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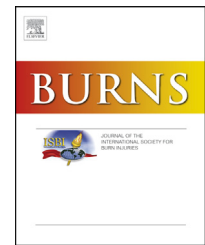
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# A systematic review and meta-analysis of randomized trials evaluating the efficacy of autologous skin cell suspensions for re-epithelialization of acute partial thickness burn injuries and split-thickness skin graft donor sites

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## ABSTRACT

**Background:** This systematic review evaluated the efficacy of autologous skin cell suspensions (ASCS) on the re-epithelialization of partial thickness burn injuries and skin graft donor site wounds.

**Methods:** Four databases (EMBASE, Google Scholar, MEDLINE, Web of Science), grey literature and select journal hand-searching identified studies from 1975 - 2020. Randomized trials evaluating partial thickness burn management with non-cultured ASCS compared to any other intervention were included. Time to re-epithelialization (TTRE) was the primary

**Abbreviations:** ASCS, Autologous skin cell suspension; BRACS, Biobrane<sup>®</sup>, RECELL<sup>®</sup> Autologous Skin; Cell, Suspension and Silver Dressings; B-TBSA, burn total body surface area; BW, Burn Wound; CI, Confidence Interval; CHIPPS, Children and Infant's Post-operative Pain Scale; CHU9D, Child Health Utility 9D; DSW, Donor Site Wound; EPOC, Effective Practice and Organisation of Care; FLACC, Face, Legs, Activity, Cry, Consolability; FPS-R, Faces Pain Scale-Revised; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HRQoL, Health Related Quality of Life; IQR, Inter quartile range; IV, Inverse Variance; OR, Odds Ratio; POSAS, Patient and Observer Scar Assessment Scale; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; RES<sup>™</sup>, Regenerative Epidermal Suspension; SD, Standard Deviation; SMD, Standardized Mean Difference; SSG, Split-thickness skin graft; TiDieR, Template for Intervention Description and Replication; TTRE, Time to Re-Epithelialization; VAS, Visual Analogue Scale; VSS, Vancouver Scar Scale; WHO, World Health Organisation.

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Child  
Donor site wound  
Autograft  
Dermal  
Burn  
Wound Healing

outcome. Three independent researchers completed screening, data extraction and certainty of evidence assessment using Cochrane Risk of Bias Tool and Grading of Recommendations Assessment, Development and Evaluation.

**Results:** Five trials ( $n = 347$ ) reported on adults (2 trials) and children (1 trial) with burn wounds, and adults with donor site wounds (2 trials). The effect of ASCS compared to control on TTRE in adult burn wounds was not estimable. TTRE was shorter in pediatric burn wounds (SMD -1.75 [95% CI: -3.45 to -0.05]) and adult donor site wounds (SMD -5.71 [95% CI: -10.61 to -0.81]) treated with ASCS. The certainty of evidence was very low.

**Conclusion:** Compared to standard care, ACSC may reduce pediatric partial thickness burn wound and adult split-thickness skin graft donor site TTRE.

**Registration:** PROSPERO CRD42019133171

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## 1. Background

Globally, non-fatal burn injuries are the leading cause of morbidity including functional, aesthetic and psychological burden to patient and health care provider (1). Damage to the integrity of entire epidermis and varied depths of the dermis occur in a partial thickness burn injury which can potentially re-epithelialize without surgical management. The process of re-epithelialization begins within 24 hours of injury (2). However, delayed time to re-epithelialization (TTRE) is associated with increased risk of scar formation and inferior cosmesis (3,4). Hence, reduced time to wound re-epithelialization and scar

formation, and improved cosmesis, drive the burn wound management approaches today.

Wound management approaches influence re-epithelialization though the impact of keratinocyte proliferation and subsequent wound closure (5). Autologous skin cell suspensions (ASCS) are epidermal cells, delivered in a solution via spray or droplet form, to a wound. In the past four decades, ASCS have progressed remarkably from serial keratinocyte cultures (6) to currently available commercial ASCS formulations. However, evidence to support the role of ASCS in contemporary burn wound management is unclear as our preliminary searches identified only a handful of rigorous studies and no systematic reviews of the efficacy of ASCS.

For a proportion of individuals with partial thickness burn injuries, a skin graft may be indicated to achieve wound closure. A skin graft involves the removal of healthy skin from a donor site wound (DSW) to be applied to a clean burn wound (BW). In contrast to a burn wound, a split-thickness skin graft (SSG) DSW has an even depth, of specified size and in a pre-specified anatomical location with most epidermal appendages intact (7). The primary objective of this review was to determine the effectiveness of ASCS when compared to non-ASCS usual treatment on time to wound re-epithelialization of acute partial thickness burn injuries and split-thickness skin graft donor site wounds. The secondary objective of the review was to determine the effectiveness of ASCS when compared to non-ASCS usual treatment on the outcomes of acute pain, acute distress, anxiety, scar sensitivity (itch, tightness), scar characteristics (pigmentation, thickness), scar specific health-related quality of life (HRQoL), infection and further surgical management.

## 2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (6). A protocol was registered prospectively (PROSPERO Record ID = CRD42019133171) (8). Randomized controlled trials published from 1975 to 2020, that met the inclusion criteria (Table 1), were selected for screening. The primary outcome was wound re-epithelialization. Secondary outcomes were acute pain, acute distress, anxiety, scar sensitivity (itch, tightness), scar characteristics (pigmentation, thickness), scar specific health-related quality of life, infection, and for further surgical management (8). Publication period was based on the first description of serial keratinocyte culture in 1975 (6).

## 3. Search strategy

Three sources were searched for eligible studies: electronic databases of EMBASE (1988 to Nov 2020), Google Scholar, PUBMED (1950 to Nov 2020) and Web of Science (1900 to Nov 2020); grey literature databases (OpenGrey, New York Academy of Medicine Grey Literature Report, ProQuest, WHO Clinical Trials Registry Platform and ClinicalTrials.gov) and relevant burns journals. Database selection was based on a study indicating the selected databases yielded an overall recall of 98% for the field of medical research (9). The first 200 items were included from each Google Scholar search term entered. Keywords and Medical Subject Headings were used to complete the searches using terms such as "partial thickness burn", "non-cultured autologous cell suspension" and "donor site" or variations of these terms. The three search strategies that identified the most results are presented in Appendix A1-3. No language restrictions were applied. Reference lists of included studies were also searched for relevant studies.

