DRUGS and WOUND HEALING
Friend or Foe

What is the Impact of Anti-inflammatory and Immunosuppressive Drugs on Wound Healing

The Impact of Anti-inflammatory and Immunosuppressive Drugs on Wound Healing

- What are the diseases ?
- What are the drugs and how do they work ?
- What are the wounds?
- How might the drugs interfere with wound healing?
- What adjustments should be made to drug use and dosage to maximise healing ?
- Take home messages

What are the Diseases

- Inflammatory Arthritis
    - Rheumatoid Arthritis
    - Psoriatic Arthritis
    - Spondyloarthritis
    - Crystal Arthritis
        - Urate (Gout)
        - Calcium Pyrophosphate Dihydrate (Pseudogout/CPPD arthritis)
- SLE
- Vasculitis
- Scleroderma
- Inflammatory Muscle Disease
- Inflammatory Bowel Disease
- Pyoderma Gangrenosum

What are the Drugs

- Steroids (IV Pulse/Oral/ Intraarticular)
- Non Steroidal Anti-inflammatory Drugs (NSAIDs)
- Classic Disease Modifying Antirheumatic Drugs (cDMARDS)
  - Methotrexate/Leflunomide/Hydroxychloroquine/Salazopyrine
- Biologics (bDMARDS) (Targeted monoclonal antibodies)
- Targeted synthetic DMARDS (tsDMARDS)
- Other Immunosuppressive Agents
  - Azathioprine/Cyclophosphamide/Mycophenolate/Cyclosporine/Tacrolimus

How do the Drugs Work

- In Chronic Inflammatory disease **Inflammation is the enemy!**
- All the drugs used suppress inflammation one way or another
- NSAIDs Block cyclooxygenase
- STEROIDS Complex multiple actions. Differs with dose and duration.
- cDMARDS Different modes of action. Not specifically targeted.
- bDMARDS Monoclonal antibodies targeting specific cytokines or receptors.
    - TARGETS: TNF/Il6/Il17/Il23/Costimulating blockade/CD20
    - These agents have dramatically improved the outcome of patients with chronic inflammatory joint , skin and bowel disease.
- tsDMARDS Janus Kinase Inhibitors (JAK i) Inhibit specific JAK enzymes.
- Others Varied mechanisms aimed at suppressing activity of immunocytes.

What are the Wounds

- Elective surgical wounds.
    - Joint replacement Hips/Knees/Shoulders/Ankles
    - Arthroscopic procedures
    - Synovectomy
- Acute/emergency wounds.
    - Trauma
- Chronic persistent wounds
    - Ulcers
        - Vasculitic e.g. Rheumatoid Arthritis
        - Venous /Arterial/Pyoderma Gangrenosum
    - Calcinotic lesions

Rheumatoid Arthritis

Vasculitic Lower limb Ulcers

Pyoderma gangrenosum

This purulent ulcer with a ragged and violaceous border is consistent with pyoderma gangrenosum.

