

Approcci interdisciplinari in reumatologia - 7ª edizione

MALATTIE REUMATICHE E DISORDINI ENDOCRINO-METABOLICI



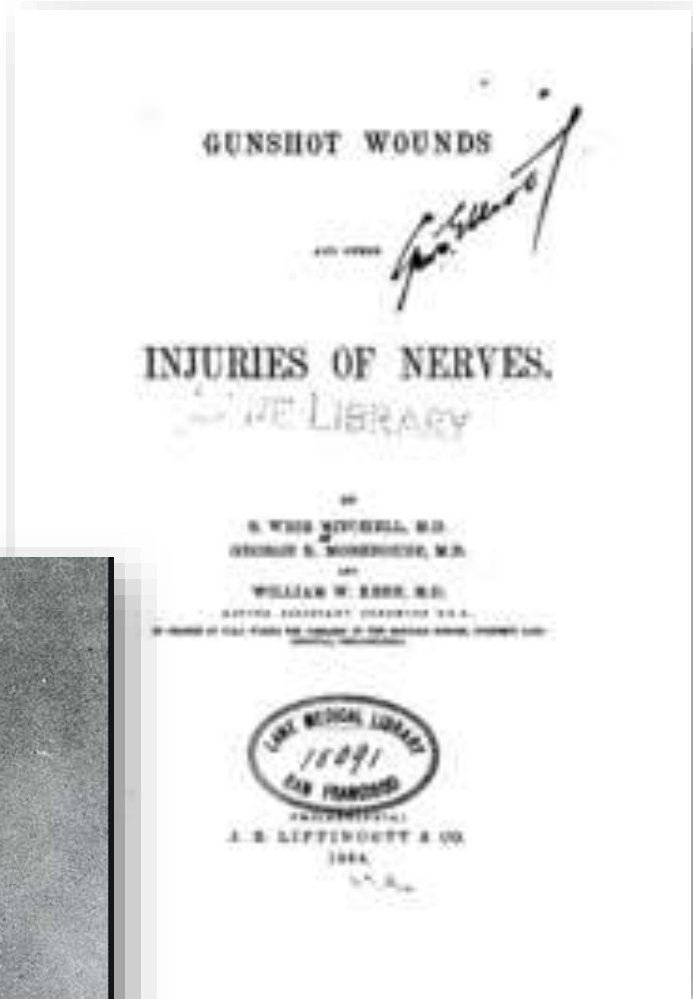
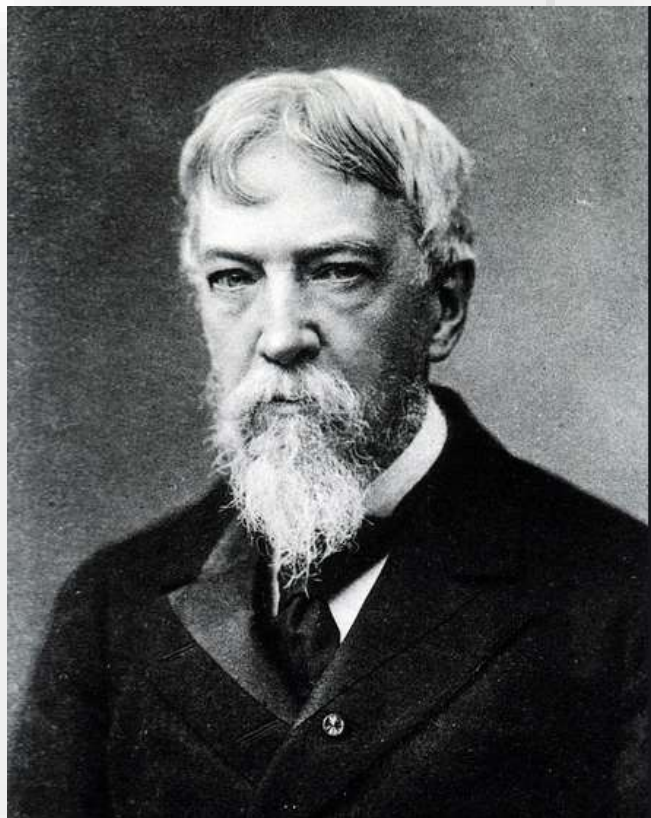
Torino - Ospedale Molinette - Lato Cervo Polonia

TORINO
16-17 ottobre 2020

La sindrome algodistrofica

Enrico Fusaro
Annacarla Finucci





CRPS - Complex Regional Pain Syndrome

Complex: eterogeneità segni e sintomi

Regional: coinvolgimento di una regione , solitamente a carico di un'estremità di un arto, che non rappresenta un territorio di innervazione

Pain Syndrome: corteo sintomatologico vario in cui il dolore è il sintomo principale

- ✓ *Terminologia e classificazione*
- ✓ *Patogenesi*
- ✓ *Epidemiologia*
- ✓ *Manifestazioni cliniche – diagnosi*
- ✓ *Trattamento*

CRPS - Complex Regional Pain Syndrome

DEFINITION

- *Complex regional pain syndrome* (CRPS) is a pain disorder that can develop after injury to a limb.

Table 8 Subtypes of complex regional pain syndrome (CRPS)

CRPS I (old name: reflex sympathetic dystrophy)

CRPS II (old name: causalgia): defined earlier with electrodiagnostic or other definitive evidence of a major nerve lesion

CRPS-NOS* (not otherwise specified): partially meets CRPS criteria; not better explained by any other condition.

* This subtype was added to capture any patients previously diagnosed with CRPS who now did not meet criteria.

Comparison of CRPS Types

Signs and symptoms	CRPS Type I	CRPS Type II
Precipitating event	Sometimes	Yes
Single Peripheral nerve involvement	No	Yes
Physiological change in affected limb	Yes	No
Cardinal signs	<ul style="list-style-type: none">• Spontaneous pain• Swelling• Different skin temperatures	<ul style="list-style-type: none">• Burning pain• Allodynia• Hyperalgesia
Progressive	Yes	Sometimes
Bone atrophy	Yes	No

BOX 82.1 TERMS USED IN THE DEFINITION OF COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) type I (the preferred term)

Causalgia (now CRPS type II)

Reflex sympathetic dystrophy (RSD)

Sudeck atrophy

Shoulder-hand syndrome

Algodystrophy

Algoneurodystrophy

Posttraumatic dystrophy

Posttraumatic osteoporosis

Painful osteoporosis

Transient osteoporosis

Some terms are listed that are or have been used to describe what is now considered under the definition of CRPS.

DEFINITION

- *Complex regional pain syndrome (CRPS) is a pain disorder that can develop after injury to a limb.*

*Complex regional pain syndrome type I (CRPS-I) is a severely **disabling pain** syndrome characterized by **sensory and vasomotor disturbance, oedema and functional impairment** that in most cases develop **following a trauma or surgery**.*

*Reflex sympathetic dystrophy or Complex Regional Pain Syndrome type I (CRPS I) is a painful **regional** disease with **non-metameric topography**, which shows **extreme pathomorphological variability**, from forms in which pain is the only clinical manifestation, to “pseudo-purulent” forms characterized by impressive local manifestations.*

