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Research Article

CONTEMPORARY APPROACHES TO LIMB TRANSPLANTATION

[1] Sowndarya G S., [2] Saalini Vellivel, [3] Kiran Kumar S, [4] Kaaviya A A and [5] Sujitha K

[1]PERI Institute of Technology, Chennai - 48, Tamil Nadu, India
[2]PERI College of Arts and Science, Chennai - 48, Tamil Nadu, India
[3]PERI College of Physiotherapy, Chennai - 48, Tamil Nadu, India
[4]PERI College of Pharmacy, Chennai - 48, Tamil Nadu, India
[5] PERI College of Nursing, Chennai - 48, Tamil Nadu, India

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ABSTRACT

Limb loss due to trauma, disease, or congenital defects remains a major challenge for reconstructive surgery. Vascularized Composite Allotransplantation (VCA) involving transfer of a donor limb as a functional unit has emerged as a viable and transformative solution, enabling restoration of form, function, and sensation. Recent decades have seen substantial advances in microsurgical techniques, immunosuppression protocols, graft preservation (including novel perfusion strategies), and patient-selection and rehabilitation frameworks. This paper reviews contemporary surgical and peri-operative approaches in limb transplantation, analyzes current challenges (e.g. immunologic rejection, graft preservation, long-term functional outcome, ethical and psychosocial considerations), and discusses emerging alternatives and future directions such as ex-vivo perfusion, joint-specific VCA, and tissue engineering. By synthesizing current evidence and practices, we aim to outline a comprehensive framework for clinical application and future research in limb transplantation.

Keywords: Limb transplantation, Vascularized composite allograft, Microsurgery, Graft preservation, Ex-vivo perfusion.

INTRODUCTION

Limb loss, whether due to traumatic injury, oncologic resection, congenital anomalies, or chronic disease, imposes profound physical, psychological, and social burdens on patients. Conventional reconstructive methods prostheses or autologous reconstruction often fail to fully restore complex functions such as sensation, fine motor control, and proprioception. In this context, vascularized composite allotransplantation (VCA) offers a unique opportunity: by transferring a multi-tissue anatomical unit (skin, muscle, bone, nerve, vasculature) from donor to recipient, VCA aims to restore both form and function in a way that approximates the original limb. Since the first successful human limb (hand) transplant, the field has matured significantly. Advances in microsurgical techniques refining vascular anastomoses and composite tissue integration have made such complex transplants technically feasible. Meanwhile, immunosuppressive regimens derived from solid organ transplantation, though imperfect, have enabled graft survival and functional recovery in many cases. However, VCA remains challenging. Lifelong immunosuppression carries significant risks; the composite nature of grafts (skin, muscle, bone, nerve) introduces complex immunologic dynamics rarely observed in solid-organ transplantation. Additionally, perioperative factors such as ischemia time, graft preservation, and surgical logistics significantly influence outcomes. These challenges underscore the need for continuous refinement of surgical protocols, preservation strategies, and long-term post-operative care. In response, contemporary approaches to limb transplantation are evolving. Innovations include enhanced microsurgical protocols, improved immunosuppression and tolerance induction, optimized graft preservation (e.g. ex-vivo perfusion), and structured, multidisciplinary transplant programs integrating surgical, immunologic,

*Corresponding Author: G.S. Sowndarya, PERI College of Physiotherapy, Chennai - 48, Tamil Nadu, India Email: publications@peri.ac.in

rehabilitative, and psychosocial care. Moreover, emerging alternatives such as advanced bionic prostheses are being evaluated in parallel, raising important questions about the future role and sustainability of VCA. Given this dynamic landscape, a comprehensive review and analysis of current practices, challenges, and future directions is timely. The present paper titled "Contemporary Approaches to Limb Transplantation" aims to synthesize recent advances, highlight key obstacles, and propose a roadmap for clinical application and research. Overview and principles of Vascularized Composite Allotransplantation (VCA): Vascularized composite allotransplantation (VCA) refers to transplantation of multiple tissue types (skin, muscle, bone, nerve, vessels) as a single functional unit and is the contemporary framework for limb (hand/arm/leg) transplantation; VCA requires integrated microsurgical revascularization, immunosuppression, and long-term multidisciplinary care (Wells, 2022). Indications, candidate selection and eligibility: Contemporary indications emphasize traumatic or congenital limb loss where prosthetic or reconstructive options are insufficient; candidate selection focuses on medical fitness, realistic functional/psychosocial expectations, and ability to adhere to lifelong immunosuppression and intensive rehab (Klimitz, 2023; Wells, 2022). Screening protocols and eligibility criteria have been systematized in recent years to reduce risk and optimize outcomes. Surgical technique and microsurgery advances: Surgical advances include refinement of composite inset, bone fixation strategies for optimal alignment, nerve coaptation techniques, and staged approaches to complex defects. Improved microsurgical techniques and perioperative vascular management have reduced early ischemic complications and enabled more proximal transplantations with meaningful function (Lúcio, 2021; Wells, 2022).

