7) In hand (3)	In hand Pants pocket (8) In hand (2)	Pants pocket (7) Breast pocket (1)	Pants pocket (12), in hand (1) Purse (1)	Pants pocket (12), In hand (1) In mouth during use (1)	Pants pocket (6)	Pants pocket	Pants pocket (3)	Pants pocket (3)	111 In pocket (62%) 19 While using (10%) 19 In hand (10%) 6 Others (3%) 25 Unspecified (14%)	LL, lower limb (>thigh), UL, upper limb (>hand); SB, superficial burn; PT, J
2017, Ramirez at al ⁵⁴	2017, Vaught et al. ⁵⁵ 2017, Satteson et al. ⁵⁶ 2017, Anderson et al. ⁵⁷	2017, Smith et al. ⁵⁸	2018, Ackley et al. 2018, Serror et al. ⁵⁹	2018, Maraqa et al. ⁶⁰	2018, Hickey et al. ⁶¹	2018, Gibson et al. ⁶²	2019, Quiroga et al. ⁶³	2019, Michael et al. ¹⁸	2019, Ho et al. ⁶⁴	2020, Karel EY. 2020, Karel EY. Claes et al. ⁶⁶	168 Males (93%) 12 Females (7%) Mean age, 30.8 y old	LL, lower limb (>thigh); UL, u

pocket. Hand burns (type 1) may also accompany these injuries because of the person trying to remove the burning clothing from his or her body or directly from the explosion with the hand in close proximity to the explosion.

• Type 5a: Upper airway injuries that occur from the direct flash or explosion of the ENDS.

Indirect injury:

- Type 4: House or car fire injuries after an ENDS ignites, resulting in a house or car fire. These injuries are sustained during attempts to contain or extinguish the fire that was set off by the device.
- Type 5b: Chemical, subglottic inhalation injuries that occur after inhaling smoke within a closed space (house or car), from a fire that set off following explosion of the ENDS.

In 2018, Serror et al.⁵⁹ published a classification based on four different mechanisms of burn injury:

- Type A: Thermal burns with flames due to the phenomenon of thermal runaway. These are the most frequent burns. There is a deeper burn injury in the center of the burn area.
- Type B: Blasts lesions secondary to explosion. Foreign bodies should be looked for during clinical examination with radiographies or a computed tomography scan if necessary. Foreign bodies should be removed/excised.
- Type C: Chemical alkali burns caused by spreading of the electrolyte solution. This can be confirmed by means of a pH test, and mineral oil should be used to avoid an exothermic reaction.
- Type D: Thermal burns due to overheating though without flames. These are the least frequent burn injuries and happen because the button is locked in the heating position.

The most common mechanism of injury described in this systematic review is of type A (thermal burns due to thermal runaway) according to the classification of Serror et al.⁵⁹ with the most frequent injury pattern being type 3 (waist/groin injuries) according to Patterson et al.⁵³

DISCUSSION

With the increasing popularity of ENDSs, there is a rise in the incidence of burns and other injuries related to the use of these devices. Apart from ENDSs, burns can also be caused, albeit rarely, by the explosion of other devices using a lithium-ion battery, such as mobile phones and flashlights.^{70,71} The specific build shape of an ENDS battery seems to make these devices particularly susceptible to this kind of failure.⁶³ Because there is no requirement to report every ENDS injury, the number of cases reported in this review can be considered as a strong underestimation of the actual frequency of these types of injuries.