## 4. Study selection

Retrieved studies were uploaded into EndNote X9 [EndNote®, Clarivate Analytics, US] then into Covidence [Covidence® systematic review software, Australia] for screening, data extraction and Cochrane risk of bias assessment. Two independent reviewers (AB, TB) completed staged screening of titles, abstracts, and full texts of retrieved studies. Disagreements were resolved through consensus-based discussion after each stage.

**Table 1 – Eligibility Criteria.**

Criteria	Inclusion	Exclusion
Participants	Humans of all age groups, partial thickness burn injuries and split-thickness skin graft donor site wounds	Animal studies
Intervention	Autologous skin cell suspension: non-cultured mixture of epithelial cells used as wound management approaches with or without a skin graft for treatment of burn wounds or split-thickness skin graft donor sites in suspension format as a spray or droplet application.	Autologous skin cells not used in suspension format for treatment of burns. Cultured epithelial sheet autograft or cultured epithelial cells in suspension format. Use of non-cultured, autologous skin cell suspension to treat conditions other than burns or split-thickness skin graft (e.g. vitiligo, chronic ulcers, wounds, or full thickness skin graft donor site).
Comparator	Wound management approach that differ from autologous skin cell suspensions and include standard of care dressings/treatment with or without a skin graft	Where no standard of care dressings/treatment including skin, graft is part of the study design.
Outcomes	Wound re-epithelialization, pain, scar sensitivity (itch), scar characteristics (pigmentation, thickness), scar specific health related quality of life, infection and further surgery.	Cost
Study Design	Randomized controlled trials (including cross-over and cluster randomized controlled trials) and pilot randomized controlled trials	All other study designs not included as part of a randomized controlled trial: editorials, qualitative studies, surveys, systematic reviews, observational studies, quasi-experimental studies, and animal studies.
Time Frame	1975 - 2019	Studies completed before 1975

**Table 2 – Study Characteristics.**

First Author Year	Country	Study Design	Intervention	Site	Sample Size	Age (Mean ± SD, years)	Gender M:F	Skin Type/Ethnicity n (%)	Burn/Donor site wound Depth (mm)	B-TBSA (Mean ± SD, cm <sup>2</sup> )	Donor Site Area (Mean ± SD, cm <sup>2</sup> )
Gravante 2007	Italy	Parallel & within subject (n = 7) RCT	ASCS vs Control	BW	82	ASCS: 49 ± 9 Control: 53 ± 10	ASCS: 24:18 Control: 26:14	Not reported	BW: DPT DSW: 0.2 – 0.3	ASCS: 176 ± 84 Control: 180 ± 100	ASCS:2.2 ± 1 Control:110 ± 50
Holmes2018	USA	Within-subject RCT	ASCS vs Control	BW	101	39.5 ± 13.1	85:16	White 59(58.4) Black 29(19.8) Hispanic19(18.8)	BW: DPT DSW: 0.15 – 0.2	ASCS: 168 ± 68.40 Control: 165 ± 65.80	ASCS:4.7 ± 3.2 Control: 194.1 ± 158.5
Guerid 2013	Switzerland	Parallel RCT	ASCS & Platelet vs Platelet vs Control	DSW	45	ASCS & Platelet: 42.5 ± 12 Platelet: 45.5 ± 15.1 Control: 46.9 ± 20.5	ASCS & Platelet: 5:10 Platelet: 9:6 Control: 11:4	Not reported	DSW: 0.2	Not reported	180 ± 43.75
Hu2017	China	Parallel RCT	ASCS vs Control	DSW	106	ASCS: 51.3 ± 18.1 Control: 47.8 ± 16.7	ASCS: 40:13 Control: 36:17	Chinese (100)	DSW: 0.25	Not reported	ASCS: 60.5 ± 32.2 Control: 56.9 ± 28.4
Wood2012	Australia	Pilot, Parallel RCT	ASCS & Biobrane vs Biobrane vs Control	BW	13	ASCS & Biobrane: 1.32 ± 0.55 Biobrane: 4.95 ± 3.91 Control: 5.03 ± 2.50	ASCS & Biobrane: 3:2 Biobrane: 2:2 Control: 1:3	Caucasian: 7(62) Australian Ab- original: 2(15) Asian: 3(23)	Not reported	ASCS: 5.2 ± 3.19 Bio- brane: 8 ± 5.23 Control: 4.5 ± 0.58	Not reported

Abbreviation: SD: Standard deviation; M: Male; F: Female; n: number; B-TBSA: Total Body Surface Area Burned; mm: millimeter; cm: centimeter; RCT: Randomized controlled trial; ASCS: Autologous skin cell suspension; BW: burn wound; DPT: Deep partial thickness; DSW: Donor site wound; USA: United States of America; vs: versus.

## 5. Data extraction

The data extraction template incorporated items from the Cochrane Effective Practice and Organisation of Care (EPOC) and Template for Intervention Description and Replication (TiDieR) (10) checklists. Inclusion criteria, interventions, participants, setting, methods, outcomes, results limitations were the main categories covered by the EPOC checklist. Similarly, subcategories of data retrieved with the TiDieR checklist were intervention, rationale, materials, procedure, intervention provider, modes of delivery, location, schedule of delivery, tailoring, modification, and intervention adherence. The combined template was uploaded into Covidence<sup>®</sup> and data extraction was completed by two independent reviewers (AB, TB). In cases where overlapping studies arising from a single cohort were identified likely, the largest cohort from the latest publication was included for data extraction. Data available only in graphs were extracted with Plot Digitizer [v2.6.8, Software, USA].

