INTRODUCTION

The use of dermal regeneration templates was first described by Burke et al. in 1981. In its commercial form, the most widely used dermal regeneration template is Integra (Integra LifeScience Corporation, Plainsboro, N.J.), which is a bilayer composed of a matrix of bovine collagen cross-linked with glycosaminoglycans from shark chondroitin sulfate with an overlying protective silicone layer. The use of Integra templates in reconstructive surgery has been described in burns, scalp, limbs, abdominal wall, degloving injuries, keloids and hypertrophic scars, purpura fulminans, hypospadias, diabetic foot ulcers, and necrotizing soft-tissue infections among other uses.

Although Integra has been shown to be an effective reconstructive tool with excellent functional outcomes, aesthetic results, and high rates of long-term engraftment, several complications may be associated with its use. The most common complications linked to Integra use are infections. Most of the time, these infections are superficial, are associated with a lower rate of graft take, and can be resolved with antibiotics and negative-pressure therapy. In this article, we present the results of an extensive literature review of studies reporting infectious complications associated with Integra-based wound closure.

METHODS

We conducted a systematic review of the literature to identify previous articles indexed in PubMed and Ovid for Integra and its synonymous terms. We used these search terms: [Integra OR (dermal regenerative matrix) OR (dermal regeneration matrix) OR (dermal regenerative template) OR (dermal regeneration template) OR (dermal substitute) OR (skin substitute) OR (artificial skin)] AND infection.

Results: Of the 3508 articles for initial review, 69 reported rates of infection, of which 26 reported ≥1 infection within their cohort. Of these 26 articles, the patients (n = 602) underwent Integra-based reconstruction in 1254 sites and had reported infections in 212 of the sites (16.9%). Among these, we encountered a single report of a fatal case of toxic shock syndrome (TSS) related to the use of Integra in secondary burn reconstruction.

Conclusions: While Integra offers many benefits, surgeons must be aware that infectious complications are not uncommon. As a result, a careful risk–benefit analysis of its use in reconstruction must be performed, and open discussion with the patient preoperatively regarding infection rate is of utmost importance.

(Plast Reconstr Surg Glob Open 2020;8:e2869; doi: 10.1097/GOX.0000000000002869; Published online 15 July 2020.)
OR (artificial skin)] AND skin) AND infection, which generated 3508 articles for initial review.

Eligibility for Inclusion

The article selection criteria were peer-reviewed publications, case reports or case series utilizing Integra for wound repair, and articles reporting infection rate as one of the surgical outcomes. If the data used in one published article had been reported in another study, we included only the article with the most complete and recent data set. Figure 1 is a diagram showing the steps we followed to identify and select articles for this literature review.

RESULTS

Of the 26 articles that were included in the study, we extracted the following data points: type of reconstructive surgery performed (eg, burn, limb, general reconstruction), number of patients in the study, the rates of infection, proportions of superficial versus invasive infection, and wound healing outcome. Of 446 articles, only 69 cite the infection rate associated with Integra use, and 43 of these reported no infectious complications. Of the 69 articles, 26 of them reported infections related to the use of Integra.5,8,13,19–41 When grouping the patient population together from these 26 reports, the generalized incidence of infection is 16.9% out of 1254 Integra sites in 602 patients. The results of the systematic review are summarized in Table 1.

DISCUSSION

Our literature review demonstrated reports of infection associated with the use of Integra in a variety of wound categories. The highest percentage of infection with Integra use was seen in burn reconstructions. This is well supported by the number of articles (Table 1), including a relatively large study conducted by Heimbach et al.5 which included 13 participating burn centers comprising 216 patients treated with Integra, complicated by infection with an incidence of 16.3% (13.2% superficial and 3.1% invasive). Although the data point to a higher number of infections among the burn reconstruction patient population, patient characteristics, wound pathophysiology, surgeons’ technique, and numerous other confounding variables contribute to the observed differences in infection rate among the studies. There was no statistical difference in infection rate among the different categories relative to burn reconstruction. For example, looking at the incidence of infection alone, the P value of 2-tailed unpaired t test between the burn and non-burn limb reconstruction articles was 0.2316. It is not possible to generate an exact incidence of infection related to Integra use from this review because of the lack of controlled studies and endless confounding variables among the reports. However, Table 1 serves as an organized general overview to the practitioner when discussing with the patient the risks and benefits regarding the use of Integra in wound

Fig. 1. Steps taken to perform the literature review to identify articles who report cases of infections as postoperative outcomes following skin reconstruction with Integra.
coverage. Depending on the indications to which Integra is applied, the benefits of its use should routinely surpass its relatively low–moderate rate of infection (13%–15.9%). Most importantly, our literature review identified a single report of a fatal case of toxic shock syndrome related to the use of Integra in burn reconstruction. 20

This middle-age patient underwent secondary burn scar revision of neck and axilla with Integra and was readmitted 9 days postoperatively with 2 small (1 cm²) areas of nonadherent graft without purulence, but she succumbed from rapid irreversible sepsis. Culture of debrided Integra grew methicillin-resistant *Staphylococcus aureus*.