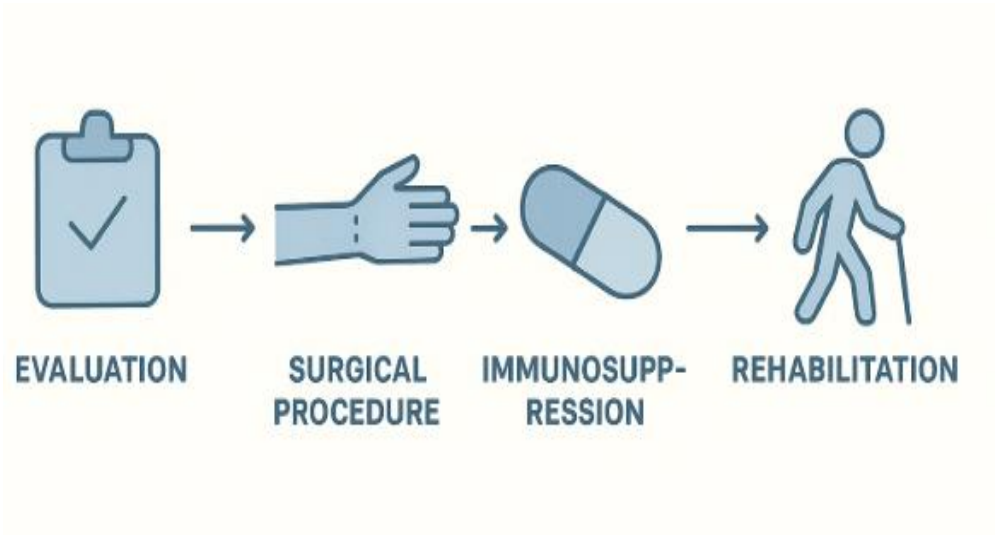

Figure 1. Contemporary Approaches to Limb Transplantation.

Organ/limb preservation and ex-vivo perfusion: A major contemporary area is ex-vivo perfusion and machine preservation of limb VCAs to extend safe ischemia times, allow viability assessment, and potentially permit interventions ex-vivo (pharmacologic conditioning, immune modulation). Recent reviews summarize multiple perfusion models and highlight that optimal perfusate composition, temperature, and timing remain active research topics. Early preclinical and translational data are promising for improving graft availability and logistics. (Duru, 2023; Muss, 2025). Immunosuppression strategies and tolerance approaches: Standard protocols have used induction agents plus calcineurin inhibitor (CNI)-based maintenance (tacrolimus), but CNI-toxicity and chronic graft injury have driven exploration of CNI-sparing regimens, costimulatory blockade (e.g., belatacept), and cellular/tolerance strategies. Reports suggest belatacept-based or hybrid regimens can improve renal outcomes or reduce CNI exposure, though rejection risk and long-term efficacy in VCA require careful evaluation. Newer work also investigates mixed-chimerism, Treg therapies, and localized immunomodulation to reduce systemic toxicity (Johnson, 2023; Kitchens, 2023; Qayyum, 2023).

Nerve repair, regeneration and neurobiology of reinnervation: Functional recovery depends chiefly on donor-to-recipient nerve coaptation and axonal regeneration across long distances. Contemporary strategies combine microsurgical nerve repair, nerve grafts/conduits, growth factor delivery, and rehabilitative neurostimulation to accelerate and guide reinnervation. Despite techniques that improve axonal regeneration, distal motor recovery remains limited by time to reinnervation and muscle/end-organ changes, especially for proximal or high-level amputations. Ongoing research in peripheral nerve therapeutics aims to shorten denervation time and improve functional outcomes. (Xu, 2024; Grosu-Bularda, 2025). Rehabilitation protocols and functional outcomes: Postoperative rehabilitation is