## 6. Certainty assessment

Three independent reviewers (AB, ZT, TB) completed the certainty assessment. At a study level, the Cochrane Risk of Bias tool was completed in Covidence<sup>®</sup> using six domains: selection, performance, detection, attrition, reporting, and 'other bias' (11,12). 'Other bias' was pre-specified to include baseline differences, outcome measure validity, publication and funding bias, study design (e.g., intention-to-treat analysis), baseline co-variables, fidelity, and adherence. The domains of randomization and blinding were deemed high priority by the author team. Certainty assessment at an outcome level (time to re-epithelialization, pain and infection), was completed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (13) using a two stage consensus approach in GRADEpro GDT [GRADEpro Guideline Development Tool software, Canada]. First stage consensus was established between AB, ZT. Second stage consensus was then established between AB, ZT and an independent third party (TB). The items completed for the GRADE tool were risk of bias, imprecision, inconsistency, indirectness, publication bias and overall judgement.

## 7. Meta-analysis

As burn wounds and donor site wounds are characteristically different, the extracted data was not pooled for these wound types. Where possible, quantitative data were aggregated for meta-analysis. Absolute effect sizes were presented as standardized mean difference (SMD) using Hedges' adjusted 'g' (14), with 95% confidence intervals (CI) for continuous outcomes and odds ratios (OR) with 95%CI for dichotomous outcomes. A random-effects model was applied to all outcomes using the inverse variance method based on heterogeneity identified in studies (12,15). Between study variance was assessed with Tau<sup>2</sup>( $\tau^2$ ), and heterogeneity was calculated with Chi<sup>2</sup> ( $\chi^2$ ), inconsistency measured with the I<sup>2</sup> statistic, and the

p value for heterogeneity (16). Outcomes not amenable to meta-analysis were synthesised narratively.

Sub-group analyses were conducted for all outcomes, where possible, stratified by patient age and wound type: adult (age  $\geq$  18years) and paediatric (age  $<$  18 years) burn wounds, and adult and paediatric donor site wounds. A two-part sensitivity analysis was planned. Firstly, the impact of risk of bias was examined by excluding studies with high or unclear risk of bias across greater than 50% of the risk of bias items at the study level. Secondly, the impact of sample size of included studies (greater than 30 participants) on the outcomes was evaluated. Considerable heterogeneity between studies was considered present when I<sup>2</sup>  $>$ 75% and other heterogeneity statistics (e.g. p  $<$ 0.05) supported the presence of heterogeneity (17,18). The Review Manager (RevMan) [Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014] was used to present risk of bias results and conduct meta-analyses.

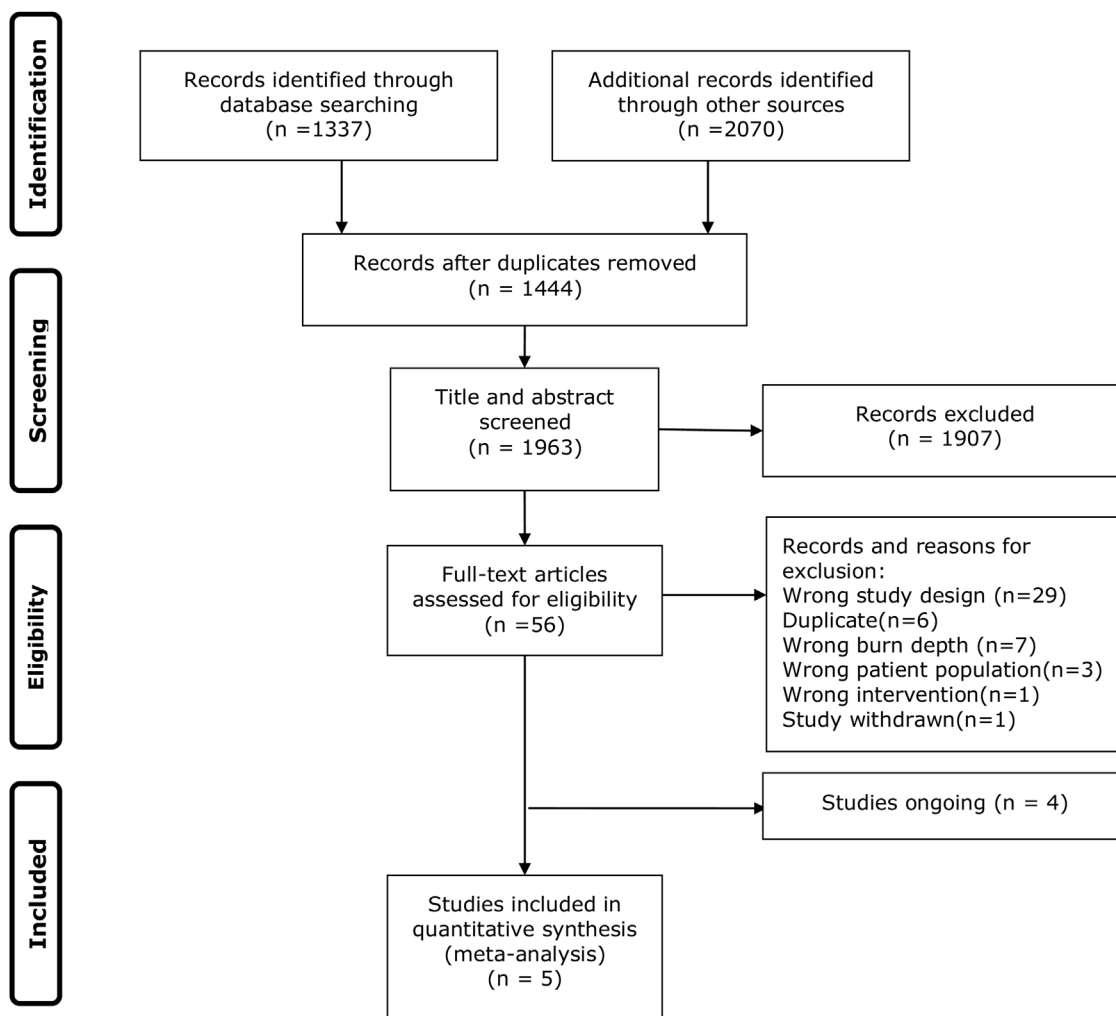
## 8. Results

### 8.1. Study Selection

A total of 3407 studies were screened for eligibility, with five studies (19–23) included for data extraction and analysis (Table 2). Four ongoing studies were not included due to no available results. The selection process and reasons for exclusion are shown in the PRISMA flow diagram (Fig. 1). Excluded studies are detailed in Appendix B. Authors of five included studies were contacted for further information. Authors from two studies (20,23) replied with data and helpful clarifications.