If a lithium-ion battery gets breached, patients can be exposed to lithium cobalt oxides or lithium manganese oxides. These may leak onto the skin and can be absorbed by the body.^{35,47,60,72} Increased blood levels of these metals can sporadically lead to heavy metal poisoning.⁶⁰ Since (burn) physicians usually have limited experience with this pathology, they should

be made aware of this risk when encountering ENDS-related injuries. Cobalt toxicity occurs when serum concentrations reach about 100 µg/mL. This chemical can have adverse effects on heart, skin, and nervous systems and may lead to dysfunction of vision and hearing.⁶⁰ Manganese toxicity, on the other hand, has psychological and neurological effects, which may lead to changes in behavior and hallucinations.⁷³ Kite et al.³⁵ reported high cobalt and manganese levels in a patient's plasma because of an ENDS explosion. Debridement and removal of all foreign materials from the wound led to subsequent decrease of these metals' concentration in the patient's plasma.³⁵

Although some authors advise to irrigate the affected burn site with water,⁴⁹ a thorough irrigation should not be performed because contact between these chemical compounds and water can set off a vigorous exothermic reaction producing alkali lithium hydroxide and hydrogen gas.⁷⁴ Nicoll et al.³⁶ reported this phenomenon of alkali chemical burns, and Herlin et al.³⁴ as well as Claes et al.⁶⁶ mentioned their patients experiencing severe pain after local wound care including irrigation with water. This corroborates the findings of Nicoll et al.³⁶ concerning the possible interaction between lithium metals and water causing an exothermic reaction. According to the authors, the symptomatology was discordant with the apparent depth and surface of the burns.

As mentioned previously, there are no specific guidelines for the management of lithium-ion battery chemical burns. Different articles advise pH testing in case of a suspected exposure to these compounds. An alkali pH around 9 to 10 at the site of injury, with a normal pH of the adjacent unaffected skin, confirms the hypothesis. When confirmed, these burns should not be irrigated with water, as the exothermic reaction can lead to both thermal and chemical burns.³⁴ In accordance with Nicoll et al.,³⁶ some authors recommend early cleaning and debridement of the wounds and the use of mineral oil to cover the burns.^{36,48,72} Herlin et al.³⁴ also advocate the idea of an early and aggressive debridement to remove chemical deposits. They describe an incomplete skin graft take and persistent severe pain in their patient, indicating that their debridement only led to a partial elimination of the chemical agents.

When ENDSs ignite or explode in close proximity of the face (e.g., when smoking), there is a risk for ocular injury. Ocular exposure to alkaline substances can cause significant cornea, conjunctiva, and anterior segment injuries, which carry a poor prognosis depending on the grade of the injury.⁷⁵ In our center, the Ghent Burn Centre, a hypertonic, amphoteric, polyvalent, and chelating decontamination solution (Diphoterine; Laboratoire Prevor, Valmondois, France) is now used in the treatment of cutaneous and ocular chemical burns.⁷⁶

Literature review showed that a variety of different management options have been used in the treatment of ENDS-related burns, ranging from conservative treatment with conventional dressings to surgical debridement, enzymatic debridement, or hydrosurgery, with or without skin grafting.⁶⁴ However, these ENDS-specific treatments are based on limited experiences in single cases or case series and therefore provide a poor quality of evidence. The standard care of a burn injury remains surgical techniques (debridement with or without skin grafting) combined with outpatient management (dressing and ointment). In this systematic review, 43% of patients underwent a surgical procedure. Enzymatic debridement on the other hand, has gained greater relevance in the past few years.^{77,78} Nexobrid (Mediwound Germany GmbH, Russelsheim) is a recent nonsurgical, enzymatic tool to treat deep partial thickness and full-thickness burn injuries. It is specific and selective in the removal of the eschar and other dead tissues without harming the surrounding healthy tissues, reducing blood loss, and possibly the need for skin grafting.⁶ Its use is contraindicated by the manufacturer for the treatment of chemical or mixed burns. Off-label use, however, as suggested by Claes et al.,66 can be recommended after thorough irrigation of the burn, to remove the chemical substance. Despite the long mean healing time of 48 days (range, 35-61 days), no hypertrophic scarring was observed at follow-up. No clinical nor laboratory adverse events occurred, substantiating the safety and value of enzymatic debridement after ENDS-related burns.66 Furthermore, the selectivity and simplicity of the enzymatic method make bedside treatment of burns possible (TBSA <10% and without comorbidities).⁷⁸ This is certainly useful in the treatment of older patients and patients with health issues for whom surgical debridement is not advised.