critical and highly structured — protocols combine early range-of-motion, graded motor re-education, sensory re-training, occupational therapy, and activity-based functional tasks. Recent protocol papers and outcome series report significant gains in form, sensibility, and function for many recipients but highlight variable outcomes depending on transplant level, time since amputation, and patient adherence. Long-term follow-up remains essential to capture durability of gains. (Sankaran, 2025; Kim, 2024). Outcomes, complications, and survival: Systematic reviews of hand/limb transplants over the past two decades show functional restoration is achievable, but challenges include acute and chronic rejection episodes, infection, renal dysfunction from CNIs, psychosocial issues, and occasional graft loss. Published series emphasize multidisciplinary selection, patient education, and standardized outcome measures to accurately report benefit vs risk. (Wells, 2022; HealthyBlue summary, 2025). Ethical, psychosocial and cost considerations: Limb transplantation raises distinct ethical questions because it is life-enhancing rather than life-saving: the requirement for lifelong immunosuppression, potential adverse effects, and psychosocial integration (body image, identity) require rigorous informed consent, psychosocial screening, and long-term support. Cost-effectiveness and access (resource-intensive surgery, rehab, and monitoring) remain central barriers to broader implementation. (Lúcio, 2021; Vacca/other ethicists—see reviews). Emerging technologies and research directions: Key emerging areas are: (a) machine perfusion and organ conditioning to increase graft availability and allow interventional modification ex-vivo; (b) localized (graft-targeted) immunomodulation and tolerance induction to reduce systemic toxicity; (c) biomaterials and engineered nerve grafts to accelerate reinnervation; and (d) digital health and remote monitoring to support home-based rehabilitation — all aimed at improving safety, outcomes, and scalability (Muss, 2025; Johnson, 2023; Grosu-Bularda, 2025). Major gaps and research priorities: Despite progress, core gaps include: standardized multicenter outcome registries for VCA, randomized or comparative effectiveness data vs advanced prosthetics for matched indications, validated CNI-sparing immunosuppression protocols in VCA, and translational work to improve distal motor recovery. High-quality longitudinal studies and multidisciplinary trials are priority steps to clearly define indications and improve patient selection and long-term graft health. (Wells, 2022; Castanho/other recent commentators).

MATERIALS AND METHODS

Literature Search Strategy

Databases searched: PubMed, Scopus, Web of Science, Google Scholar. Inclusion criteria: Peer-reviewed articles published from 2000–2025, human and relevant preclinical studies, English language. Exclusion criteria: non-peer-reviewed sources, editorials without original data, case reports with insufficient follow-up (<6 months), and studies focused solely on prosthetic replacement.

Selection and Screening

Initial screening by titles and abstracts → identification of potentially relevant studies. Full-text review to extract data on surgical techniques, immunosuppression strategies, graft preservation, functional outcomes, complications, and patient-reported quality-of-life.

Data Extraction and Synthesis

Data extracted included: number of patients, type of VCA, surgical protocols, immunosuppressive regimen, graft preservation methods, functional outcomes, complication rates, follow-up duration. Qualitative synthesis of trends, challenges, and emerging technologies; quantitative comparison where sufficient data was available (e.g., graft survival rates, incidence of acute rejection).

RESULTS AND DISCUSSION

Surgical Techniques and Outcomes: Microsurgical VCA techniques have evolved, with improved vascular anastomosis and composite tissue integration. Upper-limb transplant survival rates are now reported as ~85–90% at 1 year**,** with functional recovery improving due to standardized post-op rehabilitation. Joint and lower-limb transplantation remain experimental, with limited success due to complexity and immunologic risk. Graft Preservation: Traditional static cold storage remains standard, but ex-vivo perfusion shows promise in preclinical studies. Normothermic or subnormothermic perfusion can reduce ischemia-reperfusion injury and improve graft viability. Standardization of perfusion protocols is still lacking, and clinical adoption remains limited. Immunosuppression and Rejection: Lifelong immunosuppression is necessary; acute rejection remains common but manageable. Skin is the most immunogenic tissue, often acting as the first indicator of rejection. Emerging approaches (local drug delivery, tolerance induction, regulatory T-cells) may reduce systemic immunosuppression and associated complications. Functional Outcomes & Quality of Life: Most hand transplant recipients regain sensation, fine motor skills, and partial proprioception. Psychosocial benefits include improved self-image, social integration, and life satisfaction. Long-term data (>10 years) remain limited, especially for joint or lower-limb transplants. Challenges and Comparative Analysis: Risks: lifelong immunosuppression, infection, metabolic complications, ethical concerns. Alternatives: advanced prosthetics increasingly offer functional outcomes comparable to some VCAs without immunosuppression risk. Integration of VCA with rehabilitation, immunomodulation, and psychosocial support is key to maximizing outcomes.

CONCLUSION

Limb transplantation has progressed from experimental procedures to a clinically viable option for select patients. Contemporary surgical techniques, perioperative care, and immunosuppression protocols have significantly improved graft survival and functional outcomes. Challenges persist, especially regarding long-term immunosuppression, graft preservation, and accessibility. Multidisciplinary care involving surgery, immunology, rehabilitation, and psychosocial support is crucial for successful outcomes.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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