### 8.2. Study Characteristics

Four randomized trials and one pilot randomized trial enrolled 347 patients for this review (19–22). The patient and study characteristics are summarised in Table 2. Four studies were conducted in adults (n = 334). Only one study was conducted in children (n = 13) (23). There were more male (n = 242) than female (n = 105) participants. The intervention (ASCS) was applied to burn wounds in three studies and SSG DSW in two studies. The depth of DSW reported, ranged from 0.15 mm to 0.25 mm in the adult studies. The non-cultured ASCS was prepared with the RECELL<sup>®</sup> autologous cell harvesting device (19,20,22,23) and using a laboratory method (21). In two of the studies, ASCS was combined with a second intervention as part of a three-arm trial (21,23). All five studies evaluated wound re-epithelialization, acute pain, and infection. Four studies reported time to re-epithelialization (19,21–23). Secondary outcomes of scar sensitivity, scar characteristics, and further surgical intervention were measured by some of the studies, Table 3. None of the studies evaluated anxiety, distress, or scar specific HRQoL. The studies were published over an 11-year period (2007 – 2018) and data collection for these studies occurred over a 12-year period (2004 – 2016). Four randomized trials are prospectively registered and aim to evaluate ASCS prepared with the RECELL<sup>®</sup> autologous cell harvesting device in children aged 0-16 years, accumulating



**Fig. 1 – PRISMA Flow diagram of included and excluded studies.**  
n – number.

further evidence regarding the efficacy of ASCS in children (24–27). Two of these trials have been suspended in response to the COVID-19 global pandemic (24,27). Data is currently being analysed for one of these studies, hence was not eligible for inclusion in this review (28).

### 8.3. Certainty assessment at study level

The risk of bias at a study level is illustrated in Fig. 2 and was mostly high or unclear. Random sequence generation (19,20,23) and allocation concealment (19–22) were predominantly of unclear risk of bias. No domain had a predominantly low risk of bias. Unclear ratings were mainly attributed to lack of adequate description in the study methodology. Four out of five studies (19,20,22,23) received industry funding and had results in favor of the funders' product (AVITA Medical, California, USA), thus funding bias may have been present.

### 8.4. Certainty assessment at outcomes level

The three outcomes of time to re-epithelialization, pain and infection had a very low certainty of evidence, across all the

studies (19–22) using the GRADE approach (Table 4A–B). The very low certainty of evidence was due to serious to very serious ratings for risk of bias, indirectness, imprecision, inconsistency, and strongly suspected publication bias. For the same three outcomes, in the single pediatric study examining burn wounds (23), certainty of evidence was very low, with serious to very serious ratings for risk of bias and imprecision and strongly suspected publication bias (Table 4C).

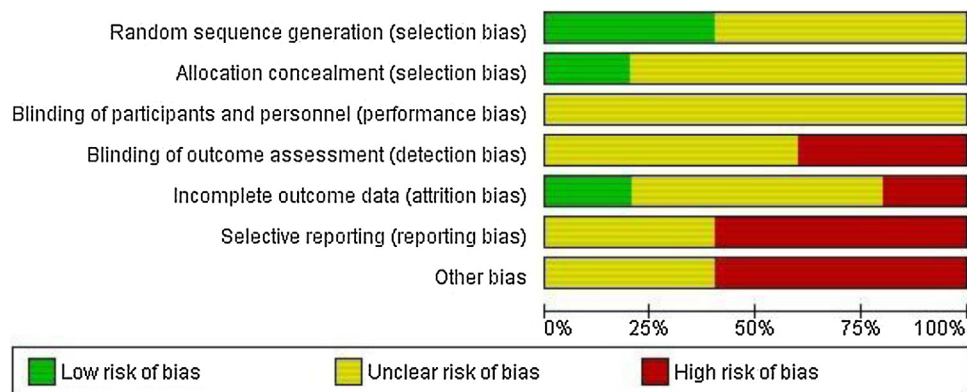
## 9. Synthesis of Results

### 9.1. Primary outcome: wound re-epithelialization

Wound re-epithelialization was determined clinically for all five studies using two approaches: time to wound re-epithelialization (19,21–23) and incidence of complete wound re-epithelialization at four weeks (20). Planimetry was also used to measure re-epithelialization in two studies (20,23). In adult BW, it was not possible to pool the TTRE findings due to the inconsistency in the direction of effect from only two studies thus an average value may be misleading. In one study,

