



Adjunct Methods of the Standard DFU Therapy and HBOT

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Epidemiology of DFU

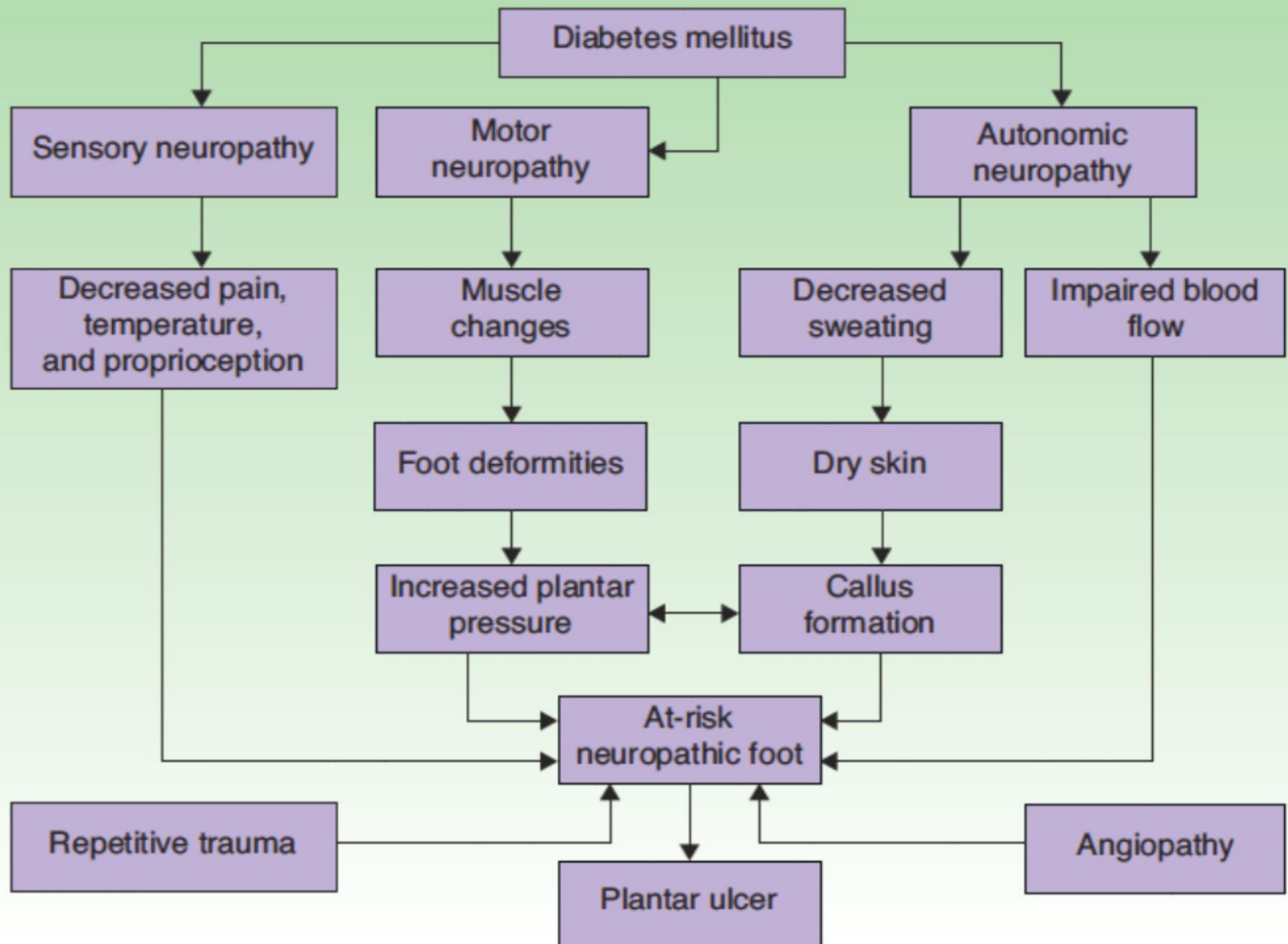
- DM is a **serious** and **complex** disease affecting almost all the vital organs in the body.
- DFU which affects **15 %** of people with DM
- Approximately **15–25%** of those cases require **amputation**
- The **morbidity** and **mortality** associated with **amputation** are significant
- Treatment of DFU remains challenging because of **unsatisfactory results** from surgical and non-surgical treatment.

Epidemiology of DFU

- Many adjunctive therapies are designed to improve the care of DFU: Negative pressure wound therapy, ultrasound, recombinant human platelet-derived growth factor-BB (r-PDG-BB), cellular matrix product, extracorporeal shockwave therapy (ESWT), **HBOT**
- The results of preclinical and clinical trials show that **HBOT** can **reduce treatment time, short-term morbidity** and **risk of major amputation**

Etiopathogenetic factors of DFU

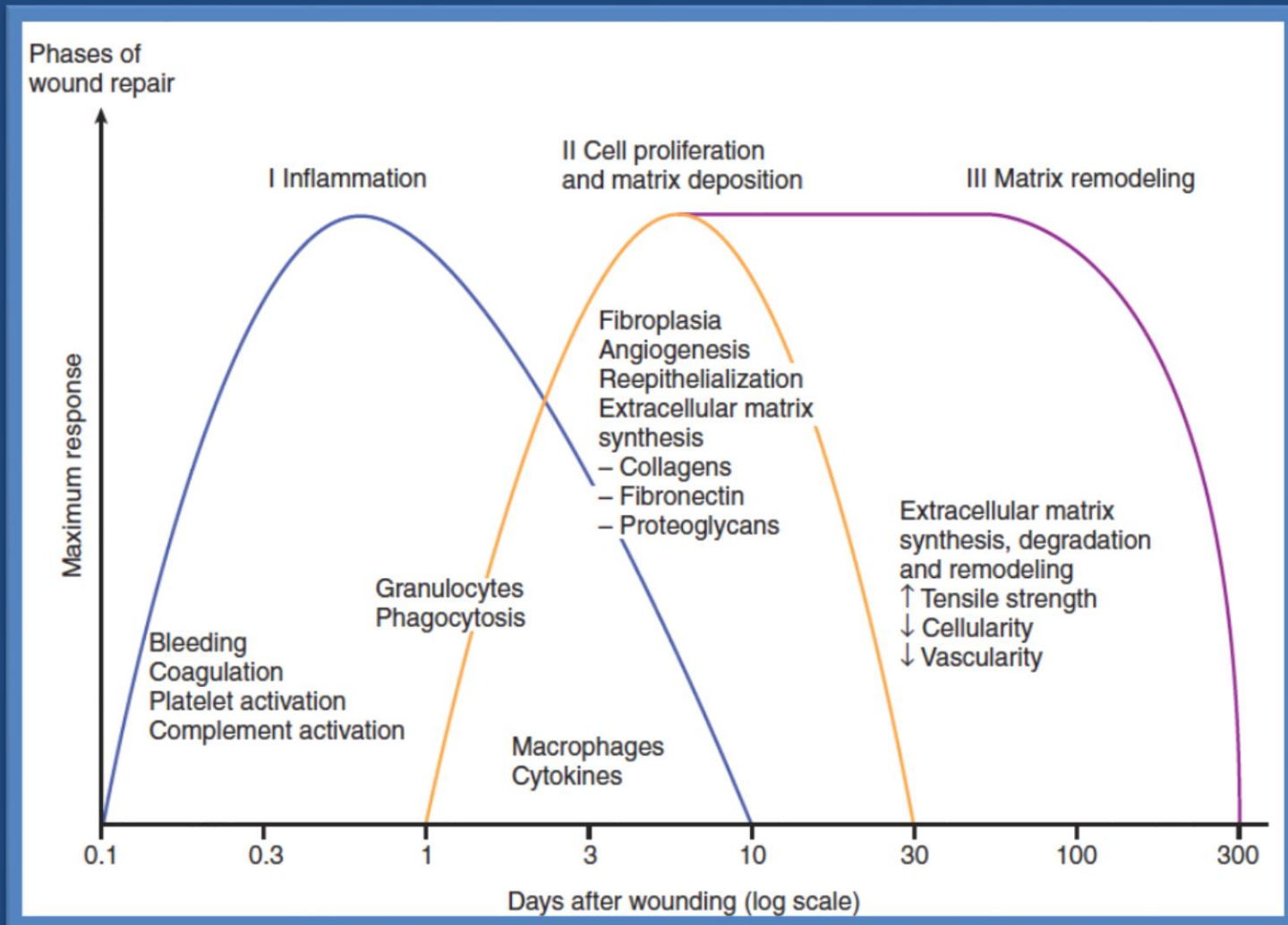
Etiopathogenetic factors of DFU involve **neuropathic**, **ischaemic**, **infection** (super infection), **mechanic**, **metabolic** and **systemic risk factors**