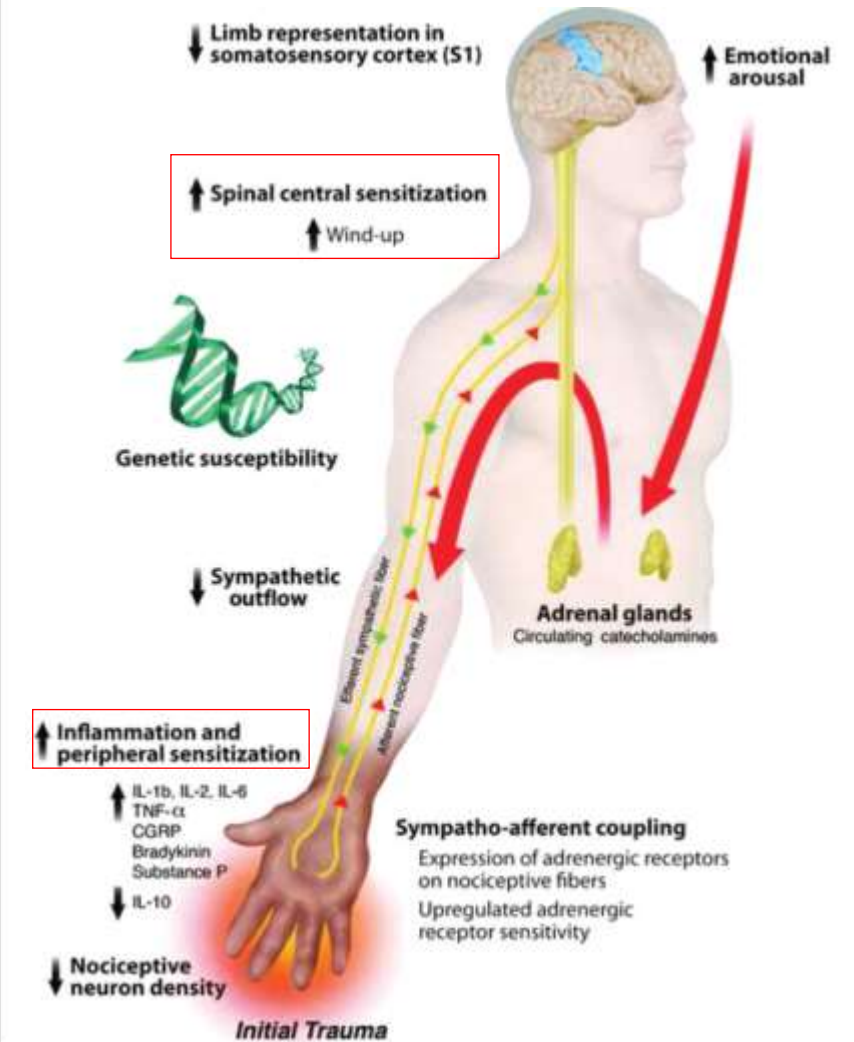
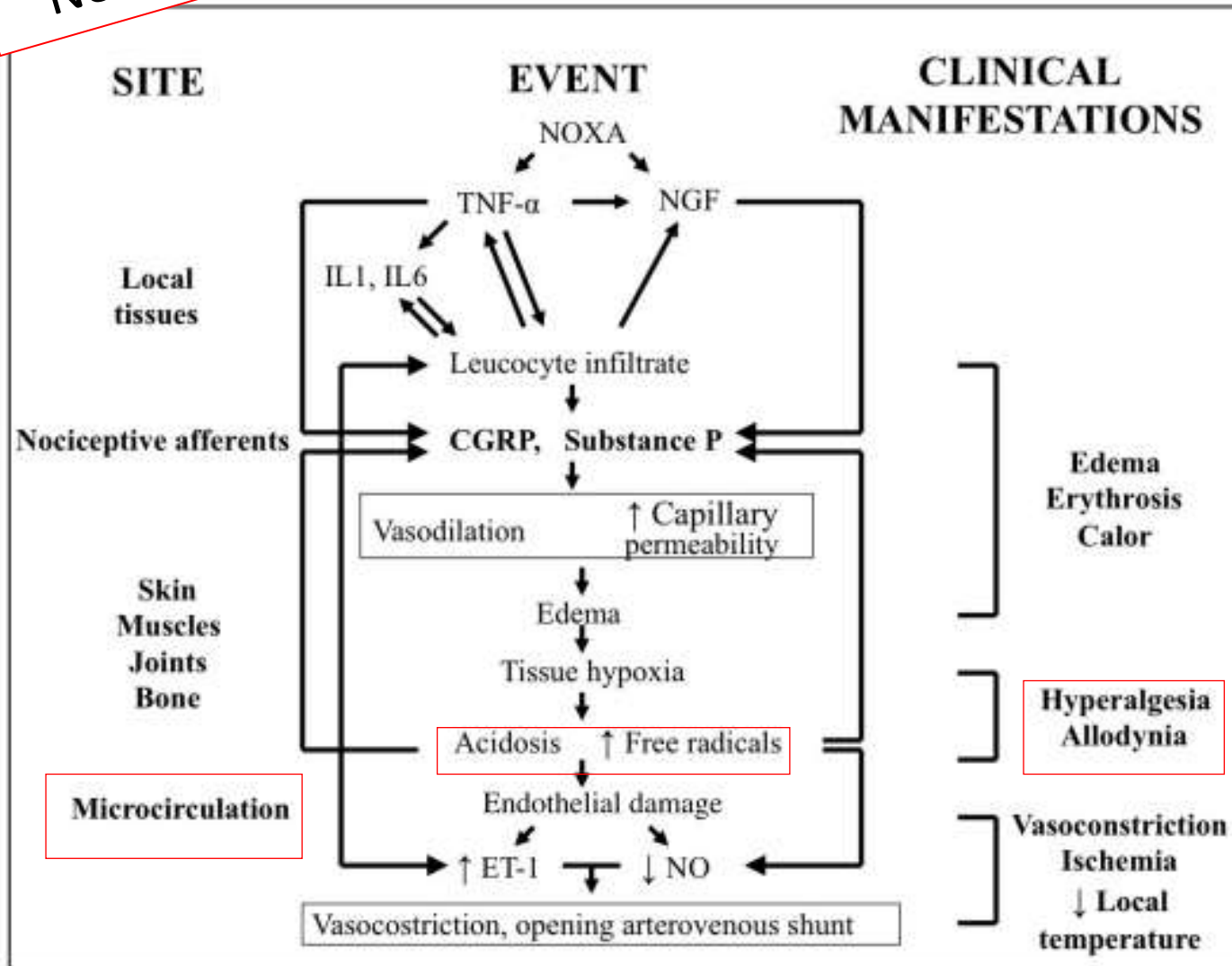
- ✓ *Terminologia e classificazione*
- ✓ *Patogenesi*
- ✓ *Epidemiologia*
- ✓ *Manifestazioni cliniche – diagnosi*
- ✓ *Trattamento*

Neuroflogosi

CRPS I – patogenesi

Fase
calda

Fase
fredda



Varenna et al. Clin Cases Miner Bone Metab. 2015

Bruehl Anesthesiology 2010

CRPS I – patogenesi

RUOLO CENTRALE DELL'OSSO

- Fratture e distorsioni (microfratture?) → eventi scatenanti in 2/3 dei casi
- CRPS I più frequente nelle donne in post-menopausa (osteoporosi)
- CRPS I più frequente in patologie/farmaci associate a fragilità scheletrica

(AR, OI, uso cronico di barbiturici)

- Modelli animali
 - Coinvolgimento osseo all'imaging
- Iperespressione markers turn-over osseo

- ✓ Terminologia e classificazione
- ✓ Patogenesi
- ✓ Epidemiologia
- ✓ Manifestazioni cliniche – diagnosi
- ✓ Trattamento

CRPS I - epidemiologia

- F:M= 4:1
- fascia d'età più interessata: 40-60 anni
- Incidenza: 26,2/100.000/anno (coorte Olandese)
5,5 casi/100.000/anno (coorte Nord-Americana)
- Evento scatenante
 - *trauma* (40-65% casi)
 - fratture – 45%
 - distorsioni – 18%
 - interventi chirurgici – 12%
 - *mancaza eventi scatenanti* (10-26%)
- Fattori favorenti:
 - Menopausa
 - Fumo
 - S. ansioso-depressiva (?)



