RIUNIONE MACROAREA SINC
LA TOSSINA BOTULINICA NEL TRATTAMENTO DELLA SPASTICITA'

MARCELLO ROMANO
AOOR VILLA SOFIA CERVELLO PALERMO

SPASTICITA’

- Disturbo del controllo sensori-motorio, esito di una lesione del motoneurone superiore, che si presenta come una intermittente o continua attivazione muscolare involontaria

Burridge, Wood et al 2005

- L’iperattività muscolare è uno dei tre aspetti più importanti e disabilitanti,… si associa alla debolezza e all’accorciamento muscolare….

J.M. Gracies, 2009

LESIONE CORTICOSPINALE

- Debolezza
- Perdita di destrezza
- Difficoltà del controllo volontario della movimento (cocontrazione, sincinesie)
- Posture anomale
- Aumento del tono muscolare

- La tossina botulinica di tipo A (BoNT-A) è usata per il trattamento della spasticità da almeno 30 anni ed è un riconosciuto metodo di cura per la spasticità focale e multifocale
- E’ noto che il trattamento con BoNT-A è sicuro ed efficace per attenuare la spasticità sia agli arti superiori che inferiori
- BoNT-A è un presidio farmacologico di prima linea nella terapia della spasticità

AAN Guidelines, Neurology 2016; J Rehab Med 2021

- L’attenta selezione dei pz, la definizione di un chiaro, realistico, raggiungibile e misurabile obiettivo sono cruciali per l’uso con successo della BoNT-A nella cura della spasticità, nel contesto del processso riabilitativo.

- Gli obiettivi del trattamento devono essere discussi tra il pz., i familiari ed il gruppo multidisciplinare (medico iniettore, neurologo, riabilitatore, fisioterapista, infermiere, etc.)

NHS Guidelines, Royal College of Physicians, 2018

Spasticity is a motor and sensory disorder characterised by an *intermittent or sustained increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex*. It is common after stroke, with the prevalence of motor impairments estimated at up to 80% in stroke survivors. Spasticity is estimated to occur in almost 25% of patients within 2 weeks post-stroke. However, after 12 months, the overall prevalence of spasticity increases to 38% in patients surviving a first stroke and 44% for those with recurrent stroke admissions. Severe or disabling spasticity has been reported in approximately 15% of post-stroke patients.

Early Identification, Intervention and Management of Post-stroke Spasticity: Expert Consensus Recommendations
Bavikatte et al., J Central Nerv Syst Dis, 13:1-8, 2021

Dimensioni del problema

Ogni anno in Italia, delle 200.000 persone colpite da ictus cerebrale, circa 80.000 sviluppano una spasticità entro 6 mesi, che può essere di entità grave nel 16% dei casi (12.800 persone l'anno).

RACCOMANDAZIONE CIVICA PER LA GESTIONE DEI PAZIENTI COLPITI DA SPASTICITA' POST ICTUS.

I PERCORSI DI RIABILITAZIONE NEL LAZIO. Rapporto Cittadinanza Attiva

The epidemiology in terms of a 250.000 population, thus equates to:

- 320 new first-time strokes with a prevalence of 1675 people
- 48 people with severe traumatic brain injury with a prevalence of 260 people
- 500 people with multiple sclerosis, of whom 100 are severely disabled
- 31 adults with cerebral palsy
- Plus other conditions affecting the UMN
- About 500 patients require treatment for spasticity at some point in time.

Handbook Clin Neurol 2013

Malattie con spasticità nelle quali può esistere indicazione alla terapia con tossina botulinica

- Ictus
- Paralisi cerebrale infantile
- Lesione encefalica traumatica
- Lesione midollare traumatica
- Sclerosi Multipla
- Malattie Neurodegenerative

Table 1 Baseline patient characteristics

Characteristic	Upper-limb spasticity				Lower-limb spasticity			
	k	t	n/N	Frequency (%)	k	t	n/N	Frequency (%)
Total	44	59*	1,670	–	37	47	1,347	–
Gender	36	47	1,464	100.0	31	40	1,200	100.0
Male	36	47	883/1,464	60.3	31	40	699/1,200	58.3
Female	36	47	581/1,464	39.7	31	39	501/1,200	41.8
Spasticity origin	44	59	1,670	100.0	37	47	1,347	100.0
Stroke only	24	31	1,105/1,670	66.2	16	21	837/1,347	62.1
Stroke/Traumatic brain injury	6	8	107/1,670	6.4	3	3	70/1,347	5.2
Traumatic brain injury only	1	2	21/1,670	1.3	1	1	7/1,347	0.5
Multiple sclerosis	2	3	43/1,670	2.6	5	6	80/1,347	5.9
Spinal cord injury	1	1	28/1,670	1.7	1	2	36/1,347	2.7
Mixed/Other	10	14	366/1,670	21.9	11	14	317/1,347	23.5
	k	**t**	**Mean**	**Range of means**	**k**	**t**	**Mean**	**Range of means**
Age (years)	39	53	51.7	26 – 66.3	35	45	49.9	26 – 66.3
Time since onset (months)	31	43	46.9	4.7 – 120	26	34	53.6	0.35 – 218.4

k = Number of studies, *t* = Number of treatment arms, *n* = Number of patients with this characteristic, *N* = Total number of patients in treatment arms reporting characteristic. *The 44 studies that reported on patients with upper-limb spasticity had a total of 59 onabotulinumtoxinA treatment arms; however, only 58 of these arms consisted of at least 1 patient with upper-limb spasticity, as shown in Table 2.