Physiological Process of Wound Healing

- The physiological process of wound healing is traditionally divided into four phases: **haemostasis**, **inflammation**, **proliferation**, and **maturation or remodeling**.
- Wound healing occurs as a **cellular response** to **injury** and involves activation of keratinocytes, fibroblasts, endothelial cells, macrophages, and platelets.
- Many growth factors and cytokines released by these cell types are needed to coordinate and maintain healing.
- These phases are orchestrated by a subtle interplay of **cellular** and **humoral** factors

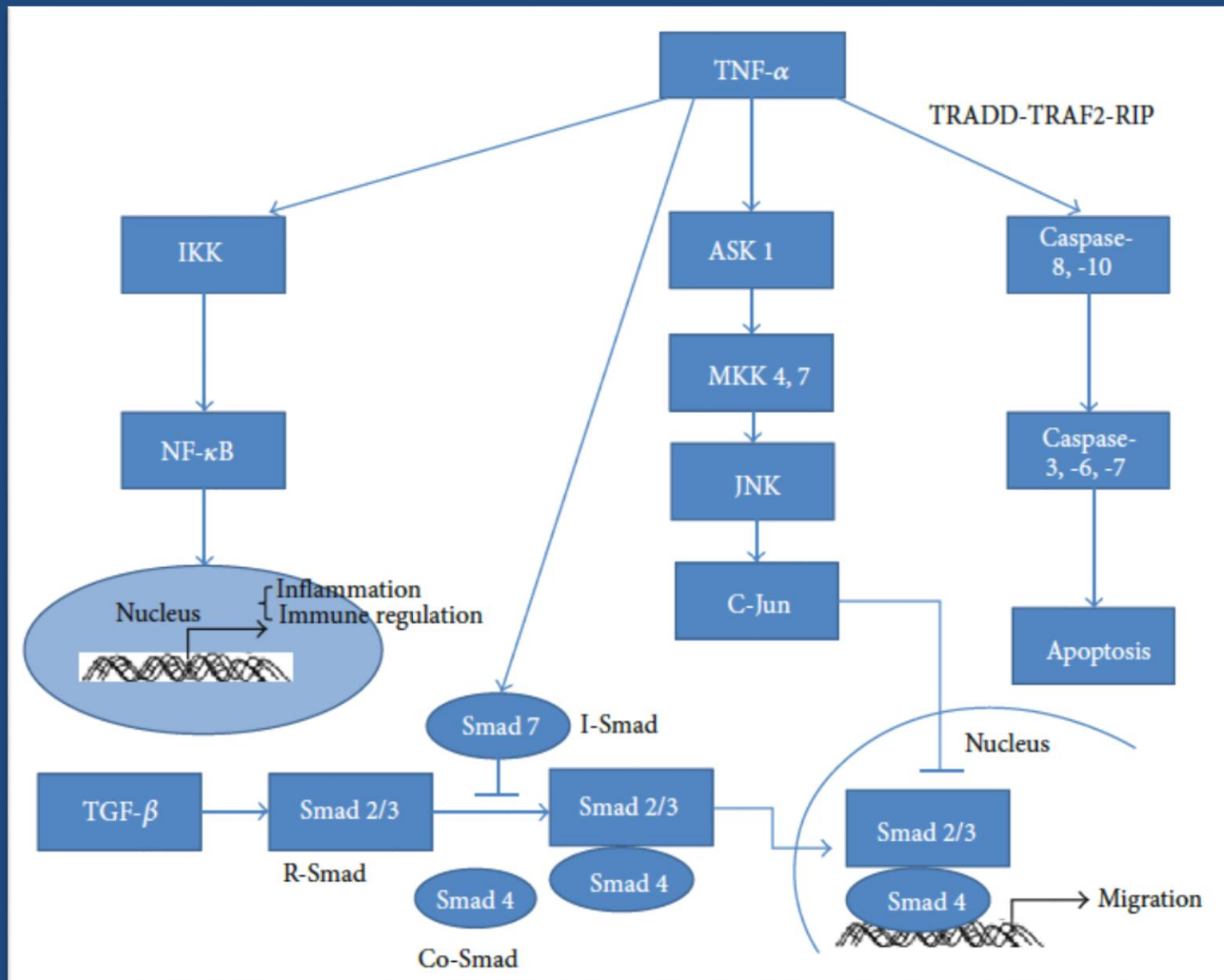
Time sequence of normal wound healing



Kevin P. Conway and K.G. Harding, 2008

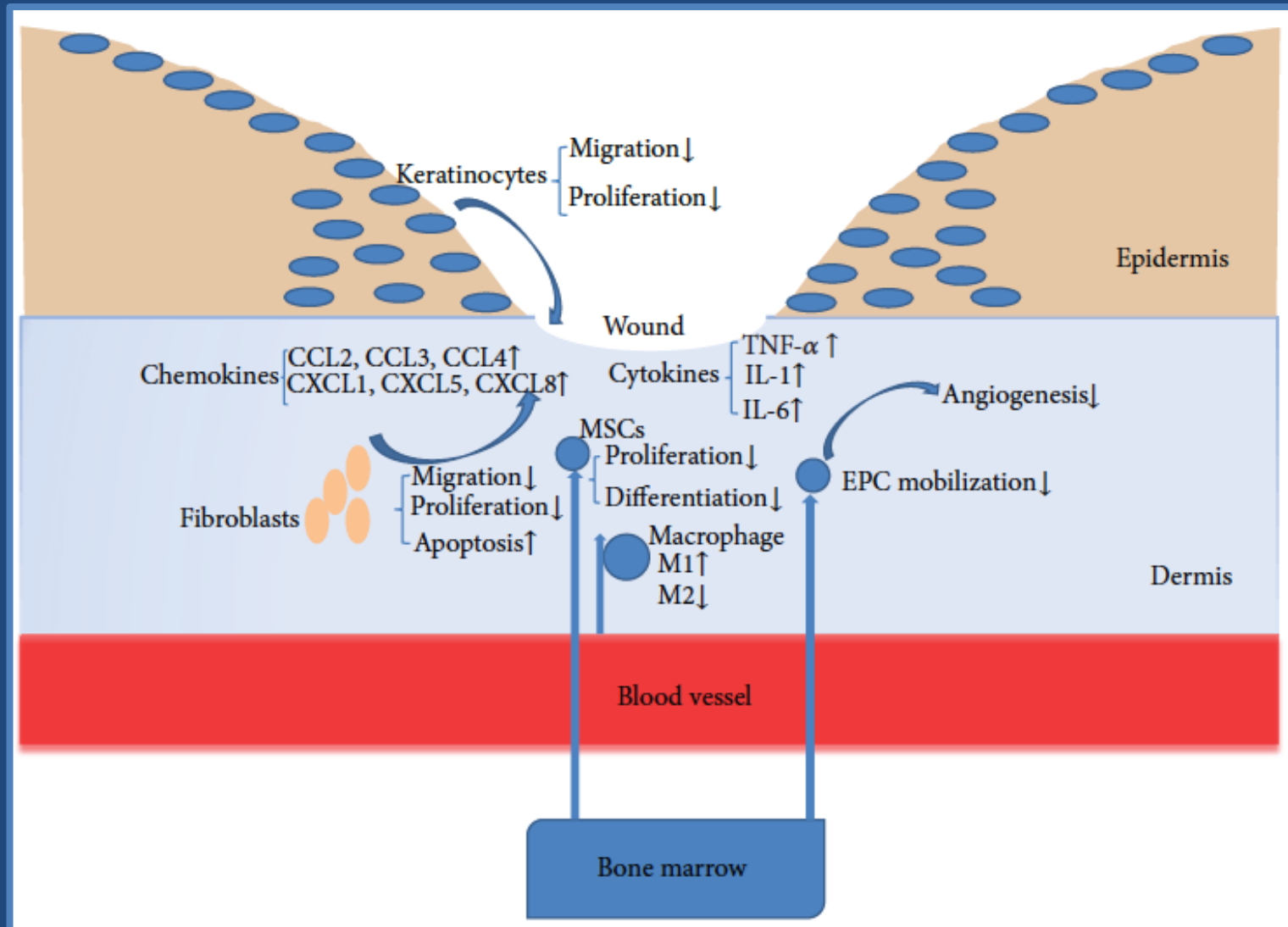
Molecular pathogenesis of diabetic wound healing

- **Over 100** known **physiologic factors** contribute to wound healing deficiencies in individuals with DM