There are various prophylactic measures that may be taken to prevent the development of infection when using dermal regeneration templates such as Integra. Rigid infection control measures must be exercised, including meticulous wound handling techniques to avoid wound contamination during and after surgery, especially with resistant staphylococcal organisms. Preventive dressing options include nanocrystalline silver products such as Acticoat (silver-coated polyethylene; Smith & Nephew, London, United Kingdom) 42,43 and silver-coated polyurethane negative-pressure wound therapy sponge.44,45 Antibiotic prophylaxis may also be used.13,16 The use of these prophylactic measures when employing Integra requires prospective investigation.

**CONCLUSIONS**

While Integra offers many crucial benefits, such as better chance for revascularization than a direct skin graft in certain situations, the surgeon should be aware that infectious complications are not uncommon. As a result, a careful risk–benefit analysis of its use in reconstruction must be performed, and informed consent openly discussing the risk of infection with the patient is paramount. However rare, acknowledging the possibility of toxic shock syndrome as a complication is crucial in early recognition and expedient life-saving surgical and medical intervention.

James C. Yuen, MD
Division of Plastic Surgery
Department of Surgery
University of Arkansas for Medical Sciences
4301 W. Markham Street
Slot # 720
Little Rock, AR 72205
E-mail: yuenjamesc@uams.edu

---

**Table 1. Twenty-six Articles That Reported ≥1 Infection with the Use of Integra**

| Authors/Year | Reconstruction Type | Patients (#) | Sites (#) | Infections (%) | Superficial (%) | Invasive (%) | Healing Rate (%) |
|-------------|---------------------|--------------|-----------|----------------|----------------|--------------|-----------------|
| Heimbach et al21 | Burns: | 216 | 758 | 17.3 | 13.2 | 3.1 | NR |
| Shirley et al20 | Burns: | 1 | 1 | 100 | 0 | 100 | 0 (death) |
| Dantzer and Braye21 | Burns: | 31 | 39 | 12.8 | 80 | 20 | 80 |
| Groos et al22 | Burns: | 10 | 22 | 22.7 | — | — | — |
| Lee et al23 | Burns: | 7 | 9 | 11.1 | 100 | 0 | 100 |
| Bargues et al24 | Burns: | 50 | 71 | 29.6 | 71.4 | 28.6 | NR |
| Yeong et al25 | Burns: | 10 | 11 | 9.1 | 100 | 0 | 100 |
| Nesler et al26 | Pediatric burns | 15 | 19 | 21 | 100 | 0 | — |
| Lohana et al27 | Burns: | 24 | 37 | 13.5 | 100 | 0 | 100 |
| Huang et al28 | Burns: | 5 | 5 | 20 | — | — | — |
| Suzuki et al29 | General reconstruction: | 23 | 27 | 3.7 | — | — | — |
| Suzuki et al29 | General reconstruction: | 41 | 52 | 13.4 | — | — | — |
| Jeschke et al30 | General reconstruction: | 12 | 12 | 25 | 33.3 | 66.7 | NR |
| Unglaub et al31 | General reconstruction: | 12 | 19 | 5.21 | 100 | 0 | 100 |
| Total: | | 88 | 110 | 10.9 | — | — | — |
| Bhavsar and Tenenhaus32 | Limb reconstruction: | 4 | 26 | 3.8 | 0 | 100 | 0 |
| Huemer et al33 | Gracilis muscle flap | 20 | 21 | 9.5 | 100 | 0 | 100 |
| Todd et al34 | Self-femoral forearm | 6 | 6 | 16.6 | 100 | 0 | 100 |
| Weigert et al35 | Foot and ankle | 21 | 21 | 4.7 | — | — | — |
| Rodríguez Collazo et al36 | Limb reconstruction: | 17 | 17 | 23.5 | 0 | 100 | 75 |
| Total: | | 68 | 91 | 9.8 | — | — | — |
| Martínez et al37 | General reconstruction: | 11 | 14 | 14.2 | 100 | 0 | 100 |
| Stiefel et al38 | General reconstruction: | 18 | 18 | 16.5 | — | — | — |
| Ghazi and Williams39 | General reconstruction: | 8 | 8 | 12.5 | 100 | 0 | 100 |
| Greenhalgh et al39 | Face reconstruction | 23 | 23 | 17.0 | — | — | — |
| Casal-Beloy et al39 | Hypospadias fistula repair | 8 | 8 | 12.5 | 100 | 0 | 0 |
| Total: | | 68 | 71 | 15.4 | — | — | — |
| Bodmer et al40 | Others: | 6 | 6 | 50 | 0 | 100 | 0 |
| Gonzaga et al41 | Facial reconstruction after SCC | 4 | 4 | 25 | 100 | 0 | 0 |
| Total: | | 10 | 10 | 40 | — | — | — |
| Total patients: | | 602 | | | | | |
| Total Integra sites: | | 1254 | | | | | |
| Total Integra-site infections: | | 212 (16.9%) | | | | | |