CRPS I - epidemiologia

➤ Evento scatenante

- Trauma
- Immobilizzazione
- Emiplegia
- Interventi chirurgici del midollo spinale
- Affezioni pleuropolmonari
- Affezioni cardiache (infarto)
- Ipertiroidismo
- Neoplasie
- Farmaci (antitubercolari, anticonvulsivanti)
- Elettrocuzione
- Manovre intra-articolari (artrocentesi, artroscopia, infiltrazioni)



➤ Sede:

- arto superiore (60%)
- arto inferiore (40%)

Varennna et al. GIOT 2011
Gatti et al. Osteoporos Int 2016

- ✓ Terminologia e classificazione
- ✓ Patogenesi
- ✓ Epidemiologia
- ✓ Manifestazioni cliniche – diagnosi
- ✓ Trattamento

CRPS I - clinica

Forme complete/incomplete

➤ DOLORE

➤ dolore cronico invalidante, sproporzionato rispetto ad eventuali traumi o lesioni associate

➤ Allodinia, iperalgesia

➤ Alterazioni della sensibilità tattile e termica

➤ coinvolgimento degli arti



Giannotti et al. Clin Cases Miner Bone Metab. 2018

Varenna et al. GIOT. 2011

CRPS I - clinica

Fase
calda

➤ FASE ACUTA o INFIAMMATORIA

dolore cronico invalidante, edema, eritema, variazioni temperatura arto



➤ FASE DISTROFICA

regressione progressiva dell'edema, cute lucida e tesa, iniziale rigidità articolare, iniziale contrattura ed ipotrofia muscolare



➤ FASE ATROFICA

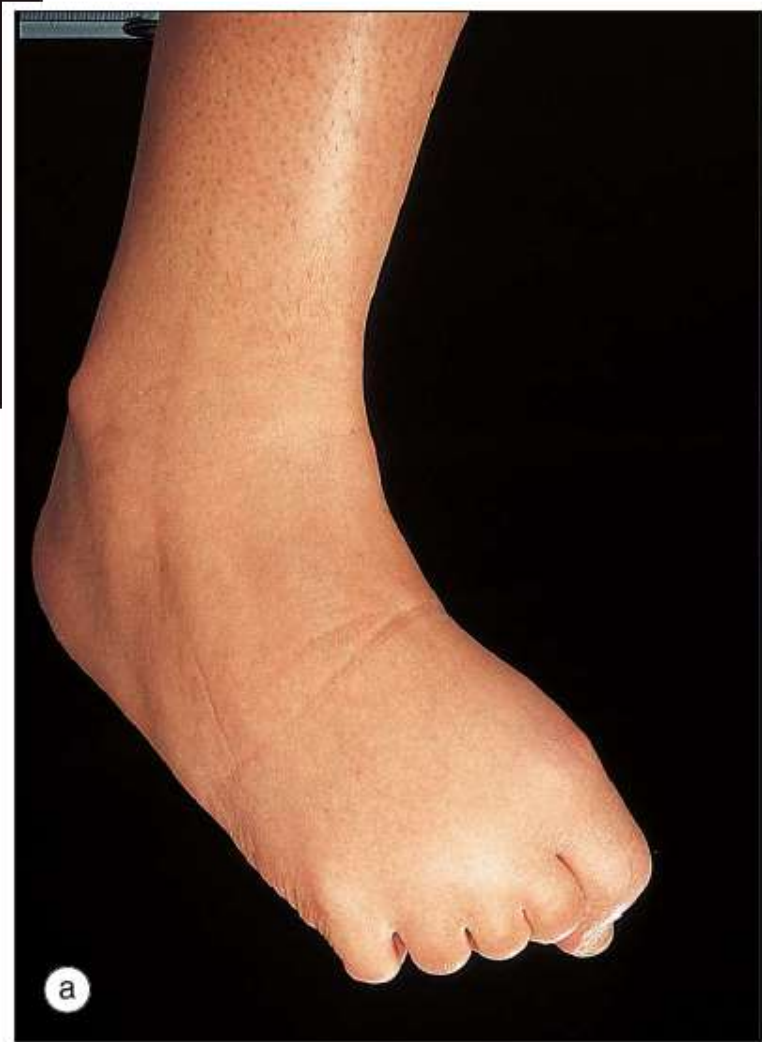
rigidità articolare, pallore cutaneo, perdita annessi piliferi, retrazione tendini ed aponeurosi, atrofia muscolare



Fase
fredda

Varenna et al. GIOT. 2011

Bussa et al. Acta Anaesthesiol. Scand. 2015



CRPS – diagnosi

Presence after an initial inciting event.

Allodynia or hyperalgesia out of proportion for the inciting event.

Evidence of skin changes, sudomotor dysfunction, or oedema.

The absence of any other syndrome that would otherwise explain the presenting syndromes.

Continued pain that is disproportionate to any inciting event

Patient must report one symptom in three of the following four categories:

Sensory: allodynia or hyperalgesia

Vasomotor: temperature asymmetry, skin colour changes

Sudomotor: oedema, changes in sweating

Motor/trophic: decreased range of motion, motor dysfunction, changes in hair and nail growth

Must display one sign at the time of evaluation in at least two of the following categories:

Sensory: evidence of hyperalgesia and allodynia

Vasomotor: evidence of temperature asymmetry or skin colour changes

Sudomotor: evidence of oedema or swelling

Motor: motor weakness/dysfunction

There is no other diagnosis that explains the patient's signs or symptoms

CRPS 1 - Without evidence of major nerve damage

CRPS 2 - With evidence of major nerve damage

CRPS I – diagnosi differenziale

➤ FASE CALDA

TVP, tromboflebiti superficiali
artropatie infiammatorie

(a. da microcristalli, infettiva, spondiloartrite periferica)

tendinopatie, borsiti

acrocianosi, f. di Raynaud

microfratture

erisipela, linfangite

➤ FASE FREDDA

neuropatie

(nevralgia post-herpetica, polineuropatia periferica, radicolopatie meccaniche)

m. di Dupuytren,

sclerosi sistemica



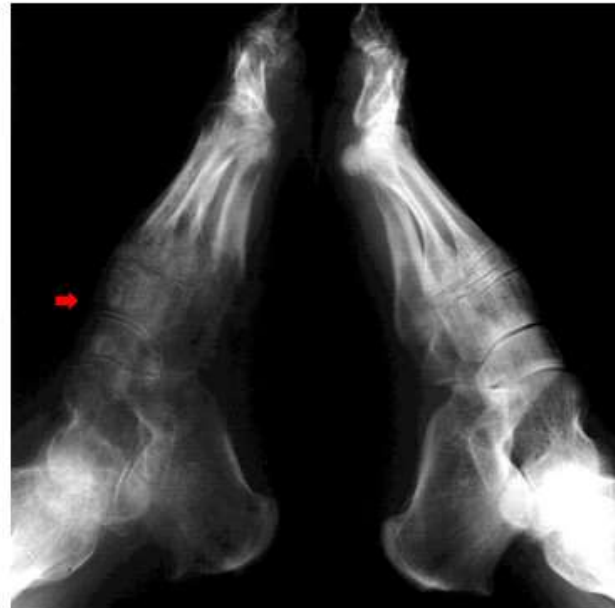
Varennna et al. GIOT 2011

Solarino et al. GIOT 2015

CRPS I – imaging

RX convenzionale

- Le alterazioni compaiono **dopo circa 2-4 settimane**
- **Demineralizzazione ossea** rispetto all'arto controlaterale
- Quadro più tipico: **OSTEOPOROSI MACULATA**
- Più tardivamente → osteoporosi omogenea