**Table 3 – Interventions and Outcomes.**

First Author Year	Intervention	Comparator	Outcomes	Follow - up
Gravante 2007	Autologous skin cell suspension prepared with RECELL <sup>®</sup> autologous cell harvesting device	Split-thickness skin graft	<ul style="list-style-type: none"> <li>• Time to re-epithelialization</li> <li>• Aesthetic and functional quality of the epithelialization (color, joint contractures)</li> <li>• Infections, inflammations or any adverse effects of the RECELL<sup>®</sup> procedure</li> <li>• Postoperative pain</li> </ul>	<ul style="list-style-type: none"> <li>• Weekly visit for first month after intervention</li> <li>• Single visit 3- and 6-months after intervention</li> <li>• Duration of Treatment: 6 months</li> </ul>
Holmes 2018	Autologous skin cell suspension prepared with RECELL <sup>®</sup> autologous cell harvesting device	Split-thickness skin graft	<ul style="list-style-type: none"> <li>• Percent epithelialization over time</li> <li>• Pain</li> <li>• Patient satisfaction</li> </ul>	<ul style="list-style-type: none"> <li>• Single review per week 1,2,3,4,8,16,24,52 after intervention</li> <li>• Duration of Treatment: 52 weeks.</li> </ul>
Guerid 2013	Autologous skin cell suspension with platelet rich plasma prepared in laboratory	Platelet rich plasma or Paraffin gauze	<ul style="list-style-type: none"> <li>• Time to re-epithelialization</li> <li>• Pain</li> </ul>	<ul style="list-style-type: none"> <li>• First evaluation five days after operation</li> <li>• Review every 2 days until complete re-epithelialization</li> <li>• Duration of Treatment: 14 days after skin graft</li> </ul>
Hu 2017	Autologous skin cell suspension prepared with RECELL <sup>®</sup> autologous cell harvesting device	Hydrocolloid dressing	<ul style="list-style-type: none"> <li>• Time to re-epithelialization</li> <li>• Pain</li> <li>• Itch</li> <li>• Treatment related complications</li> </ul>	<ul style="list-style-type: none"> <li>• First evaluation 3 days after surgery.</li> <li>• Review every second day until complete wound re-epithelialization.</li> <li>• Follow up 12 weeks after complete wound re-epithelialization</li> <li>• Duration of Treatment: 12 weeks.</li> </ul>
Wood 2012	Autologous skin cell suspension prepared with RECELL <sup>®</sup> autologous cell harvesting device	Silver-impregnated or biological dressing	<ul style="list-style-type: none"> <li>• Surgery performed after 10 days</li> <li>• Time to re-epithelialization</li> <li>• Pain experienced</li> <li>• Scar outcomes</li> <li>• Cost</li> </ul>	<ul style="list-style-type: none"> <li>• D7 after enrollment: wound re-view.</li> <li>• D7-10 surgery if wound not re-epithelialized.</li> <li>• D12-15 Wound review.</li> <li>• 3 and 6 months follow up.</li> <li>• Duration of Treatment: 6 months after burn injury</li> </ul>

**Fig. 2 – Certainty assessment at study level. Author judgement presented as percentages across all included studies.**

the ASCS had reduced the TTRE in adult BW (SMD -0.27, [95% CI: -0.57,0.03]) (20). Whereas in contrast, the second adult BW study, ASCS increased the TTRE when compared to control (SMD 0.50, [95% CI: 0.06,0.94])(19). Compared to the control group, ASCS significantly reduced time to re-epithelialization in adult DSW (SMD -5.71, [95% CI: -10.61, -0.81]) (Fig. 3) (21,22). In pediatric BW, the time to re-epithelialization was decreased (SMD -1.75, [95%CI: -3.45, -0.05]) when treated with ASCS compared to control (23). Considerable heterogeneity was noted in the adult DSW subgroup ( $I^2 = 97\%$ ,  $p < 0.001$ ).

## 10. Secondary outcomes

### 10.1. Wound pain

Pain was assessed with a Visual Analogue Scale (0-100 VAS) (29) in the adult cohort (19–22). In children, an age appropriate pain scale was used to measure pain: Children and Infant's Post-operative Pain Scale (CHIPPS, 0-23 months) (30), Face, Legs, Activity, Cry and Consolability Scale (FLACC, 2-7 years)



**Table 4A – GRADE Certainty Assessment for Adult Burn Wounds (19,20).**

Certainty Assessment								Summary of findings		
Outcome	Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of participants		Effect (95% CI)
								Control	ASCS	
Re-epithelialization Time	256 (2 RCTs)	Very serious (>25% high risk of bias)	Not Serious	Serious (Population selection by one study)	Serious (n < 400)	Strongly suspected (Industry funding)	⊕ VERY LOW	127	129	Not pooled
Pain	242 (2 RCTs)	Very serious (>25% high risk of bias)	Very serious (No overlap in CI. Significant heterogeneity)	Not Serious	Serious (n < 400)	Strongly suspected (Industry funding)	⊕ VERY LOW	120	122	SMD <b>-0.62</b> (-0.90, -0.35)
Adverse Event: Infection – Surgical Wound Infection	284 (2 RCTs)	Very serious (>25% high risk of bias)	Not Serious	Not Serious	Very serious (n < 400. Wide CI)	Strongly suspected (Industry funding)	⊕ VERY LOW	2/141 (1.4%)	3/143 (2.1%)	OR <b>1.52</b> (0.25, 9.27)

CI: Confidence Interval, SMD: Standardized Mean Difference, RCT: Randomized controlled trial, ASCS: Autologous skin cell suspension, OR: Odds Ratio.  
 GRADE Working Group grades of evidence.  
 High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.  
 Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  
 Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.  
 Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 4B – GRADE Certainty Assessment for Adult Donor Site Wounds (21, 22).

Certainty Assessment		Summary of findings								
Outcome	Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of participants	Effect (95% CI)	
								Control	ASCS	
Re-epithelialization Time	136 (2 RCTs)	Serious (>25% high risk of bias except randomization)	Serious (Significant heterogeneity)	Serious (Non-burn population included)	Very serious (n < 400. Wide CI)	Strongly suspected (Industry funding)	⊕ VERY LOW	68	68	SMD -5.71 (-10.61, -0.81)
Pain	136 (2 RCTs)	Serious (>25% high risk of bias except randomization)	Serious (Discrepant study findings)	Not Serious	Serious (n < 400)	Strongly suspected (Industry funding)	⊕ VERY LOW	68	68	Not pooled
Adverse Event: Infection – Cellulitis	136 (2 RCTs)	Serious (>25% high risk of bias except randomization)	Not Serious	Serious (Non-burn population included)	Very serious (n < 400. Wide CI)	Strongly suspected (Industry funding)	⊕ VERY LOW	2/68 (2.9%)	0/68 (0.0%)	OR 0.19 (0.01 to 4.11)

CI: Confidence Interval, SMD: Standardized Mean Difference, RCT: Randomized controlled trial, ASCS: Autologous skin cell suspension, OR: Odds Ratio.

