

### Appendix 1 - Articles for Platelet-Derived Growth Factor

Author/ Year	Study Design	Demographics	Intervention, outcome measures; instruments	Results		Methodological Comments
				Intervention group	Control group	
Glover JL, Weingarten MS, Buchbinder DS, Poucher RL, Deitrick GA, Fylling CP 1997	Retrospective, case report	N = 3830 Av age = 64.5 years 38.5% Diabetic wounds 8.1% Arterial insufficiency 21.6% Venous 10.4% Decubitus 21.4% Other	Healing of wounds Amputation rates were lower p = .00005	65.7% had complete closure	50.8% had complete closure	Uncontrolled factors - antibiotics, dressing, # of attempts to improve arterial blood flow, debridement, larger wounds in PDGF group Not randomized.
Knighton DR, Ciresi KF, Fiegel VD, Austin LL, Butler EL 1986	Prospective, uncontrolled, nonrandomized trial	N = 41 patients with 71 wounds at the end of the study Age range was 11 - 80 (41 -70 was the largest group) 35 Diabetic wounds 4 Arterial 9 Venous 32 Other	4 patients/13 wounds were excluded due to amputation, skin graft, or primary closure. 5 of 71 wounds broke down during follow-up.	50% healing $4.5 \pm 3.5$ wks 80% healing $7.1 \pm 5.1$ wks 100% healing $10.6 \pm 6.1$ weeks		Uncontrolled
Knighton DR, Ciresi K, Fiegel VD, Schumerth S, Butler E, Cerra F 1990	Double-blind, randomized, crossover, placebo- controlled trial	N = 32 (initial) N = 24 (ending); Age of control group was $62 \pm 10$ yrs; Age of treatment group was $64 \pm 8$ ; underlying cause of ulcers not given	Measurements based on achieving 100% epithelialization 3 patients excluded for amputation	17 of 21 achieved 100% epithelialization In second time period, the 4 patients that hadn't healed in the first 8 weeks had 100% epithelialization	2 of 13 achieved 100% epithelialization After crossover, 100% Epithelialization in an average of 7.1 weeks	Small sample and study was not stratified for different types of wounds Or for severity of wounds - wound and infection scores varied considerably between the treatment and control group

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Knighton DR, Fylling CP, Doucette MM 1989	Retrospective, chart review Only patients that had been recommended for amputation	N = 20 9 patients greater than 65 years	Measured 100% epithelialization and tolerance of limited weight bearing; restoration of bipedal ambulation or limb function Wound severity scoring system used to measure wounds	Treatment failed in 2 of 20 patients; 16 achieved highest level of successful outcome; 2 functional but not ambulatory;		Non-controlled																												
Krupski WC, Reilly LM, Perez S, Moss K M, Crombleholme PA, Rapp JH 1991	Prospective randomized, double-blind placebo-controlled Only patients that had at least one chronic, nonhealing, cutaneous lower extremity wound of 8 weeks duration or longer were eligible	N = 18 All male patients 57 - 75, average age 66 ± 5.0 yrs. 78% Diabetic wounds 72% Occlusive peripheral vascular disease 28% Venous	Measured 100% epithelialization	24% - 4/17 had 100% epithelialization	33% - 3/9 had 100% epithelialization	Small number of patients Treatment group had higher incidence of peripheral vascular disease and diabetes (although text notes no difference) Large difference between glucose levels of control versus treatment group																												
Margolis DJ, Kantor J, Santanna J 2001	Retrospective, with propensity scoring to minimize bias using age, insurance status, referral status, sex, and number of wounds in addition to wound variables, duration, size, volume, debridement status, and grade, plus four clinic variables: # of patients seen at the clinics, year of treatment, individual clinic, and # of years the clinic has been open Patients separated into quintiles based on propensity	N = 26,599 patients from the Curative Health Services Database treated between 1988 and 1997 61 - 68 years of age Diabetics only with plantar ulcers	Wound severity scoring system used to measure wounds	By 32 wks of care proportion of those healed:  <table style="border: none;"> <tr> <td style="padding-right: 10px;">Group</td> <td>PR</td> </tr> <tr> <td>1</td> <td>51.9</td> </tr> <tr> <td>2</td> <td>55.0</td> </tr> <tr> <td>3</td> <td>49.8</td> </tr> <tr> <td>4</td> <td>49.1</td> </tr> <tr> <td>5</td> <td>48.5</td> </tr> <tr> <td>6</td> <td>50.0</td> </tr> </table> Magnitude of effect was not the same for all groups - Greatest effect for those with largest wounds of highest grade. Also, a leveling off of effect after 20 weeks of care.	Group	PR	1	51.9	2	55.0	3	49.8	4	49.1	5	48.5	6	50.0	By 32 wks of care proportion of those healed:  <table style="border: none;"> <tr> <td style="padding-right: 10px;">Group</td> <td>No PR</td> </tr> <tr> <td>1</td> <td>46.6</td> </tr> <tr> <td>2</td> <td>46.6</td> </tr> <tr> <td>3</td> <td>40.4</td> </tr> <tr> <td>4</td> <td>35.2</td> </tr> <tr> <td>5</td> <td>31.6</td> </tr> <tr> <td>6</td> <td>41.0</td> </tr> </table>	Group	No PR	1	46.6	2	46.6	3	40.4	4	35.2	5	31.6	6	41.0	Did not control for glycemic control, history of cigarette use, and microbiologic status of the wound. Only those who started treatment with PR by wk 12 of care were included in study. Commencement of treatment and standard of care was not standardized. Greatest weakness of propensity scoring is the possibility of exclusion of a covariate that might have a substantial effect on the propensity of a patient to be treated with PR.
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Stacey MC, Mata SD, Tren Grove NJ, Mather CA 2000	Randomised Double-blind placebo controlled trial	N = 86 Median age 70 years 100% venous stasis ulcers	Measured 100% epithelialization Cox regression-analysis	No major difference in outcome between treatment and control groups 33 healed	34 healed	Infection was a controlled factor, randomization was documented in the article. Demographic characteristics of groups was similar. No need for stratification of ulcer type since only one type was evaluated.