CRPS I - imaging

RX convenzionale



CRPS I – imaging

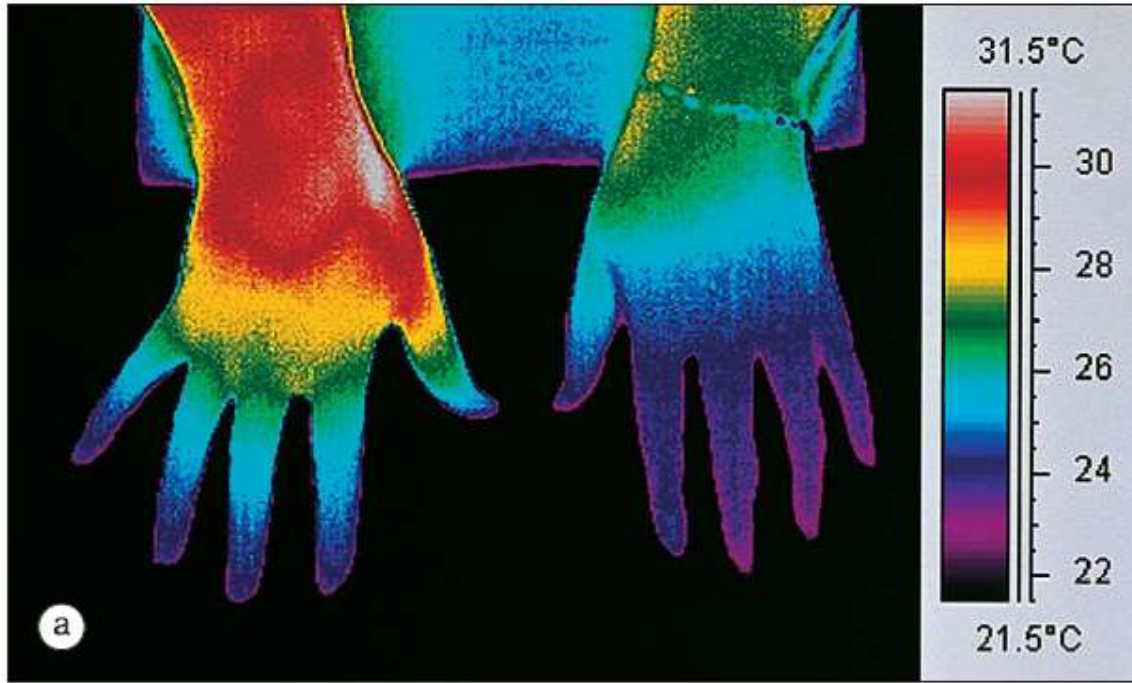
Scintigrafia trifasica



Varennna et al. GIOT 2011
Galve Villa et al. Man Ther 2016

CRPS I - imaging

Termografia



CRPS I - imaging

RMN

- Utile in fase precoce di malattia
- Mostra edema osseo ± edema tessuti molli e versamento articolare

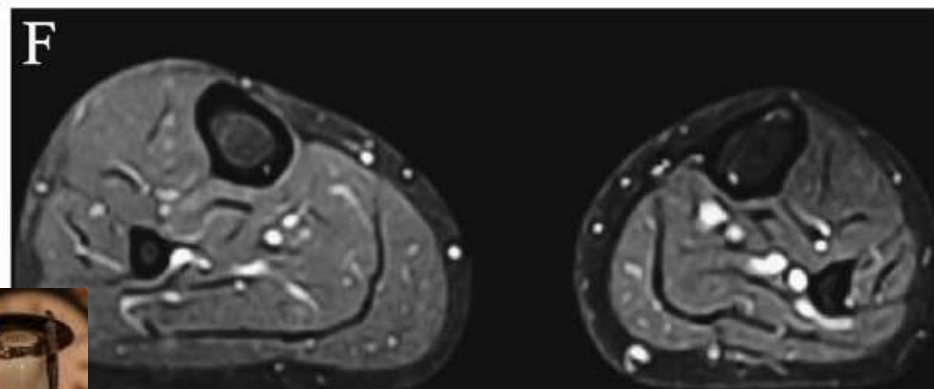
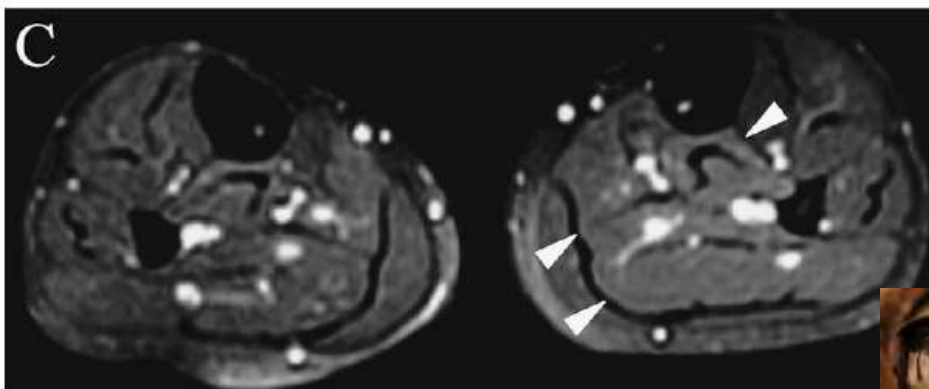
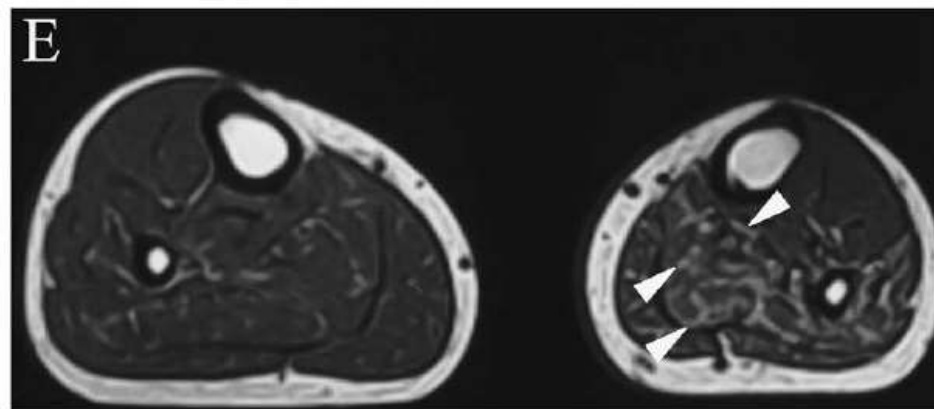
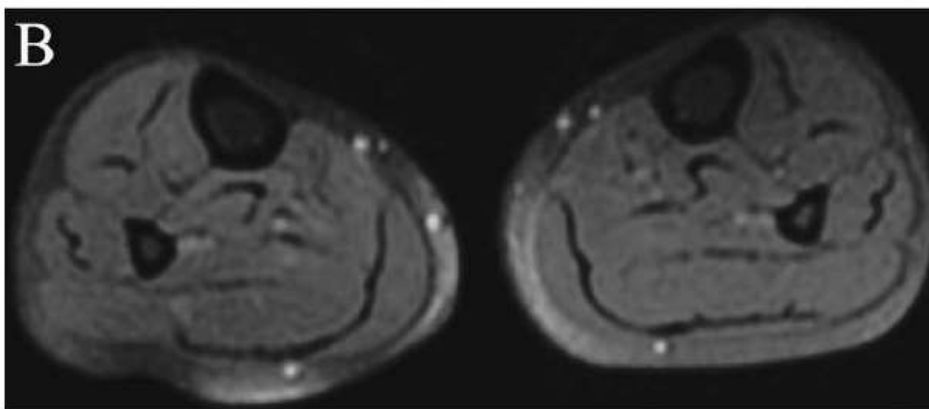
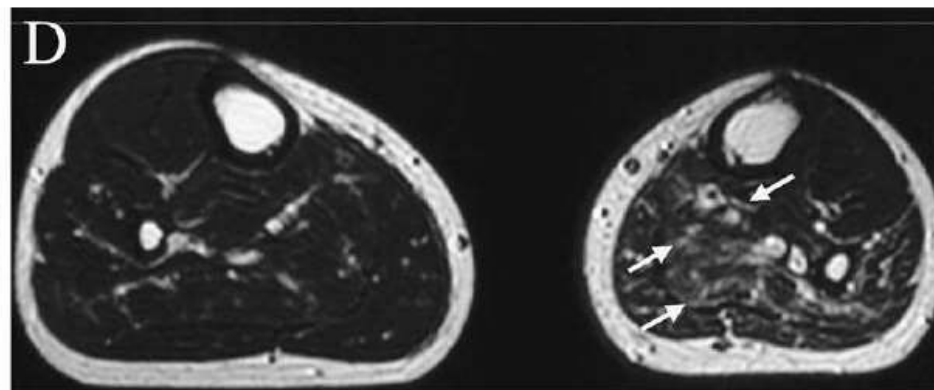
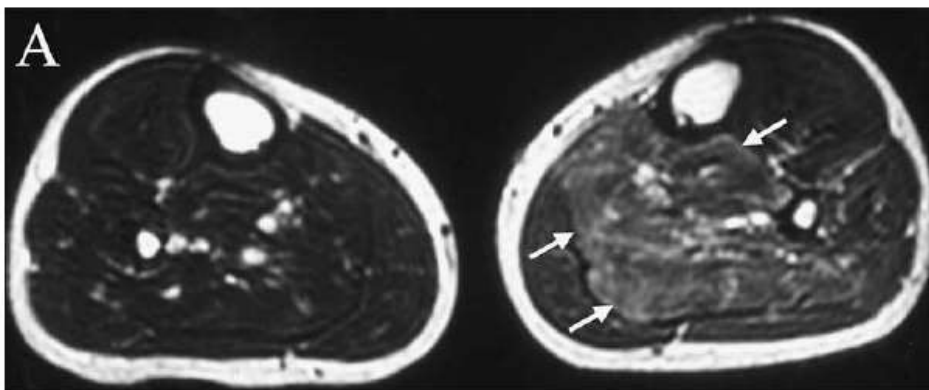
EDEMA OSSEO