- **Decreased** or **impaired** growth factor production, angiogenical response, macrophage function, collagen accumulation, epidermal barrier function, quantity of granulation tissue, keratinocyte and fibroblast migration and proliferation, number of epidermal nerves, bone healing, and balance between the accumulation of ECM components and their remodeling by MMPs
- DM enhanced and prolonged expression of **TNF- α**



Fanxing Xu, Chenying Zhang, Dana T. Grave 2013

Cellular & Molecular basis of Wound Healing in DM

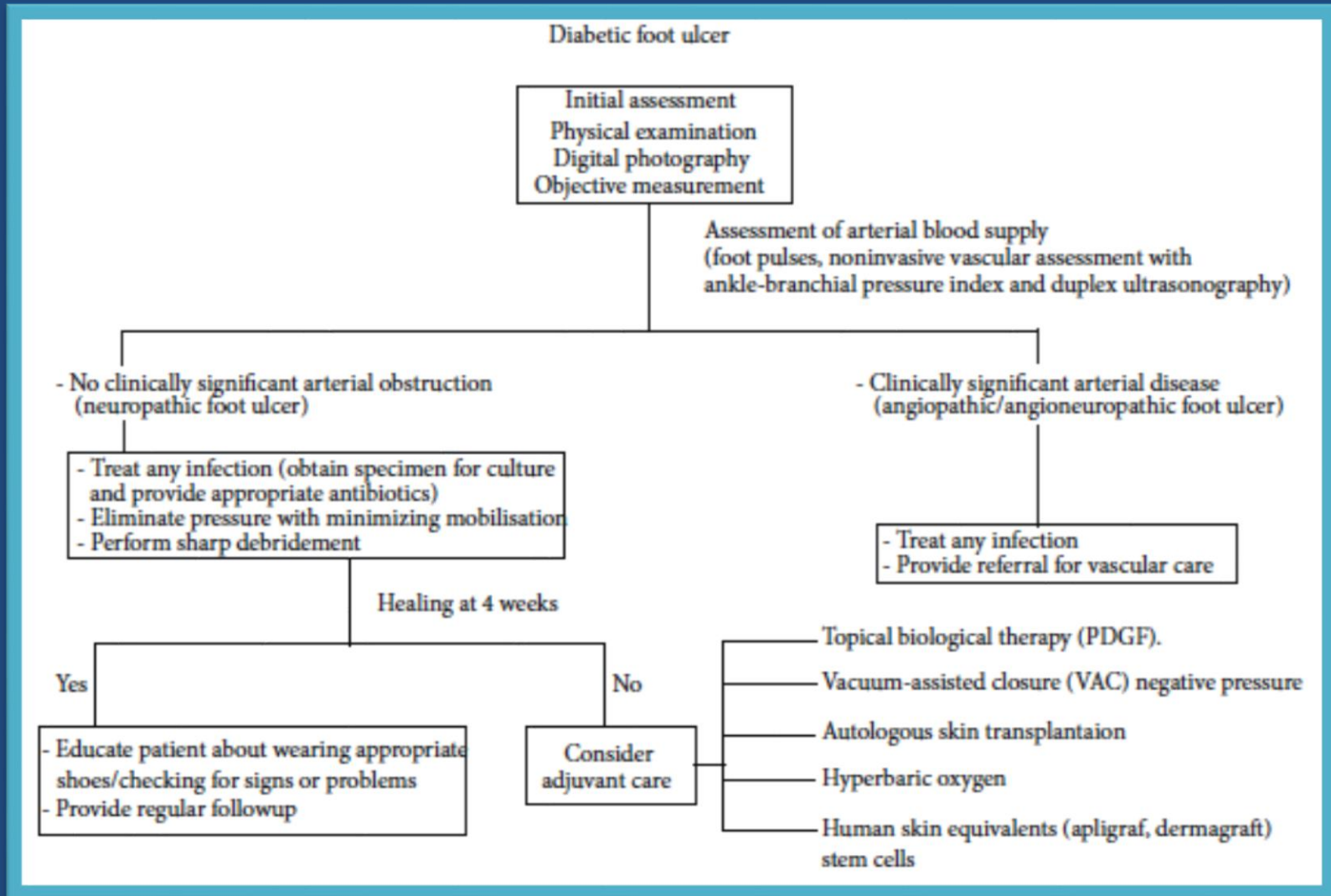


Fanxing Xu, Chenying Zhang, Dana T. Grave 2013

Standard care for DFU

- Standard care for DFU is ideally provided by a **multidisciplinary team** by ensuring glycemic control, adequate perfusion, local wound care include: regular debridement, off-loading of the foot, antibacterial actions and supplementation of growth factors and cytokines, leading to stimulation of granulation, epidermization, and angiogenesis.
- **Educating** patients helps in preventing ulcers and their recurrence.