### **Attachment 3 - Definitions<sup>1</sup>**

Angiogenesis- the ability to evoke blood vessel formation.

Autologous – pertaining to a tissue or structure occurring naturally and derived from the same individual such as blood donated by a patient before surgery to be returned to the patient during or after surgery.

Autologous graft – the transfer of tissue from one site to another on the same body.

Chemoattractant – a chemotactic factor that induces positive chemotaxis.

Chemotaxis – Chemotaxis is a cellular function, particularly of neutrophils and monocytes, whose phagocytic activity is influenced by chemical factors released by invading microorganisms.

Cutaneous – pertaining to the skin.

Cytokine – one of a large group of low-molecular-weight proteins secreted by various cell types and involved in cell-to-cell communication. Cytokines include colony stimulating factors, interferons, interleukins, and lymphokines, which are secreted by lymphocytes.

Debride- to remove dirt, foreign objects, damaged tissue, and cellular debris from a wound or a burn to prevent infection and to promote healing.

Epithelialization- the re-growth of skin over a wound.

Homeostasis- a relative constancy in the internal environment of the body, naturally maintained by adaptive responses that promote healthy survival.

Homologous – similar in structure.

Homologous graft – a tissue removed from a donor for transplantation to a recipient of the same species.

Growth factor – any protein that stimulates the division and differentiation of specific types of cells. Growth factors include platelet-derived growth factor, epidermal growth factor, nerve growth factor, and interleukins.

Matrix – also called “ground substance”, a basic substance from which a specific organ or kind of tissue develops.

Metalloprotein – a protein that contains one or more metal ions.

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<sup>1</sup> MOSBY'S Medical, Nursing, & Allied Health Dictionary, 6th edition.

Mitogen - an agent that triggers cell division.

Plasma – the watery straw-colored fluid part of the lymph and the blood in which the leukocytes, erythrocytes and platelets are suspended. Plasma is made up of water, electrolytes, proteins, glucose, fats, bilirubin, and gases. It is essential for carrying the cellular elements of the blood through circulation, transporting nutrients, maintaining the acid-base balance of the body, and transporting wastes from the tissues.

Platelets – the smallest of cells in the blood with a disk-shape containing no hemoglobin; they are essential for the coagulation of blood and in maintenance of hemostasis.

Proteinase – a proteolytic enzyme that splits protein molecules at central linkages.

Skin – the tough, supple cutaneous membrane that covers the entire body. It is composed of a thick layer of connective tissue called the dermis and an epidermis made of five layers of cells.

Sonication – the act of exposing a suspension of cells (e.g. platelets) to the disruptive effect of the energy of high frequency sound waves.

Ulcer – a circumscribed, craterlike lesion of the skin or mucous membrane resulting from necrosis that accompanies some inflammatory, infectious, or malignant processes.

Wound – any physical injury involving a break in the skin, usually caused by an act or accident rather than by a disease, such as a puncture wound.

Wound Healing – a process to restore to a state of soundness to any injury that results in an interruption in the continuity of external surfaces of the body.