- Non è specifico per CRPS I (OA, artrite, fratture, necrosi avascolare, osteoporosi regionale migrante, osteoporosi transitoria dell'anca)
- Iperintensità in T2 e sequenze STIR
segnale irregolarmente diminuito in T1

CRPS I - RMN



T2



Fat-suppressed T1

Fat-suppressed
after
administration of
gadolinium
dimeglumine

2 months



22 months



Contents lists available at [ScienceDirect](#)

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad



MRI of complex regional pain syndrome in the foot

Christoph A. Agten^{a,d,*}, Adrian Kobe^{b,d}, Isabelle Barnaure^{a,d}, Julien Galley^{a,d},
Christian W. Pfirrmann^{a,d}, Florian Brunner^{c,d}



Conclusions:

MRI cannot distinguish between CRPS and non-CRPS patients. The role of MR imaging in patients with suspected CRPS is to exclude alternative diagnoses that would better explain patients' symptoms.

BONE MARROW EDEMA

Etiology	Etiologies of Bone Marrow Edema
Trauma	Fracture (acute, osteoporotic, and stress)
	Local transient osteoporosis
	Bone bruise
	Osteochondral injuries (osteochondritis dissecans)
Degenerative lesions	Altered stress/biomechanics (plantar fasciitis, tendinitis/enthesis)
Inflammatory lesions	Osteoarthritis
	Inflammatory arthropathies and enthesitis (RA, ankylosing spondylitis, psoriasis)
Vascular lesions	Systemic chronic inflammation
	Osteonecrosis, CRPS-1
	CRPS-1
Infectious lesions	Sickle cell anemia
	Osteomyelitis, diabetic foot
	Charcot foot
Metabolic/endocrine lesions	Sepsis (bone infarcts)
	Hydroxyapatite deposition disease
Iatrogenic lesions	Gout
	Local surgery
Neoplastic lesions	Radiation therapy
	Neoplastic bone or soft-tissue lesions or neoplastic-like lesions

CRPS = chronic regional pain syndrome, RA = rheumatoid arthritis. See Starr et al⁸ and Eriksen et al.¹

- ✓ *Terminologia e classificazione*
- ✓ *Patogenesi*
- ✓ *Epidemiologia*
- ✓ *Manifestazioni cliniche – diagnosi*
- ✓ *Trattamento*

Approaches to the treatment of complex regional pain syndrome

Prevention

Early mobilization
Vitamin C

Physiotherapy

Desensitization techniques
Mirror therapy
Graded motor imagery
Transcutaneous electrical nerve stimulation
Acupuncture

Drug treatment

Possibly effective (although no large-scale studies)
Bisphosphonates
Free radical scavengers (dimethyl sulfoxide [topical] and *N*-acetylcysteine)
Ketamine (intravenous)
Insufficient evidence for effectiveness
Analgesics (including paracetamol, nonsteroidal antiinflammatory drugs, and opioids)
Anticonvulsants
Antidepressants
Baclofen (oral and intrathecal)
Botulinum toxin (intramuscular)
Calcitonin
Calcium channel blockers
Capsaicin
Corticosteroids
Lidocaine 5% plasters

Spinal cord stimulation

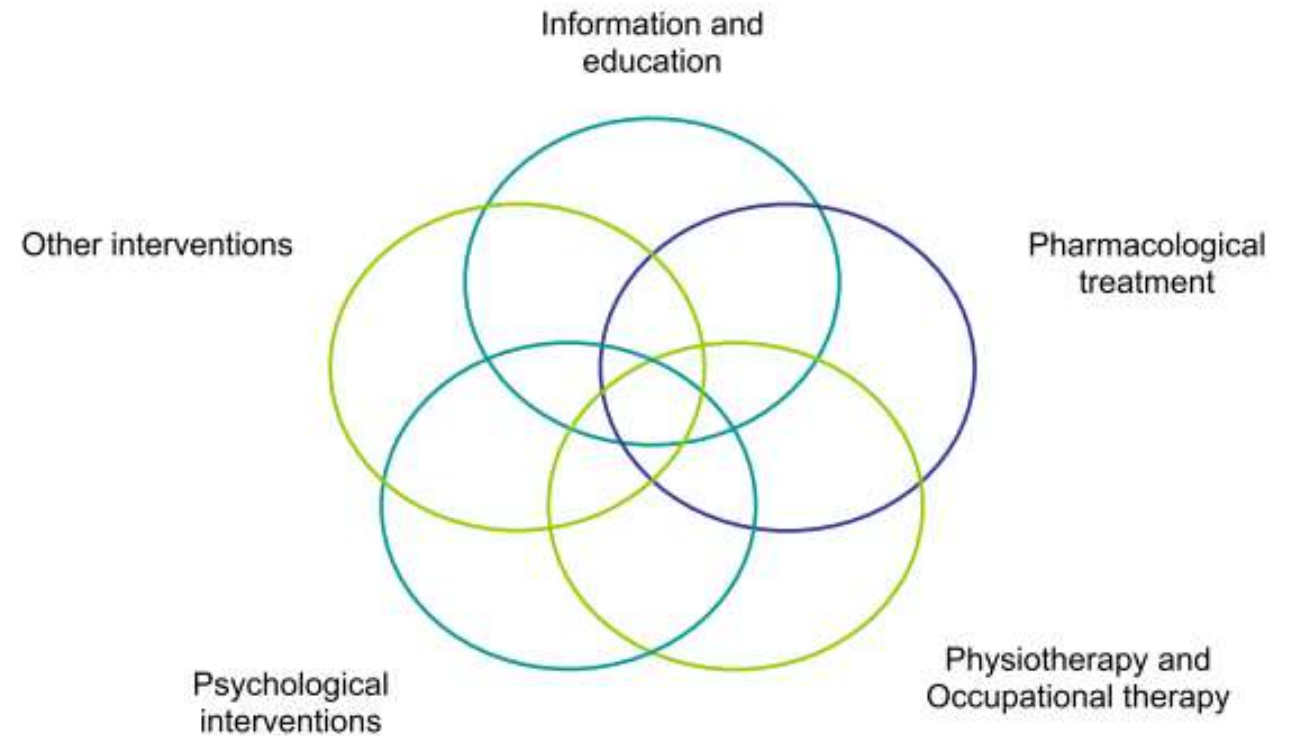
Surgery (very rarely indicated)