Ischemic Digital Ulcers in Scleroderma

How Might the Drugs Interfere with Wound Healing

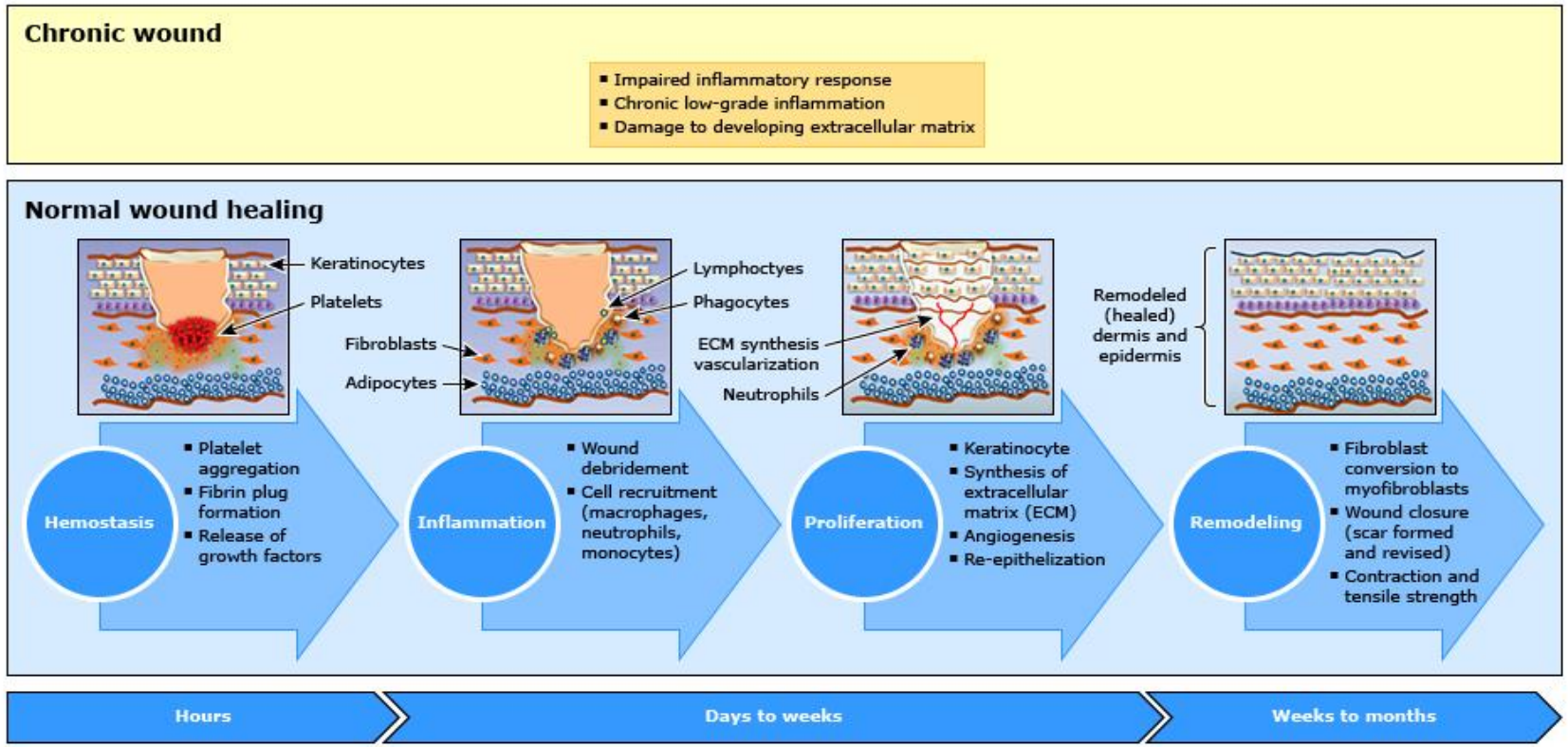
Increased risk of infection.

Interference with renal function.

Impairment of the normal wound healing process.

- Inhibition of inflammatory and proliferative phases.