Regarding preventive measures, in the first place, the manufacturers should invest in research and development so as to improve the safety features of the batteries.⁶⁷ Brown and Cheng⁵ recommend that manufacturers prevent thermal runaway by using circuits that protect against overcharging, integrating cut-offs for thermal power, and using internal overpressure relief mechanisms. Second, health professionals should advocate the regulation of ENDS batteries and the prohibition of ENDSs in places where ignition or explosion of these devices could lead to major destruction. Moreover, both the public health professionals and the ENDS manufacturers need to increase efforts to inform users about safe handling practices for batteries. This information should be targeted toward groups experiencing ENDS injuries most often, mainly young males.^{45,67}

While the long-term effects have been extensively discussed, for example, the potential carcinogenicity of certain e-liquid components as well as e-cigarette or vaping product use–associated lung injury, there has been minimal consideration of mechanical risks.⁷ The burn severity and the commonly injured locations substantiate the need for an even stricter regulation of ENDSs and their manufacturing, as well as improved dissemination of information on incidents, for safety and prevention purposes.⁶⁷

Until now, no official guidelines have been published on the management of injuries related to ENDSs. The proposed classification into burn types as put forward by Patterson et al.,⁵³ although thought-provoking, has mostly been used in their own study. The added value of this classification in its effort to provide guidance in the adequate management of these types of injuries seems limited, and therefore, it has not (yet) been adopted by the burn society. The additional value of the classification, as described by Serror et al.,⁵⁹ seems more straightforward, as there is a direct link between their proposed groups and the recommended treatment, although it has not been widely accepted by the burn society either.

In conclusion, with the increasing popularity of ENDSs, a further rise in the number of patients presenting with ENDS-related injuries, can be expected. It is thus crucial that all health care professionals treating these (burn) injuries be aware of the complexity of injuries associated with these devices and be able to manage them appropriately.¹ In accordance with

Jones et al.,¹ we propose that all patients presenting with ENDSrelated burns should receive pH testing using Litmus paper, before irrigation. In case an alkali burn is confirmed, the wound should first be managed using mineral oil or another nonaqueous substance, to prevent the potential exothermic burn injuries secondary to the chemical components of the ENDS. The flowchart put forward by Jones et al.¹ can be used by physicians as a guidance when being confronted with these types of injuries.

- 1. Assess for soft tissue or bony injury secondary to the blast component.
- 2. Assess for inhalation injury/airway compromise if a blast occurred while using the device.
- 3. Check the wound pH with Litmus paper before irrigation of the burn injury. If the pH is alkaline, use mineral oil (or another nonaqueous substance⁶⁶), and if it is neutral, use standard practice.
- 4. Consider surgical (or enzymatic⁶⁶) debridement and skin grafting versus conservative management.

CONCLUSIONS

Injuries from overheating, ignition, or explosion of ENDSs are an emerging, strongly underestimated and underresearched topic. There is growing evidence that ENDSs are in fact a public safety concern, which demands increased regulation and design changes to improve their safety.

The etiology of ENDS explosions is still unclear, and there are no specific guidelines on their unique management. Because of the risk of lithium-ion leakage following a breach in the battery, pH testing before irrigation should be advised, and caution should be exercised when exposing these burns to irrigation with water. The use of mineral oil or other nonaqueous substances to cover these burns should be advocated, followed by early cleaning and debridement to remove any residual lithium contamination. When surgical debridement is not an option (e.g., in older patients and patients with health issues), enzymatic debridement can be a treatment option for these types of injuries as well.