Surgical sympathectomy
Amputation

CRPS I – terapia



**Mancanza di
raccomandazioni
standardizzate**



Approccio multidisciplinare

Galve Villa M et al. Man Ther 2016



CRPS I – terapia



CRPS I

FASE ACUTA → prevalenza dei meccanismi infiammatori e vasomotori

Target terapeutici

Infiammatori

Vasomotori

- Reumatologo
- Ortopedico
- Fisiatra
- Endocrinologo

FASE CRONICA → prevalenza dei cambiamenti maladattativi tipici del dolore cronico

Target terapeutici

Corticali

Spinali

- Neurologo
- Algologo/anestesista

CRPS I – terapia

Trattamento precoce → buona prognosi



Determinants of Diagnostic Delay in Complex Regional Pain Syndrome Type 1

An Observational Study of 180 Consecutive New Cases

Massimo Varenna, MD, PhD,* Chiara Crotti, MD,* Nicola Ughi, MD,*
Francesca Zucchi, MD,* and Roberto Caporali, MD*†

TABLE 2. Variables Influencing Diagnostic Delay (Time From Symptoms Onset and Diagnosis) in 180 Patients with CRPS-I (Cox Proportional Model)

	HR	CI (95%)	p value
Disease localization			
Hand	Reference	—	—
Foot	2.11	(1.36–3.28)	0.001
Predisposing event			
Fracture	Reference	—	—
Trauma	2.22	(1.35–3.57)	0.002
Surgery	2.08	(1.21–3.57)	0.007
Others	3.22	(1.53–7.14)	0.002
Unknown	2.08	(1.13–3.84)	0.018
Diagnostic Criteria			
Clinical	Reference	—	—
Research	0.57	(0.40–0.83)	0.003
Age (yrs)	1.00	(0.98–1.02)	0.943
Sex			
Male	Reference	—	—
Female	0.83	(0.58–1.23)	0.363
Region of origin			
Lombardy	Reference	—	—
Out of Lombardy	1.26	(0.86–1.81)	0.228

TABLE 2. Variables Influencing Diagnostic Delay (Time From Symptoms Onset and Diagnosis) in 180 Patients with CRPS-I (Cox Proportional Model)

	HR	CI (95%)	p value
Concurrent drugs			
None	Reference	—	—
≥1 drug(s)	1.40	(0.87–2.27)	0.159
Known diseases in past medical history			
None	Reference	—	—
≥1 RDCI	1.21	(0.75–2.00)	0.415
Previous visits			
1	Reference	—	—
N visits	1.16	(1.09–1.23)	<0.001
Referral			
GP	Reference	—	—
Consultant	0.54	(0.37–0.81)	0.002
Past drug therapy			
No	Reference	—	—
Yes	1.35	(0.92–1.96)	0.120
Past physical therapy			
No	Reference	—	—
Yes	2.38	(1.56–3.57)	<0.001
Pain intensity, VAS score (0–100 mm)	1.00	(0.99–1.01)	0.982
McGill total score (0–45)	1.00	(0.98–1.02)	0.964

CRPS I – terapia

BIFOSFONATI

- **Neridronato** – in scheda tecnica dal 2014
100 mg ev ogni 3 giorni x 4 volte
Dati preliminari studio NAIMES/32 → Neridronato im
1fl da 25 mg im/die x 16 giorni
Efficacia comparabile a neridronato ev

Varennà et al. Rheumatology 2013

- **Clodronato** – utilizzo off-label
300 mg ev/die x 10 giorni
oppure
200 mg im/die x 10 giorni,
poi 200 mg im ogni due giorni x 20 giorni

Varennà et al. J Rheumatol 2000

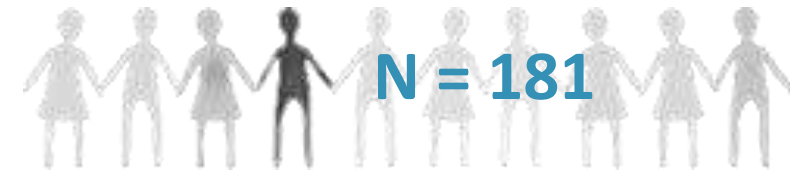
Frediani B & Bertoldi I Clin Cases Miner Bone Metab 2015

CRPS I – terapia

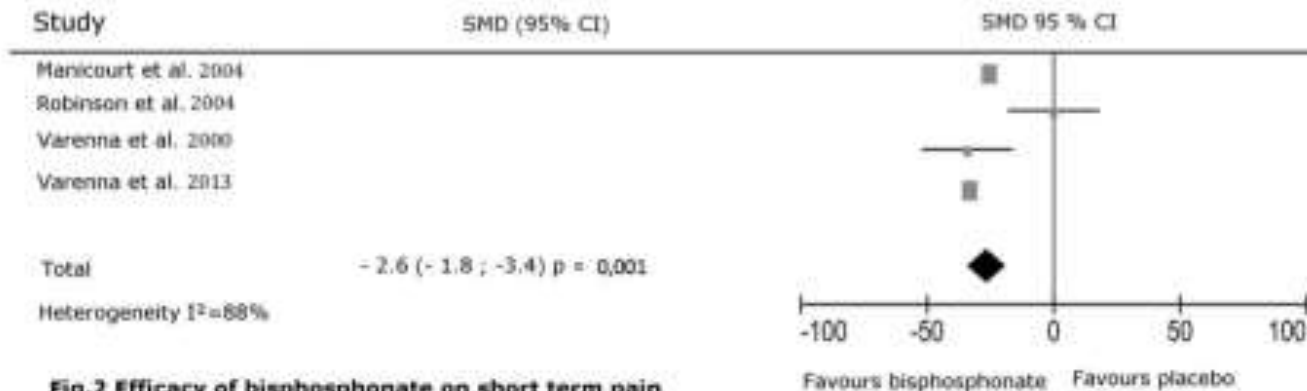
Study	Dose	Biphosphonates	Patient (n)	Years	Male n (%)	Disease Duration (month)	Localisation Upper limb/Lower limb	Etiology			
								Fracture	Trauma	Post surgery	Other
Manicourt D-H. et al. 2004	5/5	Alendronate 40 mg PO daily 8 weeks	20	44.6 (+/-12.3)*	11 (55)	7 (+/-2)	0/40	3	13	4	0
			20	45.2 (+/-12.5)*	8 (40)	8 (+/-3)		4	13	3	0
Robinson J. et al. 2004	3/5	Pamidronate 60 mg IV one time	14	45.0 (30-60)**	9	21.6	13/14	NR	NR	NR	NR
			13								
Varennna M. et al. 2000	5/5	Clodronate 300 mg IV daily for 10 days	15	58.1 (+/-7.8)*	6 (40)	3.7	2/13	4	3	1	7
			17	53.4 (+/-9.1)*	7 (41)	4.3	2/15	4	6	1	6
Varennna M. et al. 2013	5/5	Neridronate 100 mg IV four times in 10 days at J1 J4 J7 J10	41	58.2 (+/-12.7)*	16 (39)	4.7	8/33	11	10	5	15
			41	57.0 (+/-10.3)*	13 (32)	5	12/29	17	7	4	13
Adami S. et al. 1997***	4/5	Alendronate 7.5 mg IV daily for three days	10	39 - 79	3 (30)	4	12/8	6	1	NR	3
			10	48 - 80	5 (50)	4.5		7	2		1