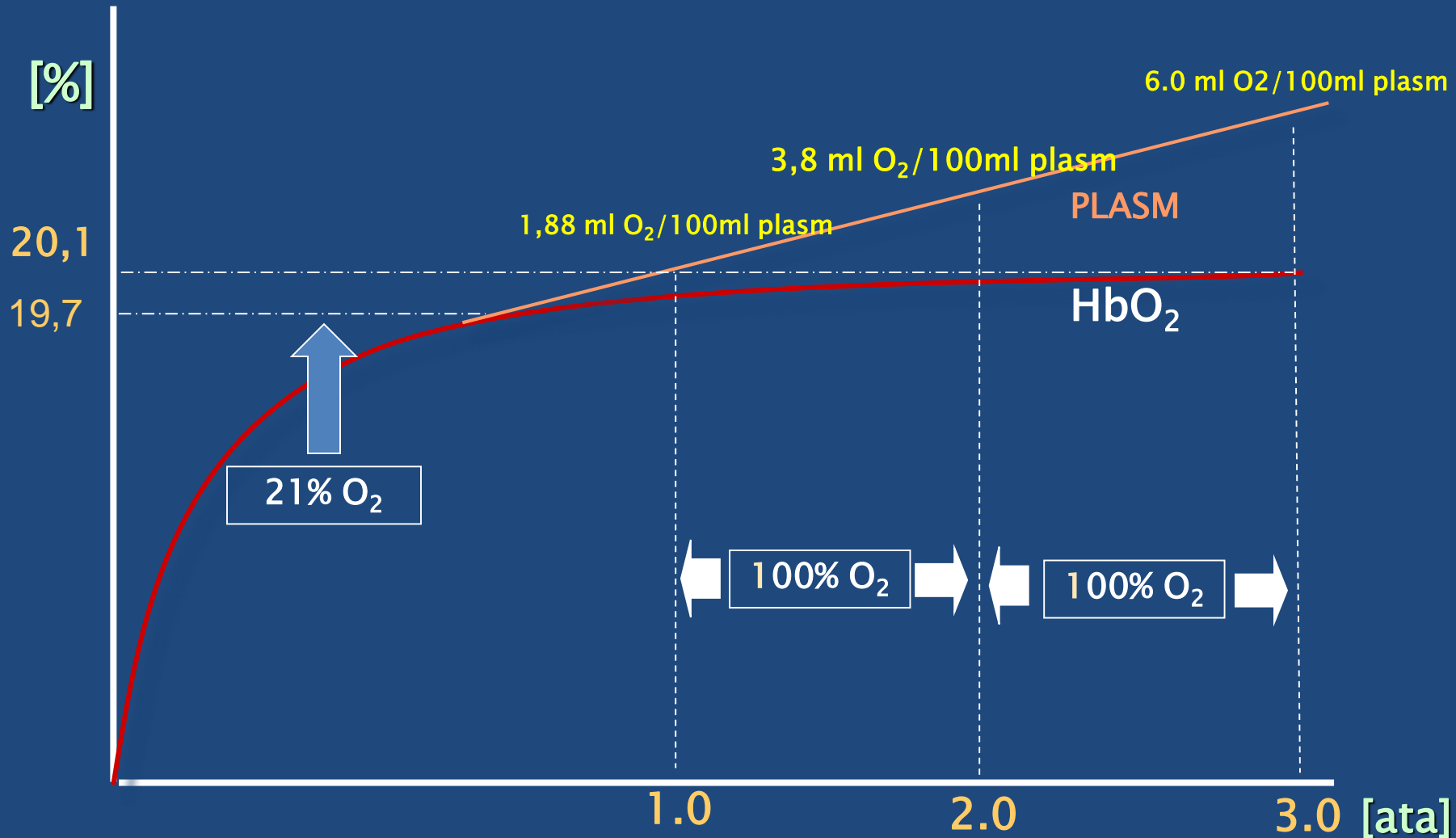
Algorithm for The Management of DFU



Hyperbaric Oxygen Therapy (HBOT)

- Hyperbaric oxygen therapy [HBOT] is a systemic treatment which involves breathing 100% oxygen and pressure of *more than 1 atmosphere* (atm).
- Treatment may be carried out either in a *mono -place chamber* pressurized with *oxygen 100%* or in *multi-place chamber* pressurized with *compressed air*, in which case the patient receives pure oxygen by *mask*, *head tent* (hood), or *endotracheal tube*.

Oxygen Saturation Curve



[Guritno, 1984]

What is the main therapeutic effect of HBOT ?

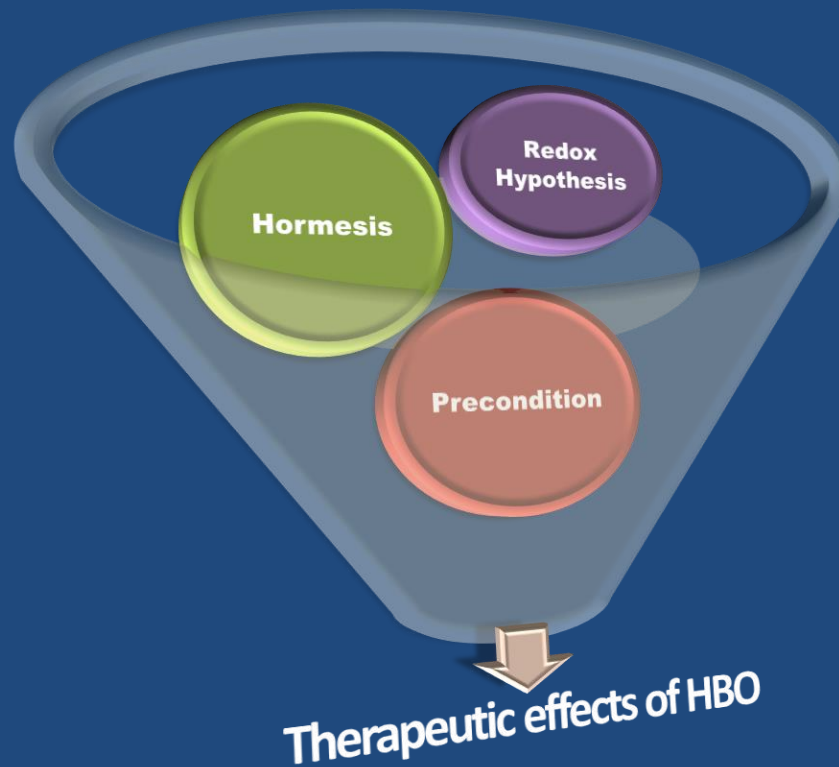
- Mechanical therapeutic effect of the increased barometric pressure
- Bio-molecular therapeutic effects of enhanced oxygen partial pressure. The initial effects that occur due to increased production of ROS [H_2O_2] and RNS [NO]

[Guritno, 1997]

How hyperbaric oxygen can be beneficial for treatment ?