GRADE Working Group grades of evidence.  
 High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.  
 Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.  
 Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.  
 Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

(31), and the Revised Faces Pain Scale (FPS-R, older children) (32). Timing of initial pain assessment varied, however were all within the first week after intervention: day two (23), day three (22), day five (21) and day seven (19,20). Adult BW pain (SMD -0.62, [95%CI: -0.90, -0.35]) was reduced when treated with ASCS (Fig. 4). The data from the adult DSW studies was not amenable to meta-analysis. Adult DSW pain was markedly reduced when treated with ASCS (SMD -6.80, [95%CI: -7.30, -6.30]) (21) in one study. In the second adult DSW study, pain scores were low in both ASCS (median 1.7, IQR 1.3 – 2.1) and control (median 1.6, IQR 1.3 – 2.3) groups and not significantly different ( $p < 0.444$ ) (22). In children, pain in BW was reduced (SMD -0.24 [95%CI: -1.56, 1.08]) when treated with ASCS. There was considerable heterogeneity in adult BW ( $I^2 = 98\%$ ,  $p < 0.001$ ).

## 10.2. Scar sensitivity

Itch was reported in two of the five studies using the following methods: incidence of pruritis (20) and itch intensity using a VAS (0=none to 10=maximum) (22). There was no difference in the incidence of itch between ASCS and control (OR 1.00 [95% CI: 0.28, 3.57]) for adult BW. No significant difference in itch intensity ( $p < 0.277$ ) was reported between the ASCS (median 1.1, IQR 0.9 – 1.4) and control (median 1.2, IQR 0.9 – 1.6) DSW groups, with mean itch intensity low in both groups (22). Tightness was not identified as an outcome in any of the included studies.

## 10.3. Scar characteristics

Scar characteristics were measured in four of five studies (19,20,22,23). Four methods of assessment were used: pigmentation and vascularity items of the Vancouver Scar Scale (VSS) (19), all items of the VSS (20,23,33), a single item VAS (20), and Patient Observer Scar Assessment Scale (POSAS) (22,34). Timing of assessment was three (21) and six (19,20,23) months after intervention or date of injury (23). Scar characteristics were evaluated by clinicians (19,20,22,23) and patients (20,22). Pigmentation and vascularity were similar between ASCS and unmeshed SSG and slightly superior for ASCS compared to meshed SSG as reported in one study of adult BW (19). Similarly, ASCS compared to control group had no effect on BW scarring (SMD 0.04 [95%CI: -0.28, 0.37]) in the second adult BW study (20). Scarring in DSW was better when treated with ASCS (ASCS [median 9, IQR 8-10], Control [median 10, IQR 9-11],  $p < 0.007$ ) (22). Scarring of pediatric BW treated with ASCS compared to control was better (SMD -0.46 [95%CI: -1.80, 0.89]) (23)

## 10.4. Adverse event: infection

Incidence of infection was reported as absent (19,21), or as a descriptive account of infection per patient (22,23). One study provided insufficient details to determine how infection was measured (20). There was a 52% higher odds for surgical wound infections in adult BW treated with ASCS (OR 1.52 [95% CI: 0.25, 9.27]), when compared to the control

**Table 4C – GRADE Certainty Assessment for Pediatric Burn Wounds (23).**

Certainty Assessment								Summary of findings			
Outcome	Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Number of Participants	Control	ASCS	Effect (95%CI)
Re-epithelialization Time	9 (1 RCT)	Serious (>25% high risk of bias except allocation)	-	Not Serious	Very Serious (n < 400. Wide CI)	Strongly suspected (Industry funding)	⊕ VERY LOW	127	129		<b>SMD -1.75</b> (-3.45, -0.05)
Pain	9 (1 RCT)	Serious (>25% high risk of bias except allocation)	-	Not Serious	Very Serious (n < 400. Wide CI)	Strongly suspected (Industry funding)	⊕ VERY LOW	120	122		<b>SMD -0.24</b> (-1.56, 1.08)
Adverse Event: Infection – Sepsis	9 (1 RCT)	Serious (>25% high risk of bias)	-	Not Serious	Very Serious (n < 400. Wide CI)	Strongly suspected (Industry funding)	⊕ VERY LOW	0/4 (0.0%)	1/5 (20.0%)		<b>OR 3.00</b> (0.09 to 95.17)
Adverse Event: Infection – Surgical Wound Infection	9 (1 RCT)	Serious (>25% high risk of bias)	-	Not Serious	Very Serious (n < 400. Wide CI)	Strongly suspected (Industry funding)	⊕ VERY LOW	0/4 (0.0%)	1/5 (20.0%)		<b>OR 3.00</b> (0.09 to 95.17)

CI: Confidence Interval, SMD: Standardized Mean Difference, RCT: Randomized controlled trial, ASCS: Autologous skin cell suspension, OR: Odds Ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

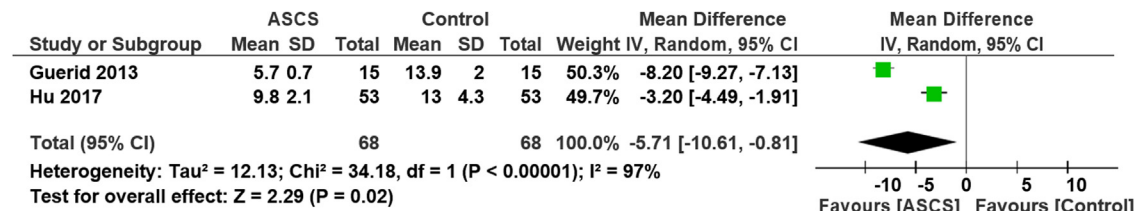
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