Alterations in normal wound healing process



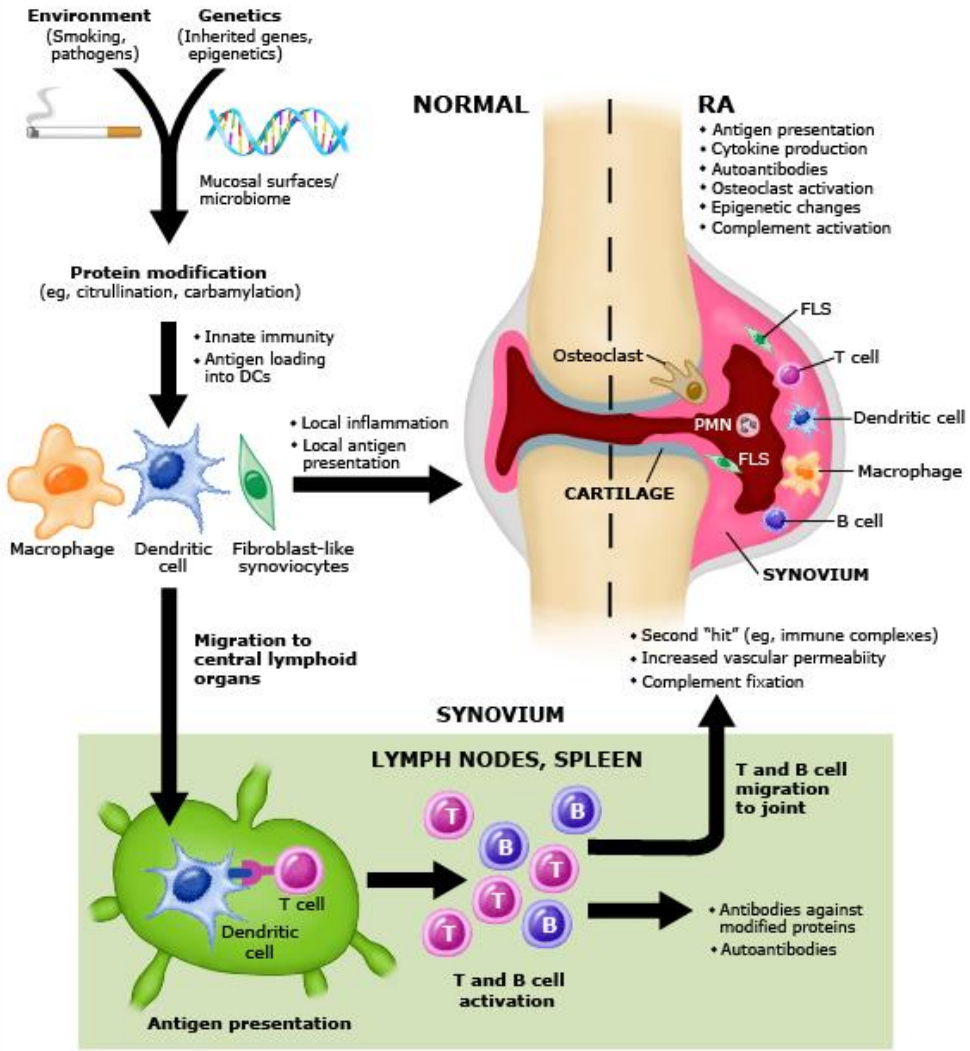
Normal wound healing follows an orderly progression involving initial hemostasis, inflammatory, proliferative, and remodeling phases. The chronic wound is frequently characterized by persistent inflammation, which damages the newly developing extracellular matrix.

Adapted from: Gomes A, Teixeira C, Ferraz R, et al. Wound-healing peptides for treatment of chronic diabetic foot ulcers and other infected skin injuries. Molecules 2017; 22:1743. Copyright © 2017 MDPI. Available at: https://www.mdpi.com/1420-3049/22/10/1743 (Accessed on June 18, 2019). Reproduced under the terms of the Creative Commons Attribution License.

Additional information from:

1. Armstrong DG, Gurtner GC. A histologically hostile environment made more hospitable? Nat Rev Endocrinol 2018; 14:511.

Pathogenesis of rheumatoid arthritis



DCs: dendritic cells; RA: rheumatoid arthritis; FLS: fibroblast-like synoviocytes.

Do Drugs Interfere with Wound Healing?

What is the Evidence - Elective/Acute Wounds

- There have been many studies assessing the impact of DMDs/immunosuppressants on wound healing time and Surgical Site Infection (SSI) rates.
- Results vary from no impact to increased infection rates and delayed healing.
- Probably other factors are important:
    - Is the underlying autoimmune disease stable ? (Remission or Low Disease Activity)
    - Comorbidities
        - Diabetes
        - Venous and Arterial disease
        - Renal or Liver disease
        - Poor nutrition
        - Age
- Goals are :
    - Rapid uncomplicated wound healing.
    - Avoidance of a flare of the underlying autoimmune disease.
    - Avoidance of infection

Adjustments to Medications

- **Elective/Acute Wounds**
  - **STEROIDS:** Maintain Prednisolone. May need peri-operative increased oral dose/IV Hydrocortisone because of adrenal suppression.
  - **NSAIDs:** Avoid during acute illness/surgery because of renal function impact.
  - **cDMARDs:** Suspend Methotrexate the week before , the week of and the week after surgery. Note risk of incorrect dosing when inpatient.
  - **b/tsDMARDs:** Suspend one dose before surgery. Resume when wound healed. Delay if any infective complication.
  - **Other Immunosuppressives:** Decision will be based on the activity of underlying disease and risk of infection.