Most incidents could be prevented through battery design regulation and public education related to ENDS battery safety. Improved surveillance of ENDS-related injuries is needed, and both the users and health care providers should be made aware of the risks and be advised about how to safely handle these devices.

In contrast to other articles, this systematic review included all injuries related to ENDS overheating, ignition, and explosion. To our knowledge, this is the most extensive systematic review performed to date.

AUTHORSHIP

T.V. contributed in the literature search, data analysis, data interpretation, and writing. E.D.W. contributed in the literature search, study design, and data interpretation. H.H. contributed in the data collection and study design. J.V. contributed in the data collection and study design. P.D.C. contributed in the data collection and study design. M.B. contributed in the data interpretation, writing, and critical revision. S.M. contributed in the data interpretation, writing, and critical revision. K.E.Y.C. contributed in the literature search, study design, writing, and critical revision.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

- Jones CD, Ho W, Gunn E, Widdowson D, Bahia H. E-cigarette burn injuries: comprehensive review and management guidelines proposal. *Burns*. 2019; 45(4):763–771.
- Available at: https://www.nhs.uk/smokefree/help-and-advice/e-cigarettes. Accesed June 1, 2020.
- Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control.* 2014; 23(2):133–139.
- Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health.* 2014;11(4):4356–4373.
- Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. *Tob Control*. 2014;23 Suppl 2(Suppl 2):ii4–ii10.
- Warner KE. Frequency of e-cigarette use and cigarette smoking by American students in 2014. Am J Prev Med. 2016;51(2):179–184.
- Shastry S, Langdorf MI. Electronic vapor cigarette battery explosion causing shotgun-like superficial wounds and contusion. West J Emerg Med. 2016; 17(2):177–180.
- Archambeau BA, Young S, Lee C, Pennington T, Vanderbeek C, Miulli D, Culhane J, Neeki M. E-cigarette blast injury: complex facial fractures and pneumocephalus. *West J Emerg Med.* 2016;17(6):805–807.
- Farsalinos KE, Poulas K, Voudris V, Le Houezee J. Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries. *Addiction*. 2016;111(11):2032–2040.
- Pisinger C, Dossing M. A systematic review of health effects of electronic cigarettes. *Prev Med.* 2014;69:248–260.
- Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control.* 2010;19(2):98–103.
- Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, Polosa R. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One*. 2013;8(6):e66317.
- Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*. 2013;382(9905):1629–1637.
- McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev.* 2014;(12): CD010216.
- Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols. N Engl J Med. 2015;372(4):392–394.
- Lerner CA, Sundar IK, Yao H, Gerloff J, Ossip DJ, McIntosh S, Robinson R, Rahman I. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. *PloS One*. 2015;10(2):e0116732.
- Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, Riggs NR, Stone MD, Khoddam R, Samet JM, Audrain-McGovern J. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA*. 2015;314(7):700–707.
- Michael R, Ebraheim N, Maier J, Tanios M, Kouri A. Electronic cigarette burns: a case report and review of current literature. *Case Rep Orthop.* 2019;2019:4231764.
- Taylor J, Wiens T, Peterson J, et al, Lung Injury Response Task Force. Characteristics of e-cigarette, or vaping, products used by patients with associated lung injury and products seized by law enforcement — Minnesota, 2018 and 2019. MMWR Morb Mortal Wkly Rep. 2019;68(47):1096–1100.
- Kalininskiy A, Bach CT, Nacca NE, Ginsberg G, Marraffa J, Navarette KA, McGraw MD, Croft DP. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. *Lancet Respir Med.* 2019;7(12):1017–1026.
- Moritz ED, Zapata LB, Lekiachvili A, et al, Lung Injury Response Epidemiology/Surveillance Group; Lung Injury Response Epidemiology/ Surveillance Task Force. Update: characteristics of patients in a national outbreak of e-cigarette, or vaping, product use-associated lung injuries — United States, October 2019. *MMWR Morb Mortal Wkly Rep.* 2019; 68(43):985–989.