THE APPROACHES OF 3 HYPOTHESES [“HYPERBARIC OXYGEN HYPOTHESES”]

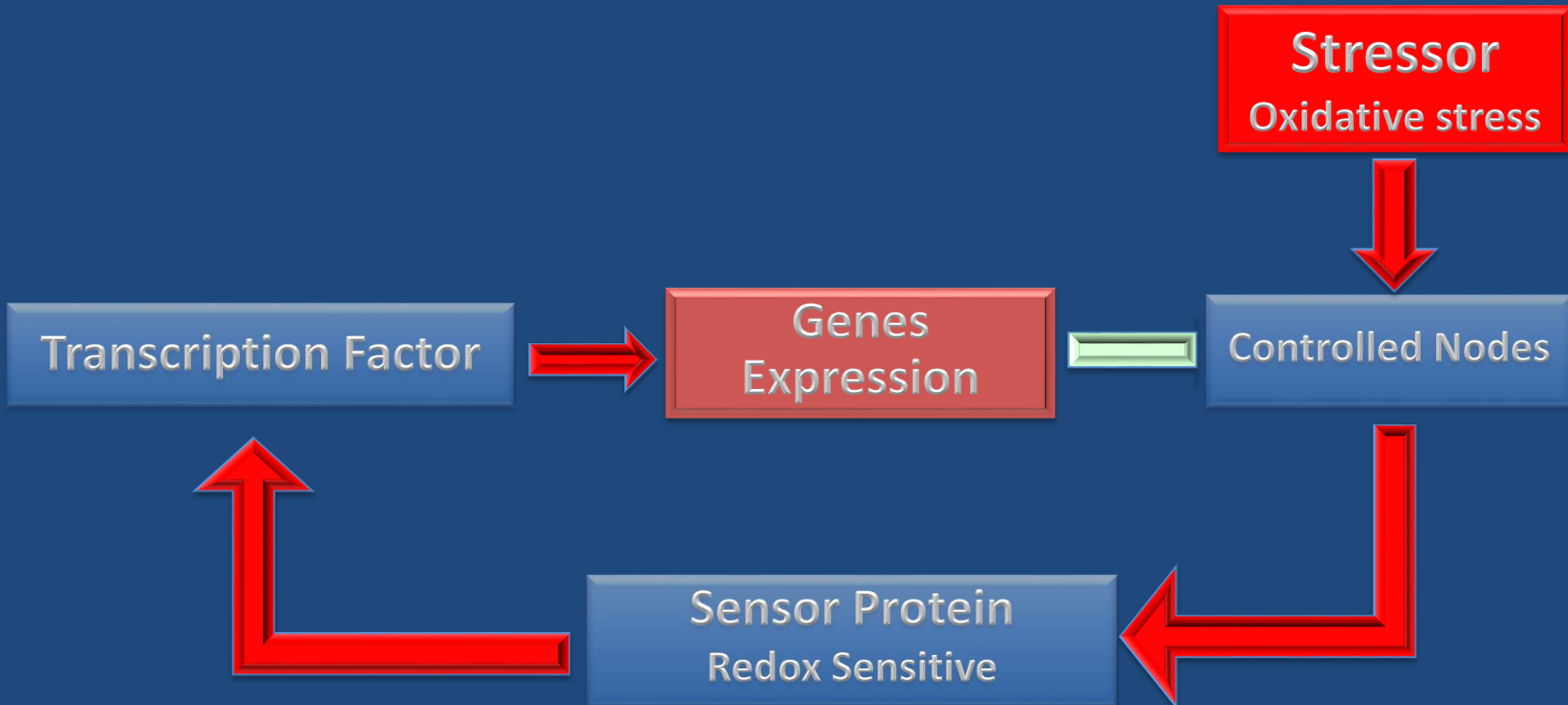
GURITNO, 2010



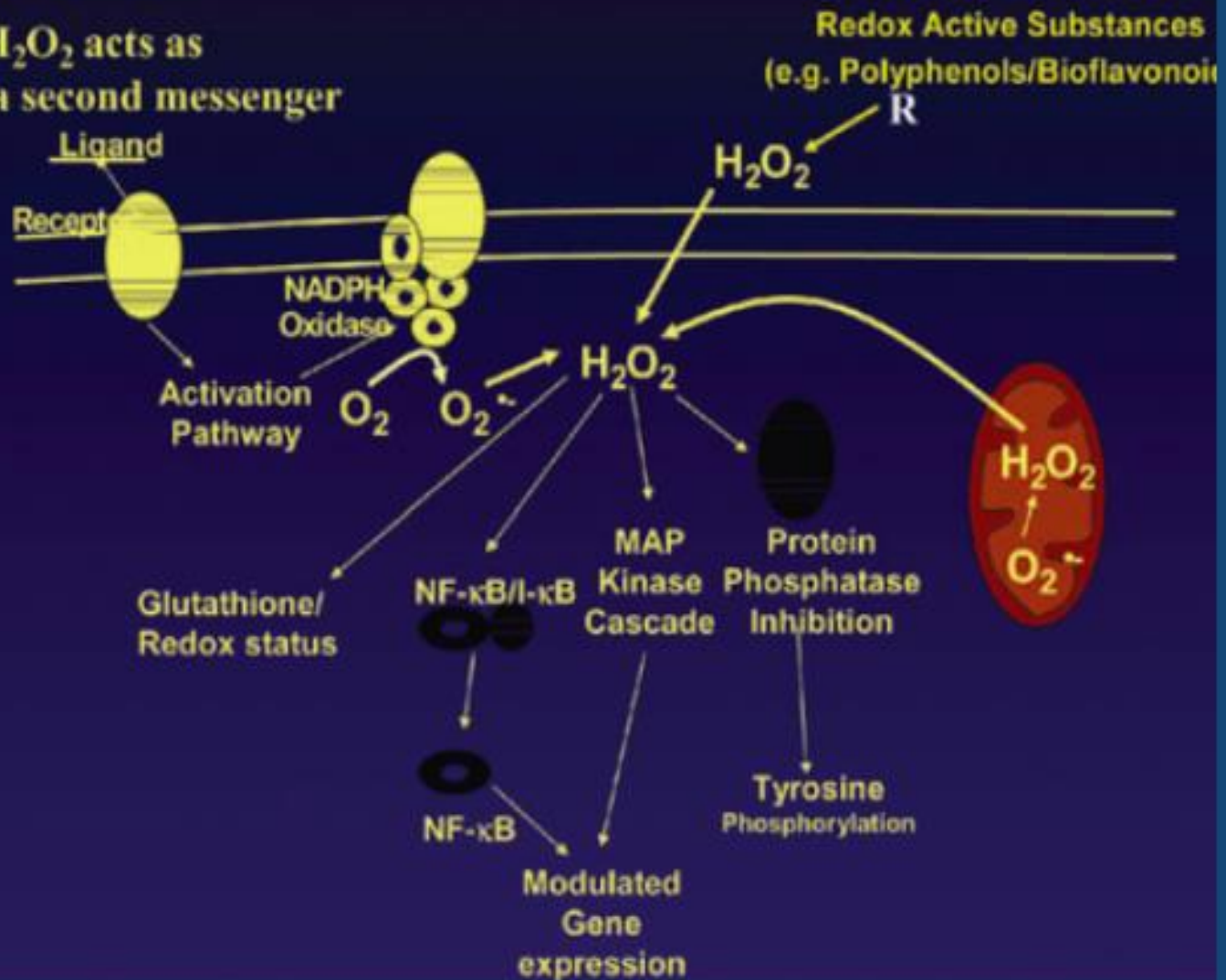
“Redox Hypothesis”

[1st HBO Hypothesis]

[Qiang Zhang et al, 2008]