What is the Evidence - Complex Chronic Wounds

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The Relationship Between Autoimmune Disease and Disease-Modifying Antirheumatic Drugs on Wound Healing

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What is the evidence - Complex Chronic Wounds

- Retrospective review of patients with chronic wounds and history of inflammatory disease presenting to a tertiary wound centre 2014-2018
- 58 patients with 296 wounds.
- Wide variety of conditions. (See table)
- 75% female
- Median age at wound onset 65.
- 87% lower limb.
- 73% taking DMDs or Immunosuppressive drugs.

Table 3. Inflammatory condition and disease-modifying antirheumatic drug usage among patients in the studied cohort

Characteristic N (%)
Condition
Rheumatoid arthritis 16 (27.6)
Pyoderma gangrenosum 13 (22.4)
Vasculitis 9 (15.5)
Raynaud 6 (10.3)
Systemic lupus erythematosus 5 (8.6)
Crohn's disease 4 (6.9)
Hidradenitis suppurativa 3 (5.2)
Sarcoid 1 (1.7)
Other 7 (12.1)
Taking DMARDs at time of presentation with wound (n = 296)
No 79 (26.7)
Yes 217 (73.3)
Average number of DMARDs 1.5 (SD 1.2)

DMARD, disease-modifying antirheumatic drug.

KEY FINDINGS

In the studied cohort, 70.9% of all wounds healed and median time to healing was 229.5 days.

Patients who were taking at least one DMARD at wound onset healed significantly faster than patients who were not on any DMARD therapy at the time of wound onset (190.5 days vs. 340 days, p = 0.016).

Wounds that healed were associated with a higher number of DMARDs at wound onset compared with wounds that did not heal (1.6 – 1.3 vs.1.2 – 1.1; p = 0.021).

CONCLUSIONS

DMARDs/immunosuppressive drugs may be beneficial in promoting more rapid healing of chronic wounds in patients with Autoimmune disease.
Suppression of damaging chronic inflammation may be positive.

Adjustments to Medications

- **Complex Chronic Wounds**
  - **cDMARDS/ b/tsDMARDS:** Continue **unless infection is present**.
  - **Steroids:** Taper to lowest dose needed to control underlying auto-immune disease.
  - **Other immunosuppressives:** Continue to ensure underlying disease is controlled.

  - **NB:**
    - **Some auto-immune diseases cause chronic wounds that respond to the use of steroids and immunosuppressive agents.**

      eg: Vasculitic Ulcers

      Pyoderma Gangrenosum

      Internal organ granulomas

Take Home Messages

- Inflammation is a normal and necessary mechanism to deal with infections and tissue damage, including acute/surgical wounds. (**GOOD INFLAMMATION)**
- Chronic inflammation can lead to increased tissue damage. **(BAD INFLAMMATION)**
- Antinflammatory and immunosuppressant drugs should be avoided or minimized

  in the setting of an elective or acute wound.

The same agents may be helpful in managing persistent chronic inflammation.

The Challenge is to Balance The Good and The Bad and avoid the Ugly

The UGLY

Amputation stump wound breakdown

This picture depicts transmetatarsal amputation stump wound breakdown due to ischemia. Full-thickness wound dehiscence is seen medial and lateral with a fibrotic wound base and there is dependent rubor characteristic for ischemia of the dorsal and plantar amputation flaps.

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Pyoderma gangrenosum

A large ulcer with undermined borders and a purulent base is present on the lower extremity.

Balancing The Good and The Bad to avoid The Ugly

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