

# Platelet rich plasma for nonhealing diabetic wounds

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Policy contains: Diabetic wounds; platelet-derived growth factors; platelet rich plasma.

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## Coverage policy

Platelet rich plasma is investigational/not clinically proven and, therefore, not medically necessary for any clinical indication except the following:

- As an adjunct treatment for chronic diabetic wounds, when both criteria are met (Qu, 2020):
  - There is a lack of healing progress with standard wound care (e.g., offloading, infection control, glycemic control, and wound bed preparation including debridement).\*
  - Platelet rich plasma is prepared using devices that are U.S. Food and Drug Administration-approved for management of exuding cutaneous wounds, such as diabetic ulcers.

\*Note: Generally defined as ulcer reduction of less than 40% after at least four weeks of standard therapy (Wound Healing Society, 2017).

### Limitations

Required documentation includes wound history, recurrence, and characteristics (location, staging, size, base, exudates, infection condition of surrounding skin and pain). The rate of wound healing should be evaluated to determine if treatment is optimal (Wound Healing Society, 2017).

The effectiveness of platelet rich plasma for treating chronic non-healing diabetic wounds should be reevaluated at 20 weeks of treatment (Qu, 2020). Continuation of treatment beyond 20 weeks requires secondary medical review.

#### Alternative covered services

Primary care and specialty physician (including surgical) evaluation and management including:

- Simple analgesics.
- Anti-inflammatory medications.
- Corticosteroid injections.
- Physical or occupational therapy.
- Immobilization.
- Thermal therapy.
- Reducing workload and increasing rest.
- Relaxation and biofeedback techniques.
- Strengthening and conditioning exercises.
- Stretching exercises and therapeutic massage.

## Background

Platelets contain hundreds of growth factors important to healing injuries and regenerating tissue (Roffi, 2013). Platelet rich plasma is a blood derivate containing a higher concentration of platelets and a correspondingly higher concentration of growth factors above levels in peripheral blood. Although the mechanism of action is unclear, laboratory studies suggest a correlation between the increased concentration of growth factors in platelet rich plasma and an increase in the native inflammatory healing cascade.

A wide variation of protocols used for standardization and preparation of platelet rich plasma exists (Dhurat, 2014). It may be produced in an autologous manner or homologous manner from blood from multiple donors. The basic protocols involve a two-stage centrifugation process to separate platelets from blood plasma and red blood cells, require intrinsic or exogenous activation of platelet rich plasma to initiate formation of a fibrin network, and ultrasonographic guidance to inject autologous platelet rich plasma into the injured area. Platelet rich plasma may be leukocyte-rich or leukocyte-poor.

The U.S. Food and Drug Administration Center for Biologics Evaluation and Research regulates both the systems used to separate out platelets and the clinical use of platelet rich plasma (21CFR640.34). Nearly all of these systems have received 510(k) clearance for producing platelet rich preparations intended to be mixed with bone graft materials to enhance bone graft handling properties in orthopedic practices to treat bony defects (21CFR864.9245). Uses in other fields such as dermatology (for tissue regeneration and scar revision) and chronic wound care (U.S Food and Drug Administration, 2021) are expanding.

## Findings

The literature on the safety and effectiveness of platelet rich plasma has been subject to secondary analysis for several clinical indications. The most popular areas are autologous platelet rich plasma administration in orthopedics (Laudy, 2015; Moraes, 2014), dentistry/oral surgery (Hou, 2016), and wound care (Martinez-Zapata, 2016). Limitations in the evidence base that are common to all indications are relatively few, adequately powered published randomized controlled studies, overall low quality studies with high risk of bias, heterogeneous study methods, and variable and incomplete reporting of patient selection criteria, treatment methods, and treatment

outcomes. For all indications, the evidence supporting the superiority of platelet rich plasma is inconclusive or conflicting, and no firm conclusions regarding clinical use can be made.

Few evidence-based guidelines have considered platelet rich plasma in their recommendations. The American Academy of Orthopaedic Surgeons (2013) was unable to recommend for or against growth factor injections and/or platelet rich plasma for patients with symptomatic knee osteoarthritis due to a paucity of evidence. Neither the National Institute for Health and Care Excellence (2015) nor the Wound Healing Society (Lavery, 2016) recommend platelet rich plasma to treat diabetic foot ulcers due to a lack of effect on wound healing improvement.

In 2018, we added five systematic reviews and meta-analyses of five clinical indications for platelet rich plasma: patellar tendinopathy (Andriolo, 2018); temporomandibular joint disorders (Bousnaki, 2018); hip osteoarthritis (Ye, 2018); knee osteoarthritis (Zhang, 2018a); and chronic Achilles tendinopathy (Zhang, 2018b). The evidence base continues to be of low quality with inconclusive or conflicting results. The new information updates earlier findings with no changes to the policy. The policy ID was changed from CP# 05.02.10 to CCP.1278.

In 2019, we updated the citation for Andriolo (2018, updated to 2019, see references). We added several systematic reviews and meta-analyses of platelet-rich plasma products for treatment of bony defects of the knee (Vannabouathong, 2018) and intraoral bones (Dragonas, 2019; Liu, 2019; Strauss, 2018; Yao, 2018), along with several off-label uses: Achilles tendonitis (Wang, 2019); erectile dysfunction (Scott, 2019); androgenic alopecia (Chen, 2018; Gupta, 2018); diabetic foot ulcers (Del Pino-Sedeno, 2019; Li, 2019a); and plantar fasciitis (Al-Boloushi, 2019; Ling, 2018). The new information supports earlier conclusions of insufficient evidence, and no policy changes are warranted.