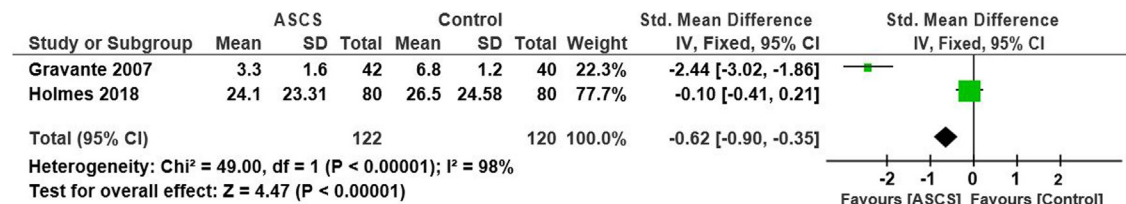
Please cite this article in press as: A. Bairagi, et al. A systematic review and meta-analysis of randomized trials evaluating the efficacy of autologous skin cell suspensions for re-epithelialization of acute partial thickness burn injuries and split-thickness skin graft donor sites. Burns (2021), <https://doi.org/10.1016/j.burns.2021.04.005>

## Adult Donor Site Wound: Re-epithelialization Time



**Fig. 3 – Forrest Plot for adult donor site time to re-epithelialization.**  
 ASCS - Autologous skin cell suspension.

## Adult Burn Wound: Pain



**Fig. 4 – ForrestPlot for adult donor site wound pain.**  
 ASCS - Autologous skin cell suspension.

group (19,20). In adult DSW treated with ASCS, there was a 81% lower odds for cellulitis (OR 0.19, 95%CI: 0.01 to 4.11), when compared to the control group (21,22). The odds of sepsis and surgical wound infection in pediatric BW treated with ASCS compared to the control was markedly increased (OR 3.00 [95%CI: 0.09, 95.17]) (23) in a single study involving a very small number of children ( $n = 9$ ). Neither toxic shock syndrome nor impetigo were reported as adverse effects in the included studies.

### 10.5. Adverse event: requirement for further surgical management

Three studies reported further surgery after the initial attempt at wound closure (19,20,23). Indications for further surgery were delayed re-epithelialization (19) and graft failure or loss (20,23). In adult BW, there was a 38% higher (OR 1.38 [95%CI: 0.46, 4.18]) odds for further surgery when treated with ASCS compared to control (19,20). There was a 96% lower (OR 0.04 [95%CI: 0.00, 1.25]) odds of further surgery in pediatric BW treated with ASCS compared to control (23).

## 11. Sensitivity analysis

The planned sensitivity analysis based on risk of bias was unable to be conducted as risk of bias was unclear to high across greater than 50% of the domains of all five included studies. Sample sizes restricted sensitivity analysis to the adult BW and DSW cohort only. The review had no evidence from sensitivity analyses pertaining to pediatric BW due to the

small sample size of 13 pediatric participants in the cohort. Due to the small number of studies per analysis ( $< 10$ ), publication bias was not examined statistically using funnel plots or the ‘Trim and Fill’ method.

## 12. Discussion

Autologous skin cell suspensions have been in clinical use for over thirty years (35). Notwithstanding, the advancements made in preparation techniques (36–38), delivery systems (39) and continued publication of randomized trials, the role of ASCS in partial thickness burn injury management remains unclear. The large number of initial studies ( $n = 2851$ ) screened demonstrates the plethora of publications pertinent to this field of research but of less rigorous study design such as case series compared to the included randomized trials (40). Of the studies screened for inclusion, only five were eligible for review representing a small sample size ( $n = 347$ ). Adult skin is different from pediatric skin (41–43). Similarly, partial thickness burn wounds are not the same as SSG donor site wounds although the defect is a result of loss of the epidermis and varied depths of the dermis (7). Consequently, the review sample was further sub-grouped to maintain a more consistent cohort for statistical analysis: adult BW ( $n = 183$ ), adult DSW ( $n = 151$ ) and pediatric BW ( $n = 13$ ). Only three of the outcomes (TTRE, pain, infection) were reported by all five of the included RCT’s. Neither anxiety, distress nor scar specific HRQoL were assessed in any of the included studies. Scar sensitivity, scar characteristics and for further surgery were not reported by all the included studies.

ASCS was compared to non-ASCS usual treatment in adult BW (19,20), adult DSW (21,22) and pediatric BW (23). The certainty of evidence identified in this review was very low and not adequately robust to determine the efficacy of ASCS for partial thickness BW and split-thickness skin graft DSW re-epithelialization. Using the GRADE approach, compared to standard care, ASCS may reduce pediatric partial thickness burn and adult split-thickness donor site wound time to re-epithelialization. Pain (adult BW, adult DSW, pediatric BW) and scarring (adult DSW, pediatric BW) may be reduced by treatment with ASCS. There may be very little effect on TTRE (adult BW), scar sensitivity (adult BW, adult DSW), and scarring (adult BW) when treated with ASCS. Further surgery (adult BW, pediatric BW) and cellulitis (adults DSW) may be decreased with ASCS. In contrast, ASCS may increase the odds for surgical wound infections (adult BW, pediatric BW) and sepsis (pediatric BW).

This review has some limitations. Although publication bias was thought to be present as a result of industry funding, this was not able to be statistically analysed due to small number ( $n < 10$ ) of included trials. Heterogeneity limited the ability to pool results across studies and may be explained by non-homogeneous participant demographics, size of BW or DSW, study design, and timing of outcome assessments (e.g., pain). In addition, the varied measurement of outcomes may have contributed to heterogeneity, especially for infection which was reported as ‘no infection noted’ as well as details of the adverse event per patient. A lack of reporting on outcomes such as distress, anxiety, and scar specific HRQoL meant the balance of harms and benefits was difficult to address comprehensively. Further clarification regarding missing data was also only received from the authors of two of the included studies (20,37). Only two of the studies were registered in clinical trial registries (20,22). Donor site size reduction was not a pre-specified outcome for this review thus was not reported on. In this review, adult donor sites for burn wounds treated with ASCS (19,20) were smaller when compared to control donor sites, see Table 2. In addition, the adult donor sites treated with ASCS (21,22) were similar in size compared the control. In the pediatric burn wound study (23) donor site size was not reported. Smaller donor sites provide treating surgeons with ability to plan further management especially in the scenario where there is limited donor site availability (20). This outcome should be further evaluated in future studies.