Title: Bisphosphonates for treatment of Complex Regional Pain Syndrome type 1: a systematic literature review and meta-analysis of randomized controlled trials versus placebo

Author: Maxime Chevreau Xavier Romand Philippe Gaudin Robert Juvin Athan Baillet



CRPS I – terapia



Title: Bisphosphonates for treatment of Complex Regional Pain Syndrome type 1: a systematic literature review and meta-analysis of randomized controlled trials versus placebo

Author: Maxime Chevreau Xavier Romand Philippe Gaudin Robert Juvin Athan Baillet

Fig.2 Efficacy of bisphosphonate on short term pain

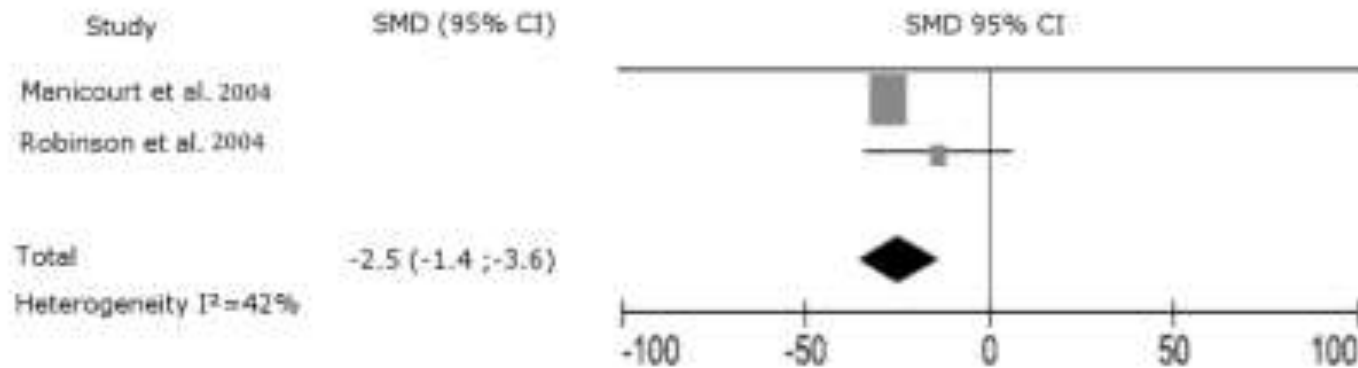


Fig.3 Efficacy of bisphosphonate on medium term pain

Funzionalità → trend verso il miglioramento; risultati non comparabili per differenze tra gli studi

Safety → No SAEs. AE lievi > gruppo di trattamento

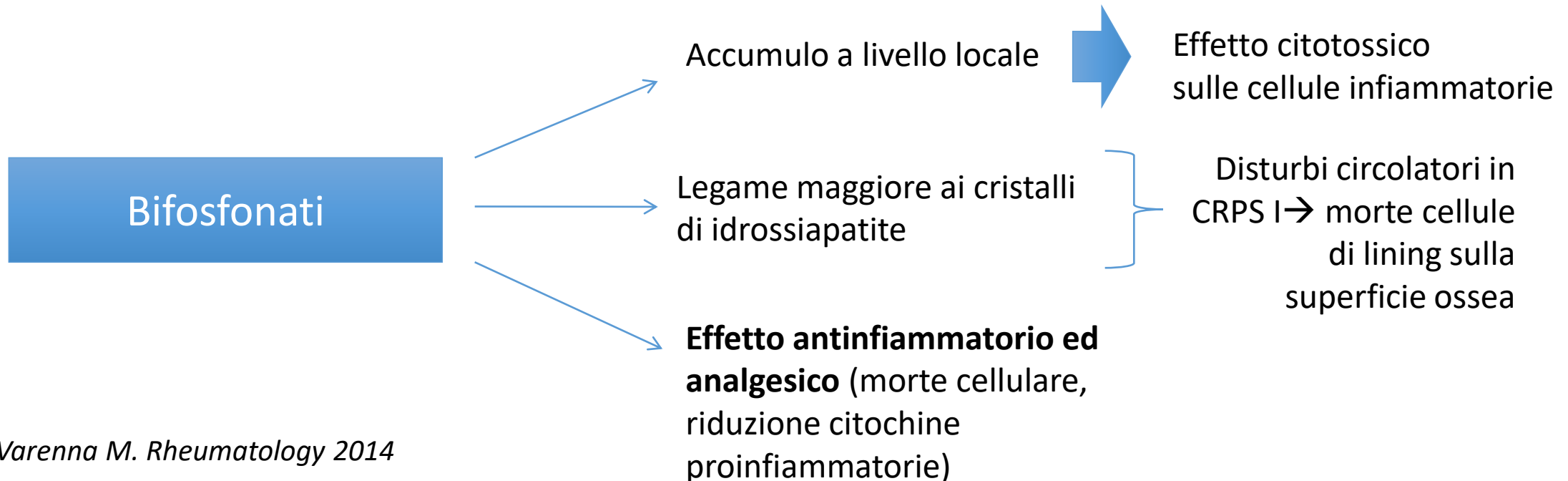
CRPS I – bifosfonati

Edema osseo nelle fasi precoci della CRPS I = **difetto di mineralizzazione ossea**