NR, not reported; SCC, squamous cell carcinoma.
REFERENCES

1. Burke JF, Yannas IV, Quinby WC Jr, et al. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. Ann Surg. 1983;198:419–428.

2. Integra Dermal Regeneration Template—How INTEGRA Works. I:training.com. Available at http://www:itraining.com/idt/idt/bx/it_04.html. Accessed June 10, 2020.

3. Heimbach D, Luterman A, Burke J, et al. Artificial dermis for major burns. A multi center randomized clinical trial. Ann Surg. 1988;208:313–320.

4. Branski LK, Herndon DN, Pereira C, et al. Longitudinal assessment of Integra in primary burn management: a randomized pediatric clinical trial. Crit Care Med. 2007;35:2615–2623.

5. Rashid OM, Nagahashi M, Takabe K. Management of massive soft tissue defects: the use of Integra artificial skin after necrotizing fasciitis and purpura fulminans. J Hand Surg Eur Vol. 2007;32:179–184.

6. Clayman DM, Warden GD, Luterman A, et al. Multicenter post-approval clinical trial of Integra dermal regeneration template for burn treatment. J Burn Care Rehabil. 2003;24:42–48.

7. Groos N, Guillot M, Zilliox R, et al. Use of an artificial dermis (Integra®) for the reconstruction of extensive burn scars in children. Burns. 2009;35:362–366.

8. Edlich RF, Winters KL, Woodard CR, et al. Massive soft tissue defects: the use of Integra artificial skin after necrotizing soft tissue infection of the chest. J Trauma. 2012;4;331–335.

9. Weigert R, Leavry LA, Reyzelman AM, et al. A clinical trial of Integra template for diabetic foot ulcer treatment. Wound Repair Regen. 2015;23:891–900.

10. Doxter DR, Teare L, Zilliox R, et al. The use of Integra artificial skin after necrotizing soft tissue infection associated with biomaterials. J Invest Surg. 1989;2:353–360.

11. Clayman MA, Clayman SM, Mozingo DW. The use of collagen-glycosaminoglycan copolymer (Integra) for the repair of hypertrophic scars and keloids. J Burn Care Res. 2006;27:404–409.

12. Edlich RF, Winters KL, Woodard CR, et al. Massive soft tissue infections: necrotizing fasciitis and purpura fulminans. J Long Term Eff Med Implants. 2005;15:57–65.

13. Casal-Beloy I, Somozzo Argibay I, García-González M, et al. Management of recurrent urethrocystocutaneous fistula after hypo-spadias surgery in pediatric patients: initial experience with dermal regeneration sheet Integra. J Pediatr Urol. 2017;30:207–210.

14. Khansa I, Schoenbrunner AR, Kraft CT, et al. Silver in wound and chronic wounds. J Burn Care Res. 2013;27:17–21.

15. Martínez L, Ros Z, López-Gutiérrez JC, et al. Integra artificial dermis in pediatric reconstructive surgery. Cir Pediatr. 2002;15:97–100.

16. Ghazi BH, Williams JK. Use of Integra in complex pediatric wounds. Ann Plast Surg. 2011;66:493–496.

17. Groos N, Guillot M, Zilliox R, et al. Use of an artificial dermis (Integra®) for the reconstruction of extensive burn scars in children. About 22 grafts. Eur J Pediatr Surg. 2005;15:187–192.