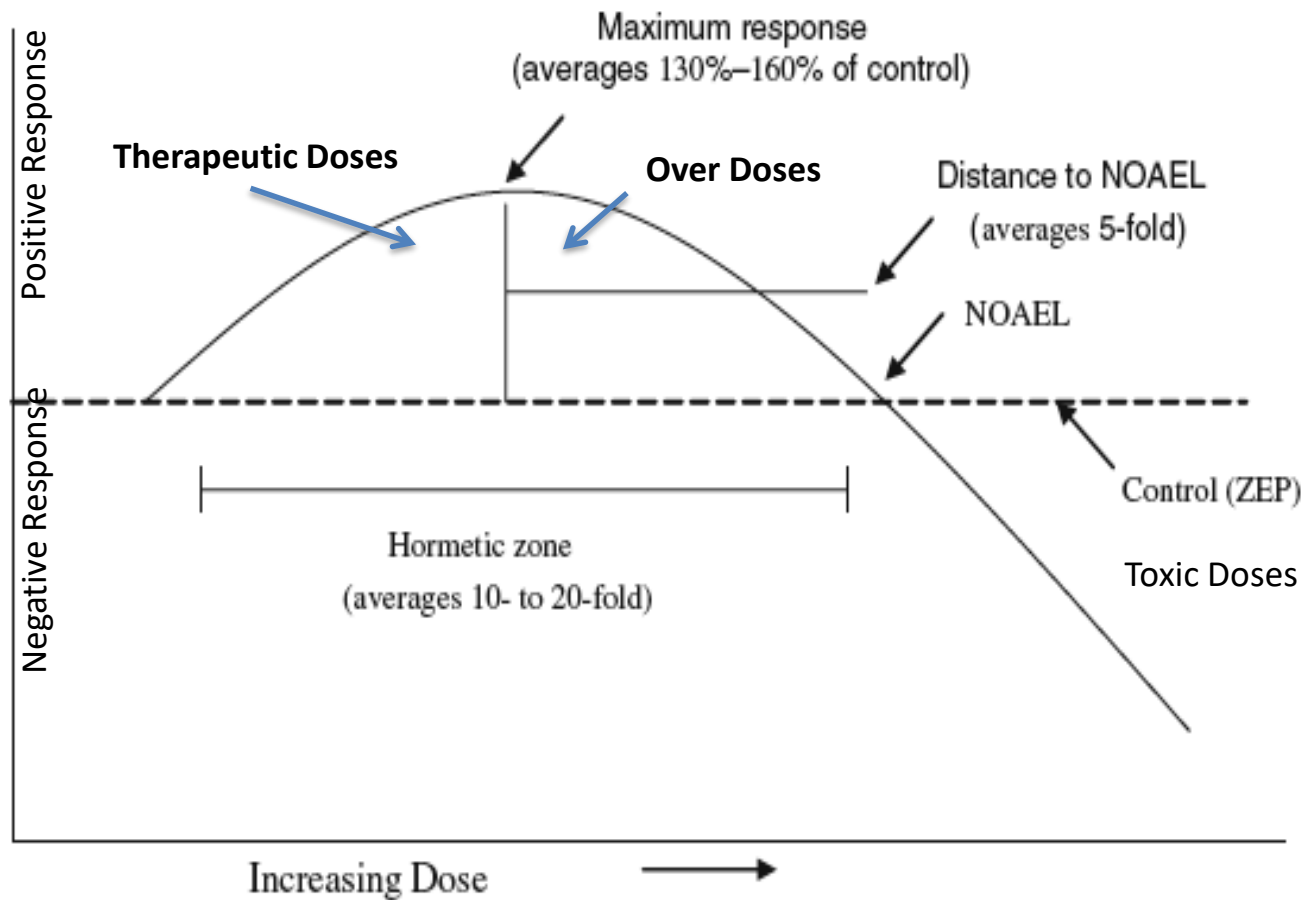


**H₂O₂ acts as
a second messenger**



“Hormesis”

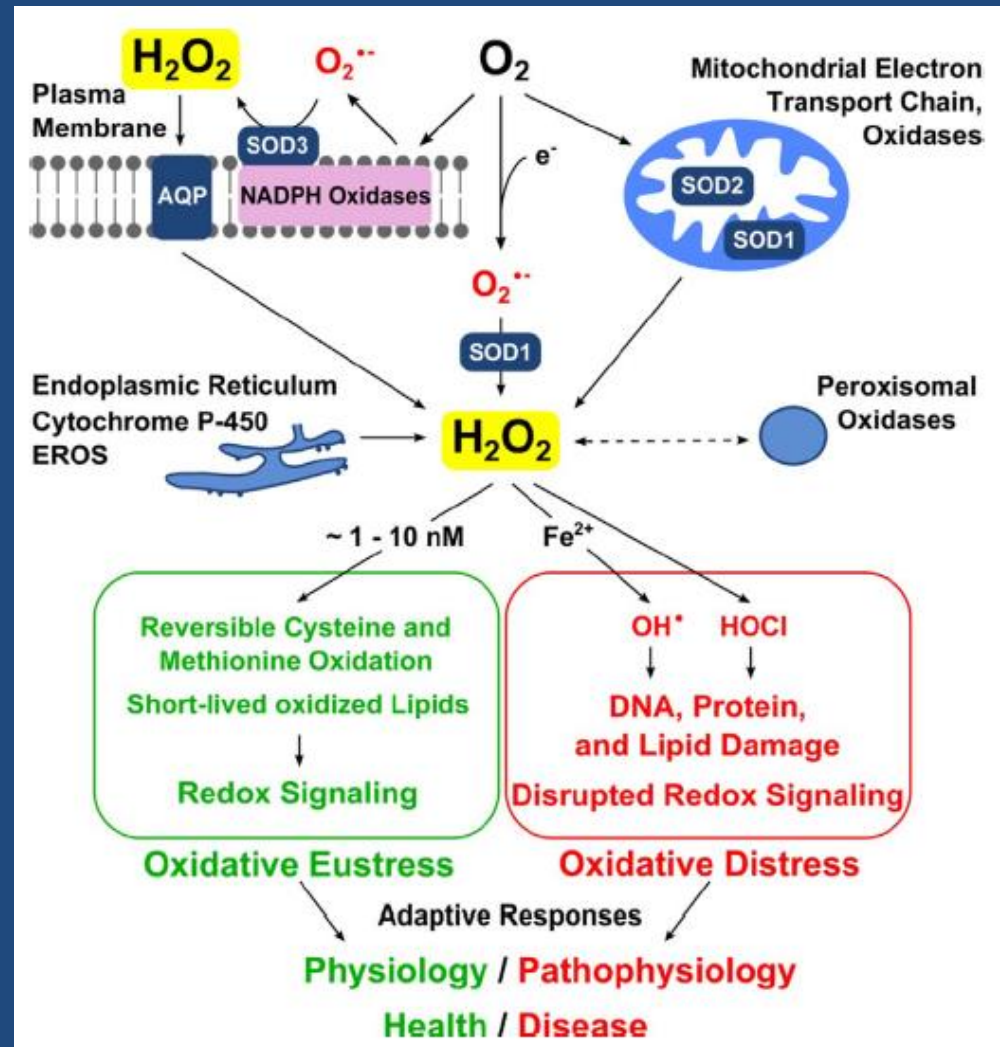
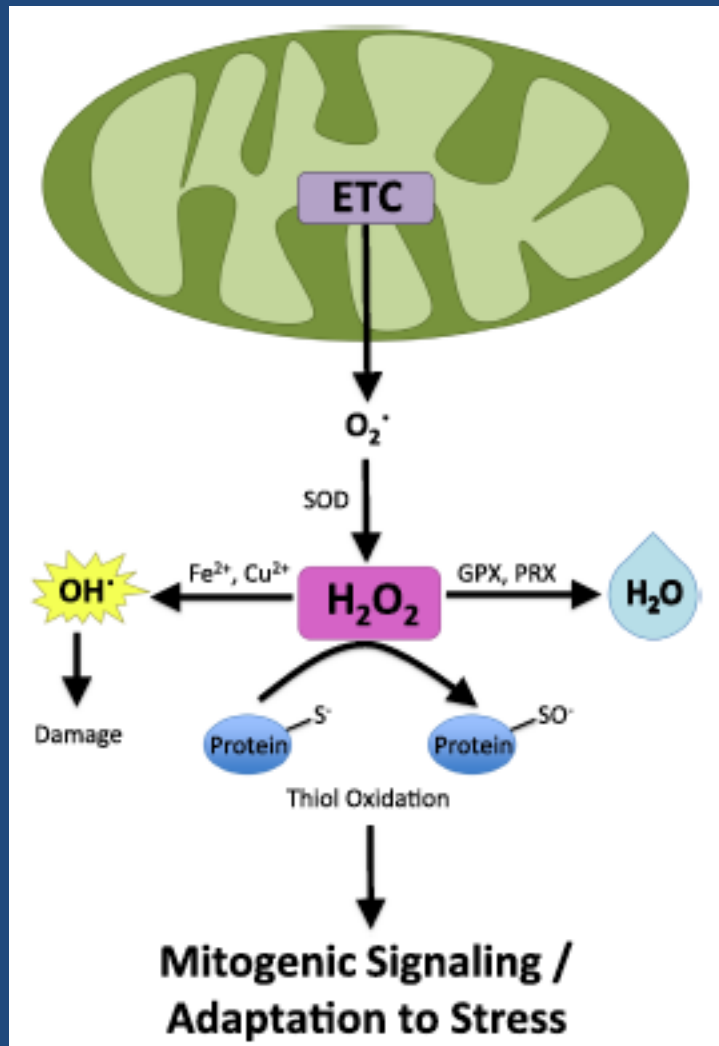
[2nd HBO Hypothesis]