- Ring Madsen L, Vinther Krarup NH, Bergmann TK, Bærentzen S, Neghabat S, Duval L, Knudsen ST. A cancer that went up in smoke: pulmonary reaction to e-cigarettes imitating metastatic cancer. *Chest.* 2016;149(3): e65–e67.
- Fracol M, Dorfman R, Janes L, Kulkarni S, Bethke K, Hansen N, Kim J. The surgical impact of E-cigarettes: a case report and review of the current literature. *Arch Plast Surg.* 2017;44(6):477–481.
- Goodenough JB, Park KS. The li-ion rechargeable battery: a perspective. J Am Chem Soc. 2013;135(4):1167–1176.
- Ackley E, Williams JTB, Kunrath C, Monson M, Ignatiuk A, Gaensbauer J. Too hot to handle? When vaporizers explode. *J Pediatr*. 2018;196:320–320.e1.
- Wang QS, Ping P, Zhao XJ, Chub GQ, Sun JH, Chen CH. Thermal runaway caused fire and explosion of lithium ion battery. *J Power Sources*. 2012;208: 210–224.
- Rossheim ME, Livingston MD, Soule EK, Zeraye HA, Thombs DL. Electronic cigarette explosion and burn injuries, US Emergency Departments 2015–2017. *Tob Control.* 2019;28(4):472–474.
- Corey CG, Chang JT, Rostron BL. Electronic nicotine delivery system (ENDS) battery-related burns presenting to US emergency departments, 2016. *Inj Epidemiol.* 2018;5(1):4.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006–1012.
- Colaianni CA, Tapias LF, Cauley R, Sheridan R, Schulz JT, Goverman J. Injuries Caused by Explosion of Electronic Cigarette Devices. *Eplasty.* 2016; 16:ic9.
- Walsh K, Sheikh Z, Johal K, Khwaja N. Rare case of accidental fire and burns caused by e-cigarette batteries. *BMJ Case Rep.* 2016;2016;bcr2015212868.
- Kumetz EA, Hurst ND, Cudnik RJ, Rudinsky SL. Electronic cigarette explosion injuries. Am J Emerg Med. 2016;34(11):2252.e1–2252.e3.
- Sheckter C, Chattopadhyay A, Paro J, Karanas Y. Burns resulting from spontaneous combustion of electronic cigarettes: a case series. *Burns Trauma*. 2016;4:35.
- Herlin C, Bekara F, Bertheuil N, Frobert P, Carloni R, Chaput B. Deep burns caused by electronic vaping devices explosion. *Burns*. 2016;42(8): 1875–1877.
- Kite AC, Le BQ, Cumpston KL, Hieger MA, Feldman MJ, Pozez AL. Blast injuries caused by vape devices: 2 case reports. *Ann Plast Surg.* 2016;77(6): 620–622.
- Nicoll KJ, Rose AM, Khan MA, Quaba O, Lowrie AG. Thigh burns from exploding e-cigarette lithium ion batteries: first case series. *Burns*. 2016;42(4): e42–e46.
- Paley GL, Echalier E, Eck TW, Hong AR, Farooq AV, Gregory DG, Lubniewski AJ. Corneoscleral laceration and ocular burns caused by electronic cigarette explosions. *Cornea*. 2016;35(7):1015–1018.
- Khairudin MN, Mohd Zahidin AZ, Bastion ML. Front to back ocular injury from a vaping-related explosion. *BMJ Case Rep.* 2016;2016: bcr2016214964.
- Jiwani AZ, Williams JF, Rizzo JA, Chung KK, King BT, Cancio LC. Thermal injury patterns associated with electronic cigarettes. *Int J Burns Trauma*. 2017;7(1):1–5.
- Norii T, Plate A. Electronic cigarette explosion resulting in a C1 and C2 fracture: a case report. J Emerg Med. 2017;52(1):86–88.
- Roger JM, Abayon M, Elad S, Kolokythas A. Oral trauma and tooth avulsion following explosion of e-cigarette. J Oral Maxillofac Surg. 2016;74(6):1181–1185.
- Harrison R, Hicklin D Jr. Electronic cigarette explosions involving the oral cavity. J Am Dent Assoc. 2016;147(11):891–896.
- Bohr S, Almarzouqi F, Pallua N. Extensive burn injury caused by fundamental electronic cigarette design flaw. *Ann Burns Fire Disasters*. 2016;29(3): 231–233.
- Cason DE, Morgan DE, Pietryga JA. Injuries from an exploding e-cigarette: a case report. Ann Intern Med. 2016;165(9):678–679.
- Hassan S, Anwar MU, Muthayya P, Jivan S. Burn injuries from exploding electronic cigarette batteries: an emerging public health hazard. *J Plast Reconstr Aesthet Surg.* 2016;69(12):1716–1718.
- Moore J, Mihalache G, Messahel A. "Exploding" electronic cigarette: a case report. Br J Oral Maxillofac Surg. 2016;54(9):1056–1057.