In 2020, we added evidence-based guidance from the National Institute for Health and Care Excellence (2019) and 11 systematic reviews and meta-analyses examining the effectiveness of platelet rich plasma and platelet-derived factors for treating a number of indications (Catapano, 2020; Chen, 2019b, 2020; Cruciani, 2019; Hsieh, 2019; Li, 2019, 2020; Mao, 2019; Marchitto, 2019; Sundaram, 2019; Xia, 2019). The results confirm previous policy findings, and no policy changes are warranted.

In 2022, we changed the coverage for platelet rich plasma to medically necessary as an adjunct treatment of chronic diabetic wounds based on evidence from an Agency for Healthcare Research and Quality systematic review (Qu, 2020) that would be applicable to the Medicaid population. These results support guidance from the Wound Healing Society (2017) that recommends selective use of adjuvant agents (e.g., topical platelet-derived growth factor for diabetic neurotrophic foot ulcers) when there is a lack of healing progress in response to more traditional therapies (e.g., offloading, infection control, glycemic control, and wound bed preparation).

The Agency for Healthcare Quality and Research systematic review included lower extremity diabetic ulcers (14 randomized controlled trials and one observational study, n = 1,096 participants), lower extremity venous ulcers (seven randomized controlled trials and three observational studies, n = 615 participants), and pressure ulcers (one randomized controlled trial and one observational study, n = 85 participants) (Qu, 2020). In addition, one randomized controlled trial evaluated autologous platelet lysate in participants with venous ulcers. While platelet rich plasma appears safe for all chronic wounds, the evidence was insufficient to determine its benefit in participants with lower extremity venous ulcers or pressure ulcers.

For chronic diabetic wounds, study participants were predominantly Caucasian males ranging in age from 40 to 70 years with cardiovascular comorbidities (e.g., smoking, hypertension, peripheral artery disease, or chronic kidney disease). Most wounds were of lower grade and ranged between 2 cm<sup>2</sup> and 4 cm<sup>2</sup>. Ten studies reported a minimum one month chronicity of the target ulcer before starting platelet rich plasma treatments. The majority of studies administered treatment once or twice weekly for up to 20 weeks. The length of follow-up after treatment ranged from none to 11 months (median of six weeks).

Compared to management without platelet rich plasma, autologous platelet rich plasma therapy significantly increased complete diabetic wound closure (relative risk 1.20, 95% confidence interval 1.09 to 1.32, moderate strength of evidence), shortened the time to complete wound closure, reduced wound area and depth (low strength of evidence), and had a similar safety profile. There were no significant differences in terms of wound infection, amputation, wound recurrence, or hospitalization. The authors support platelet rich plasma as an adjunct to multidisciplinary and comprehensive diabetic wound care.

We added 28 systematic reviews of the safety and effectiveness of platelet rich plasma for other indications published in the last year. The majority examined musculoskeletal indications, of which knee osteoarthritis and tendinopathy were the most commonly studied, but new indications continue to emerge. While platelet rich plasma appears safe to use, low quality studies and inconsistent reporting of patient and study characteristics and platelet rich plasma preparation continue to limit conclusions regarding its effectiveness across medical disciplines, which is reflected by no mention or no support for the treatment in current guidelines (American Academy of Orthopaedic Surgeons, 2014, 2017, 2019, 2021; North American Spine Society, 2020).

In 2023, we identified more than 150 systematic reviews on platelet-rich plasma as a sole treatment or treatment adjunct for a range of orthopedic and non-orthopedic indications published in the last year. As with previous findings in this policy, these secondary analyses, often duplicative, cite insufficient or conflicting evidence of effectiveness for all indications other than diabetic wounds that requires further study. The American Academy of Orthopaedic Surgeons' guideline update on management of anterior cruciate ligament injuries does not mention platelet rich plasma as a treatment option (American Academy of Orthopaedic Surgeons, 2022). No policy changes are warranted.

In 2024, we found two systematic reviews and meta analysis related to platelet-rich plasma treatment for diabetic foot ulcers and a separate systematic and network metanalysis that examined both the use of platelet-rich plasma and platelet-derived growth factor as a treatment for diabetic foot ulcers. No policy changes are warranted.

The first systematic review and meta-analysis of 22 studies (n= 1,559) assessed the use of autologous platelet-rich plasma for treating diabetic foot ulcers and found notable benefits in healing rates, quicker healing times, and a reduction in amputation rates, without an increase in adverse events, although more high-quality research is needed (Deng, 2023). Another systematic review detailed findings from 10 randomized clinical trials (n = 550) indicated that treatment with platelet-rich plasma resulted in a 38% improvement in healing rates and a 23-day reduction in healing time when compared to standard treatments, despite some inconsistencies in treatment methods (Peng, 2023). Furthermore, a network meta-analysis of 31 trials (n= 2,174) compared various growth factor therapies, including platelet-rich plasma and platelet-derived growth factor found significant enhancements in healing compared to control treatments. However, when only high-quality trials were considered, no significant differences were found, suggesting a necessity for more robust trials (Thanigaimani, 2023).

## References

On November 29, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "Platelet-derived growth factor" (MeSH), "platelet rich plasma" (MeSH), and "platelet-rich plasma." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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## Policy updates

10/2016: initial review date and clinical policy effective date: 2/2017

12/2018: Policy references updated. Policy ID changed.

12/2019: Policy references updated.

12/2020: Policy references updated.

2/2022: Policy references updated. Coverage modified.

2/2023: Policy references updated.

2/2024: Policy references updated.