[Calabresse and Baldwin 1997, Calabresse and Blain 2005]

H₂O₂ as a Central Redox Signaling:

Oxidative Eustress, Adaptive Response Oxidative Stress, Oxidative Distress



“HBO-Precondition” [3rd HBO Hypothesis]

HBOT “Ischemic Precondition”

Duration-Interval

Session - interval

Cure-Interval



“Ischemic Tolerance”

Early Phase

Hours

- Activation of existing protein
- Regulation of normal processes

Delayed Phase

Days

- Gen expression
- De novo protein synthesis
- Down regulation of genes expression during ischemia

[Miguel Blanco, Ignacio Lizasoain, Toas Sobrino, Jose Vivancos, 2006]

Ischemic Tolerance

Cellular Defense Mechanism

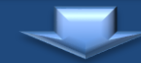
- ATP dependent K⁺ receptor
- Ionotropic Glutamate Receptor
- Immediate Early Genes
- Nitric Oxide
- P21 Ras Protein
- Phosphorylation Protein
- Apoptosis Regulating Genes
- Neurotropic Factors
- Erythropoietin
- Inflammatory Cytokines
- Nuclear Factors



**Formation of Survival Factors
Apoptosis Inhibitor**

Cellular Response to Stress

- HSP 70
- HSP 27
- HSP 90
- Guanylin Cyclase
- Muskelein
- Platelet Activating Factor Receptor
- β Actin



**Increased Capacity for Health
Maintenance Inside The Cell**

Current Justified in Indication for HBOT

- An agreement was reached on indications during the Consensus Conference (ECHM), Lille, Sept. 1994 and up-date in Dec. 2004, **April 15-16th 2016**
- In fact, one of the ways of assessing the efficiency of HBO: basic research, animal studies with control groups and human studies following **EBM** procedures (prospective, controlled, randomized clinical studies)
- EBM: ” **Integration of best research evidence with clinical expertise and patient values** ”.
- The **5 Steps EBM**: 1. Formulation of answerable clinical questions, 2. Searching for evidence, 3. Critical appraisal, 4. Applicability of evidence, 5. Evaluation of performance.



3rd INTERNATIONAL ANNUAL SCIENTIFIC MEETING “EVIDENCE BASED MEDICINE ON HYPERBARIC OXYGEN TREATMENT” ON MEDICAL HYPERBARIC OXYGEN TREATMENT

The Stone Hotel, Legian BALI

October 15rd -16th 2015

State of the art in HBOT
Accepted indications for HBO therapy
7th ECHM Consensus Conference, Lille, 2004
Methodology

The jury issued its recommendations using a three-grade scale according to the strength with each recommendation has been evaluated

Type 1 : Strongly Recommended

Recommendation of clinical importance for final outcome for the patient (quality of practice/future specific knowledge)

Type 2 : Recommended

Recommendation as positively affecting final outcome

Type 3 : Optional

The jury considers the implementation of the recommendation as optional





***10th ECHM
Consensus Conference
on Hyperbaric Medicine***

April 15-16th 2016

Lille

www.echm-lille-consensus-2016.org



Condition	Accepted			Non Accepted			Comment
TYPE II	Level Evidence			Level Evidence			
	A	B	C	D	E	F	
Crush injury without fracture			X				Added
Diabetic foot lesions		X					
Compromised skin grafts and musculocutaneous flaps			X				
Osteoradionecrosis (bones other than mandibula)			X				
Radio induced lesions of Soft tissue (other than cystitis, Proctitis)			X				
Surgery and implant in irradiated tissue (preventive treatment)			X				
Ischemic ulcer			X				
Refractory chronic osteomyelitis			X				
Burn 2sd degree more than 20 % BSA			X				
Central retinal artery occlusion (CRAO)			X				
Peumatosis cystoides intestinallis			X				
Stage IV neuroblastoma			X				
Femoral head necrosis		X					

The positive effect of HBOT on DFU

- Reduction of hyperglycemia
- Alteration of ischemic effect
- Reduction of edema
- Modulation of the production NO
- Promotion of cellular proliferation
- Acceleration of collagen deposition
- Stimulation of capillary budding
- Accelerated microbial oxidative killing
- Interference with bacterial proliferation
- Modulation of immune system response
- Enhancement of oxygen radical scavengers, thereby reducing ischemia reperfusion injury

Adjunct Methods of the Standard DFU Therapy

Interest is aroused by relatively efficient adjunct DFU treatment methods, including **Hyperbaric Oxygen Therapy (HBOT)**, **Maggot Therapy (MT)** or **Maggot Debridement Therapy (MDT)**, and **Platelet-Rich Plasma Therapy (PRPT)**.

TABLE 4: Wound healing process and the alternative methods.