Most of the research to date was conducted in adults, which cannot be directly applied to children. The epidermis and dermis differ between adults and infants at a structural and functional level (44). In infants, the stratum corneum is thinner with decreased subcutaneous adipose cells, increased trans-epidermal water loss rate, increased water absorption capacity, increased keratinocyte proliferation rates and reduced corneocyte size (42–45). These characteristics contribute to a poorer barrier function of the skin in infants thus rendering them more susceptible to inflammation and infection (43). The adult skin has a thicker stratum corneum, with developed water holding and transport capacity and larger corneocytes that contribute to a more impervious barrier function (41,42). This may explain the paucity of research evaluating ASCS in children, as pediatric burns surgeons may not yet have integrated ASCS into routine partial thickness burn management protocols based on the available evidence.

Serial keratinocyte cultures were first described in 1975 (6) followed by a hiatus of over a decade before cultured ASCS was detailed (35,36) and thereafter, nearly another decade before non-cultured ASCS was first reported as being used in clinical practice. It is important to acknowledge the contributions pioneers of this wound management approach have made to burn care, and to appreciate the considerable amount of time it has taken to develop the ASCS modalities available today. Future study designs can be improved based on knowledge accumulated from existing studies to further our understanding in this field. Evaluation of burn and donor site wound re-epithelialization time is often different. Burn wounds are usually assessed frequently for reasons such as dressing re-application, possible burn depth progression or suspected infection. However, the initial DSW assessment is usually a few days to a week after completion of the skin graft. As a donor site is a sterile wound, infective complications are considered less likely. By standardizing the frequency of dressing change and subsequent wound assessment, it is possible to obtain a more accurate measure of wound re-epithelialization time. In addition, the use of a minimally clinically important difference for TTRE is likely to be a more clinically meaningful measure of effect in comparison to a statistical null effect approach for meta-analysis interpretation. Better reporting of burn wound infection using established guidelines (46) would also assist in understanding the safety profile of ASCS in burn wound management. Examining scar specific HRQoL should be reported with validated measures (47,48) and considered in all future studies, to obtain a more comprehensive evaluation of the balance between benefits and harms.

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## 14. Conclusion

Autologous skin cell suspensions may reduce pediatric partial thickness burn wound and adult split-thickness skin graft donor site wound time to re-epithelialization. However, the certainty of evidence is not sufficient to define the role of ASCS in partial thickness burn injury management. This justifies the need for more rigorous research in this field to further knowledge of ASCS in burn care.

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No external funds were utilised to complete this systematic review.

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## Competing interests

AB is currently conducting one of two randomized controlled trials evaluating autologous cell suspension in the management of pediatric partial thickness burn injuries as part of a PhD degree (Data analysis of the results has been completed in the first study; the second trial is in recruitment). These studies are supported by a research grant from AVITA Medical (Grant Reference: 2018000489) and an Innovations Connection Grant (Grant Reference: ICG001219), both administered by

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## Appendix A

### Appendix A1: Search Strategy – Google Scholar

Line number	Google Scholar database search terms
1	burn* RECELL "autologous skin cell suspension"
2	burn* "partial thickness" "cellmist"
3	burn* RES "second-degree" "RECELL"
4	burn* cell spray "second-degree"
5	burn * non-cultured suspension
6	burn * donor site "autologous cell suspension"

### Appendix A2: Search Strategy – Web of Science

Line number	Web of Science database search terms
1	TS=(burn)
2	TS= (partial near/1 thickness near/1 burn*) OR TS= (second near/1 degree) OR TS=(donor near/1 site) AND TS=(skin near/1 graft)
3	TS=(cutaneous) AND TS=(thermal) AND TS=(trauma)
4	TS=(dermal) AND TS=(injury)
5	TS= (split near/1 thickness near/1 skin near/1 graft) NOT TS=(full near/1 thickness near/1 skin near/1 graft)
6	#5 OR #4 OR #3
7	#6 OR #2"
8	#7 AND #1
9	TS=(non near/1 cultured near/1 autologous near/1 suspension) OR TS=(autologous near/1 skin near/1 cell* near/1 suspension*) OR TS=(autologous near/1 keratinocyte* near/1 suspension*)

10	TI=(cellmist) OR TS=(skingun) OR TI= (celmist OR skingun) OR TS=(skin near/1 gun OR cell near/1 mist)
11	TI=(RECELL) OR TS=(RECELL) OR TS=(Autologous near/1 cell near/1 harvesting near/1 device) OR TI=(Autologous near/1 cell near/1 harvesting near/1 device) OR TS=(RES) OR TI=(RES) OR TS=(Regenerative near/1 epithelial near/1 suspension) OR TI=(Regenerative near/1 epithelial near/1 suspension) OR TS=(spray near/1 on near/1 skin) OR TS=(cell near/1 spray)
12	TI=(controlled OR clinical OR randomized OR randomised OR RCT)
13	#12 OR #11 OR #10 OR #9
14	#13 AND #8
15	#13 AND #8 Refined by: DOCUMENT TYPES: ( CLINICAL TRIAL) Databases = WOS, BIOABS, CCC, KJD, MEDLINE, RSCI, SCIELO Timespan = 1975-2020 Search language = Auto

### Appendix A3: Search Strategy – Indian Journal of Burns

Line number	Indian Journal of Burns search terms
1	[WORD]-autologous skin cell suspension partial thickness skin graft donor site dressing
2	" [WORD]-autologous skin cell suspension partial thickness"
3	" [WORD]-acute burn partial thickness burns autologous suspension"
4	" [WORD]-Cellmist, skingun "
5	" [WORD]-regenerative epithelial suspension, RECELL, RES, spray-on skin, cell-spray"
6	" [WORD]-Non-cultured suspension partial thickness "
7	" [WORD]-keratinocyte non-cultured suspension"

### Appendix B. Excluded studies

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## Appendix C. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.burns.2021.04.005>.

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