- Brooks JK, Kleinman JW, Brooks JB, Reynolds MA. Electronic cigarette explosion associated with extensive intraoral injuries. *Dent Traumatol.* 2017; 33(2):149–152.
- Bauman ZM, Roman J, Singer M, Vercruysse GA. Canary in the coal mine—initial reports of thermal injury secondary to electronic cigarettes. *Burns*. 2017;43(3):e38–e42.
- Harshman J, Vojvodic M, Rogers AD. Burns associated with e-cigarette batteries: a case series and literature review. CJEM. 2018;20(S2):S20–S28.
- Foran I, Oak NR, Meunier MJ. High-pressure injection injury caused by electronic cigarette explosion: a case report. JBJS Case Connect. 2017;7(2):e36.
- Arnaout A, Khashaba H, Dobbs T, Dewi F, Pope-Jones S, Sack A, Estela C, Nguyen D. The Southwest UK Burns Network (SWUK) experience of electronic cigarette explosions and review of literature. *Burns*. 2017;43(4):e1–e6.
- Treitl D, Solomon R, Davare DL, Sanchez R, Kiffin C. Full and partial thickness burns from spontaneous combustion of e-cigarette lithium-ion batteries with review of literature. *J Emerg Med.* 2017;53(1):121–125.
- Patterson SB, Beckett AR, Lintner A, Leahey C, Greer A, Brevard SB, Simmons JD, Kahn SA. A novel classification system for injuries after electronic cigarette explosions. *J Burn Care Res.* 2017;38(1):e95–e100.
- Ramirez JI, Ridgway CA, Lee JG, Potenza BM, Sen S, Palmieri TL, Greenhalgh DG, Maguina P. The unrecognized epidemic of electronic cigarette burns. *J Burn Care Res.* 2017;38(4):220–224.
- Vaught B, Spellman J, Shah A, Stewart A, Mullin D. Facial trauma caused by electronic cigarette explosion. *Ear Nose Throat J.* 2017;96(3):139–142.
- Satteson ES, Walker NJ, Tuohy CJ, Molnar JA. Extensive hand thermal and blast injury from electronic cigarette explosion: a case report. *Hand (N Y)*. 2017;13(3):NP1–NP5.
- Anderson H, Richie C, Bernard A. A surprisingly volatile smoking alternative: explosion and burns as risks of E-cigarette use. *J Burn Care Res.* 2017; 38(5):e884.
- Smith SL, Smith C, Cheatham M, Smith HG. Electronic cigarettes: a burn case series. *Jnp-J Nurse Pract.* 2017;13(10):693–699.
- Serror K, Chaouat M, Legrand MM, Depret F, Haddad J, Malca N, Mimoun M, Boccara D. Burns caused by electronic vaping devices (e-cigarettes): a new classification proposal based on mechanisms. *Burns*. 2018;44(3):544–548.
- Maraqa T, Mohamed MAT, Salib M, Morris S, Mercer L, Sachwani-Daswani GR. Too hot for your pocket! Burns from e-cigarette lithium battery explosions: a case series. *J Burn Care Res.* 2018;39(6):1043–1047.
- Hickey S, Goverman J, Friedstat J, Sheridan R, Schulz J. Thermal injuries from exploding electronic cigarettes. *Burns*. 2018;44(5):1294–1301.
- Gibson C, Eshraghi N, Kemalyan N, Mueller C. Electronic cigarette burns: a case series. *Dent Traumatol.* 2019;21(2):103–106.