Elements of wound healing	Methods		
	HBOT	MT	PRPT
Inflammation	Bactericidal and bacteriostatic effects on both aerobic and anaerobic bacteria through the action of the super oxide enzyme*	Antibacterial potential effect of alkaline pH of maggot secretion [77, 78] Wound bacteria are killed as they pass through the maggot's digestive tract* Presence of a potent bactericide present in maggot secretions* Cytokine regulation and enhanced phagocytosis [75]	Suppresses cytokine release and limits the amount of inflammation, interacting with macrophages to improve tissue healing Enhances phagocytosis and chemotaxis [54]* Antimicrobial host defence enriched with growth factors and other active substances [83]*
Granulated tissue formation—epithelialization	Increases epidermal cells and fibroblast proliferation and differentiation [29]	The healing of wounds is an interactive process (regulators as growth factors, cytokines and chemokines) [42] Synthesized and released locally proteins or polypeptides [42, 43] Increases fibroblast proliferation through maggots excretions and secretions [75]	Influences on chemotaxis, mitogenesis, and differentiation Promotes healing by stimulating fibroblast and keratinocyte proliferation Promotes granulation tissue formation [55, 61]* and epithelialisation
Matrix formations	Increases fibroblast proliferation and collagen production	Stimulates extracellular matrix and remodeling processes [45]	Stimulates the deposition of extracellular matrix and collagen [56]*
Angiogenesis	The oxygen gradient promotes the formation of new vessels required for wound healing [28, 35, 68]	Growth factors, cytokines, and chemokines provide significant vasodilation and increased capillary permeability to the wound site, allowing the infusion of recruited polymorphonuclear leucocytes (PMNs) and macrophages [48, 84]	Promotes new capillary growth [55, 56]*

* Animal models.

Clinical relevance in DFU according to th alternative methods

Clinical relevance	HBOT	MT	PRPT
Reduced area in DFU	Yes*	No	Yes**
Anti-edema effect	Yes**	No	No
Decreased risk amputation	Yes**	Yes**	Yes**
Shortening time of therapy	Yes**	Yes**	
** Clinical Studies			

Dariusz Waniczek et al. 2013

Wagner Classification of DFU

Grade	Sign
1	Superficial ulcer involving the full skin thickness but not underlying tissue.
2	Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation.
3	Deep ulcer with cellulitis or abscess formation, often with osteomyelitis
4	Localized gangrene
5	Extensive gangrene involving the whole foot.

Tc PO₂ Consideration

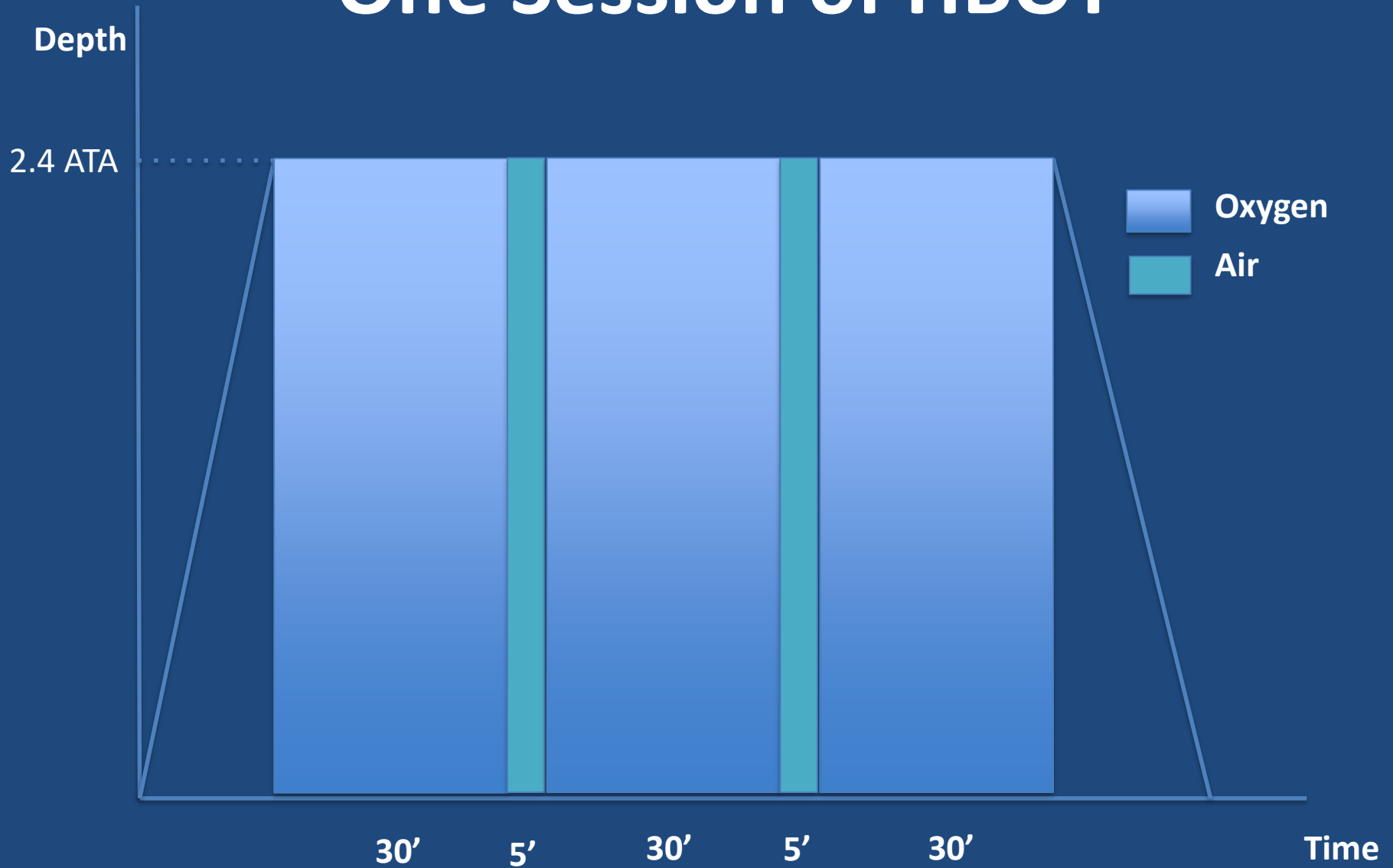
- Transcutaneous oximetry (TcPO₂) is considered an additional **criterion of classification** for HBOT, treated as a **valuable prognostic** factor for ulceration treated with the method
- In DFU patients, the TcPO₂ method-measured oxygen pressure **over 400 mmHg at 2.5 ATA** or **over 50 mmHg in pure oxygen** environment at normal atmospheric pressure should be perceived as a **good prognostic index**

TRANSCUTANEOUS O_2 , CO_2 FLOWMETER DOPPLER LASER





One Session of HBOT



Guritno, 1997

DFU before and after HBOT



Right lateral fifth ray resection before HBOT



Left dorsal great toe before HBOT



Right plantar great toe and dorsal view before HBOT



Left plantar foot after 31 HBOT treatments



Right lateral fifth ray resection after 26 HBOT treatments



Left dorsal great toe after 40 HBOT treatments



Right plantar great toe after 38 HBOT treatments

Contraindications

- **Absolute**

Untreated Pneumothorax

Pacemakers

Selected Medication:

1. Dexorubicin
2. Bleomycin
3. Disulfiram
4. Cis Platinum
5. Mafenide Acetate

- **Relative Contraindication**

Upper respiratory infections

Chronic sinusitis

Seizure disorders

High fever

History of spontaneous
pneumothorax

History of thoracic surgery

History of surgery for osteosclerosis

Viral infections

Congenital spherocytosis

History of optic neuritis



Side Effect

- Barotrauma
- Oxygen Toxicity
- Hypoglycemia (Diabetic Patient)
- Confinement Anxiety
- Decompression Sickness for Inside Attendants



TERIMA KASIH