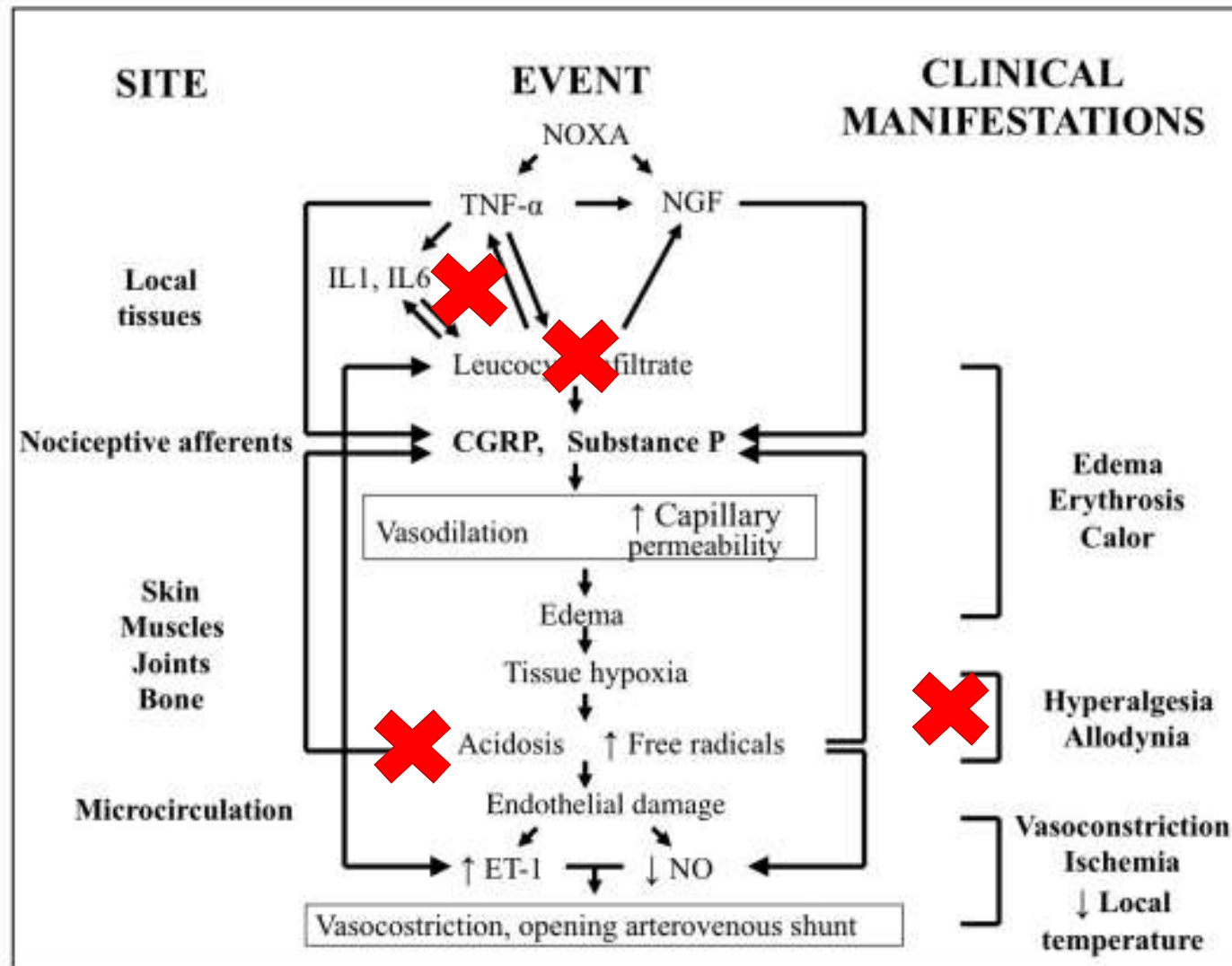
Probabilmente non dovuto ad aumento dell'attività osteoclastica

MA

Dovuto a **dissoluzione chimica idrossiapatite**, mediata dall'ipossia tissutale → metabolismo anaerobio → riduzione del pH



CRPS I – bifosfonati

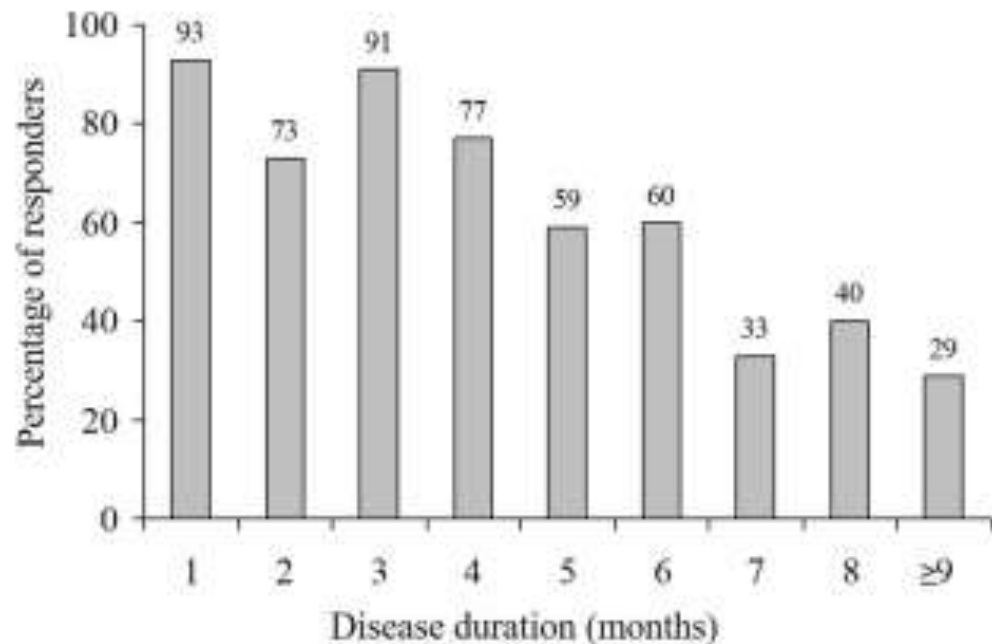


Varennna et al. Clin Cases Miner Bone Metab. 2015

Varennna M. Rheumatology 2014

CRPS I – bifosfonati

Fattori predittivi di risposta al bifosfonato



N= 194 pz CRPS I

Table 3 Logistic regression analyses of recorded variables for treatment responsiveness to bisphosphonate in patients with CRPS-I

	OR	95% CI	P
Model 1			
Age, 1-y increment	0.99	0.96–1.03	0.6
Sex, female vs male	1.27	0.58–2.79	0.5
Disease duration, 1-mo increment	0.83	0.72–0.96	0.01
Disease localization, lower vs upper limb	1.22	0.52–2.86	0.6
Subtype, warm vs cold	4.88	1.57–15.20	0.006
Fracture vs other predisposing event	3.23	1.29–8.03	0.01

CRPS I – Therapie non farmacologiche

Rehabilitation and other conservative modalities

- Physical and occupational therapy incorporating mobilization
- Mirror therapy
- Desensitization
- Contrast bath
- Acupuncture
-

Psychotherapy

- Sixteen percent of patients with a diagnosis of CRPS were found to have comorbid depression in a recent study, and two-thirds of the patients were found to have at least one psychiatric diagnosis, both significantly higher than in the general population (Brinkers et al., 2018).
- While major depressive disorder has been identified as a risk factor in the transition from acute pain to chronic pain, the studies suggest that depression and anxiety follow the onset of CRPS and are not predispositional factors (Lohnberg & Altmaier, 2013).
- Anxiety, depression, stress, catastrophizing, and pain-related fear have been all associated with poorer outcomes in CRPS (Bean et al., 2015).
- On the other hand, post-traumatic stress disorder (PTSD) may predispose patients to the development of CRPS (Speck et al., 2017).
- Comorbid psychiatric conditions may certainly serve as a major barrier to treatment of CRPS.

CRPS I – Therapie non farmacologiche

Rehabilitation and other conservative modalities

- Physical and occupational therapy incorporating mobilization
- Mirror therapy
- Desensitization
- Contrast bath
- Acupuncture

Psychotherapy

It is important to take a holistic approach and evaluate the patient's mood, stress, and sleep and help the patient understand the closely intertwined relationships between these factors and their pain.

- Psychological treatment for chronic pain
- Operant-behavior therapy
- Cognitive behavior therapy
- Mindfulness
- Biofeedback

CRPS I – Therapie non farmacologiche

Procedures

- *Sympathetic nerve blocks*
- *Surgical and chemical sympathectomy*
- *Amputation*

Neuromodulation

- *Spinal cord stimulation*
- *Dorsal root ganglion stimulation*
- *Peripheral nerve stimulation*
- *Transcutaneous electrical nerve stimulation*
- *Non-Invasive brain stimulation*

TAKE HOME MESSAGES



- Considerare l'ipotesi diagnostica (trauma, ma
- Importante la diagnosi differenziale → APPROCCIO MULTIDISCIPLINARE
- Diagnosi precoce → trattamento precoce → miglior prognosi
- I bifosfonati, in associazione alla FKT, rappresentano la migliore strategia di trattamento

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

8a edizione

REUMATOLOGIA E RIABILITAZIONE



Torino, 15 e 16 ottobre 2021

Responsabili scientifici
Enrico Fusaro
Giuseppe Massazza

SAVE THE DATE