- Quiroga L, Asif M, Lagziel T, Bhat D, Caffrey J. E-cigarette battery explosions: review of the acute management of the burns and the impact on our population. *Cureus*. 2019;11(8):e5355.
- Ho W, Jones CD, Widdowson D, Bahia H. Bromelain-based enzymatic debridement of e-cigarette burns: a single unit experience. J Wound Care. 2019;28(11):758–761.
- Chu H, Sen S. A proposed further sub-classification of burns caused by electronic vaping devices. *Burns*. 2020;46(1):241–242.
- Claes KEY, Vyncke T, De Wolf E, Hoeksema H, Verbelen J, Monstrey S. Enzymatic debridement as an effective treatment for combined flame and chemical burns caused by e-cigarettes. *Am J Emerg Med.* 2020;S0735-6757(20) 30103-0.
- Seitz CM, Kabir Z. Burn injuries caused by e-cigarette explosions: a systematic review of published cases. *Tob Prev Cessat*. 2018;4:32.
- Sunil NP, Ahmed F, Jash PK, Gupta M, Suba S. Study on surgical management of post burn hand deformities. J Clin Diagn Res. 2015;9(8): PC06–PC10.
- Greenhalgh DG, Hinchcliff K, Sen S, Palmieri TL. A ten-year experience with pediatric face grafts. *J Burn Care Res.* 2013;34(5):576–584.
- Karabagli Y, Kose AA, Cetin C. Partial thickness burns caused by a spontaneously exploding mobile phone. *Burns*. 2006;32(7):922–924.
- Mankowski PJ, Kanevsky J, Bakirtzian P, Cugno S. Cellular phone collateral damage: a review of burns associated with lithium battery powered mobile devices. *Burns*. 2016;42(4):e61–e64.
- Robinett DA, Shelton B, Dyer KS. Special considerations in hazardous materials burns. J Emerg Med. 2010;39(5):544–553.
- 73. Barceloux DG. Manganese. J Toxicol Clin Toxicol. 1999;37(2):293-307.
- Paulino JF, Busnardo NG, Afonso JC. Recovery of valuable elements from spent Li-batteries. J Hazard Mater. 2008;150(3):843–849.
- Kuckelkorn R, Schrage N, Keller G, Redbrake C. Emergency treatment of chemical and thermal eye burns. *Acta Ophthalmol Scand*. 2002; 80(1):4–10.
- Lewis CJ, Al-Mousawi A, Jha A, Allison KP. Is it time for a change in the approach to chemical burns? The role of Diphoterine[®] in the management of cutaneous and ocular chemical injuries. *J Plast Reconstr Aesthet Surg.* 2017;70(5):563–567.
- Cherubino M, Pellegatta I, Sallam D, Pulerà E, Valdatta L. Enzymatic debridement after mobile phone explosion: a case report. *Ann Burns Fire Di*sasters. 2016;29(4):273–275.
- Rosenberg L, Krieger Y, Bogdanov-Berezovski A, Silberstein E, Shoham Y, Singer AJ. A novel rapid and selective enzymatic debridement agent for burn wound management: a multi-center RCT. *Burns*. 2014;40(3):466–474.