Table I - OnabotulinumtoxinA average dose per muscle.*

Pectoralis major	Latissimus dorsi	Subscapularis	Teres major	Biceps brachii	Brachioradialis	Brachialis	Pronator teres	Pronator quadratus
75 U	75 U	50 U	35 U	75 U	50 U	70 U	40 U	30 U
Flexor carpi ulnaris	Flexor carpi radialis	Flexor digitorum superficialis	Flexor digitorum profundus	Flexor pollicis longus	Adductor pollicis	Flexor pollicis brevis	Lumbricales	
50 U	50 U	55 U	55 U	35 U	20 U	20 U	35 U	
Adductor longus	Adductor magnus	Gracilis	Iliopsoas	Rectus femoris	Medial hamstrings	Lateral hamstrings	Quadriceps femoris	Gastrocnemius
75 U	90 U	60 U	75 U	75 U	100 U	80 U	100 U	75 U
Soleus	Tibialis posterior	Tibialis anterior	Extensor allucis longus	Flexor hallucis longus	Flexor digitorum longus	Flexor digitorum brevis		
75 U	75 U	60 U	50 U	45 U	55 U	30 U		

* Italian onabotulinumtoxinA labeling for the treatment of post-stroke spasticity recommends a maximum dose of 250U for the upper limb and a maximum dose of 300 U for the lower limb.

Table 2. Statements and consensus level at Round 2. TA Total Agreement; PA Partial agreement; DA Disagreement.

TA	PA	DA	% TA	% PA	% DA
1. After the stroke onset, it is recommended to propose a treatment with botulinum toxin type A (BoNT-A) as soon as the spasticity interferes, and the clinical conditions require it, regardless of the time interval elapsed after the acute event (subacute phase)			83	17	
2. It is necessary to monitor the patients after the acute event to verify the onset of post-stroke spasticity in order to propose a specific treatment for a period of at least one year			64	27	9
3. It is necessary to monitor the patients over time after the acute event to verify the onset of post-stroke spasticity in order to propose a specific treatment, without a time limit but specifically in the first year			91	9	
4. After the onset of stroke, it is indicated to propose a spasticity treatment with BoNT-A in patients who are naïve in the presence of clinical needs, without time limitations			82	9	9
5. For patients being treated with BoNT-A, a follow-up visit should be considered 4–6 weeks after BoNT-A injection			82	9	9
6. For patients being treated with BoNT-A, after 12 months from the acute event a follow-up evaluation and a treatment are to be proposed every 3–6 months			55	36	9
7. For patients being treated with BoNT-A, after the acute event, it is advisable to continue with follow-up and subsequent treatments until it is necessary, without time limits			91		9
8. The objective of treatment with BoNT-A, if the patient is in the sub-acute or chronic phase, may be the same or different depending on the clinical conditions and/or objectives; in the acute phase, there is a greater chance of positively interfering with phenomena of maladaptive plasticity			91		9

Royal College of Physicians

Spasticity in adults: management using botulinum toxin

National guidelines 2018

2nd edition

Table 5: Common patterns of spasticity and treatment benefits

Pattern	Muscle involved	Benefits
Upper limb		
Shoulder adduction, internal rotation and retraction[1]	• Pectoralis major • Latissimus dorsi • Teres muscle group • Subscapularis • Rhomboids and interscapular muscles	• Sitting posture • Ease of dressing • Axillary hygiene • Improve balance and symmetry of gait and can sometimes help to reduce unwanted spasticity in the elbow and hand
Elbow flexion[2]	• Biceps brachii • Brachialis • Brachioradialis	• Improve flexion deformity • Improve reach/retrieve
Pronation of the forearm[3]	• Pronator teres • Pronator quadratus	• Hand function
Flexed wrist and clenched hand[4]	• Flexor carpi ulnaris and radialis • Flexor digitorum superficialis and profundus • Flexor pollicis longus	• Maintain palmar skin hygiene • Improve grasp release

	I	II	III	IV	V
					
Shoulder	Internal rotation/ adduction	Internal rotation/ adduction	Internal rotation/ adduction	Internal rotation/ adduction	Internal rotation/ retroversion
Elbow	Flexion	Flexion	Flexion	Flexion	Extension
Forearm	Supination	Supination	Neutral	Pronation	Pronation
Wrist	Flexion	Extension	Neutral	Flexion	Flexion

Upper limb spasticity patterns. Note: All five upper limb patterns could be combined with any spastic hand and finger position (e.g. claw, spastic flexed, intrinsic lumbrical).

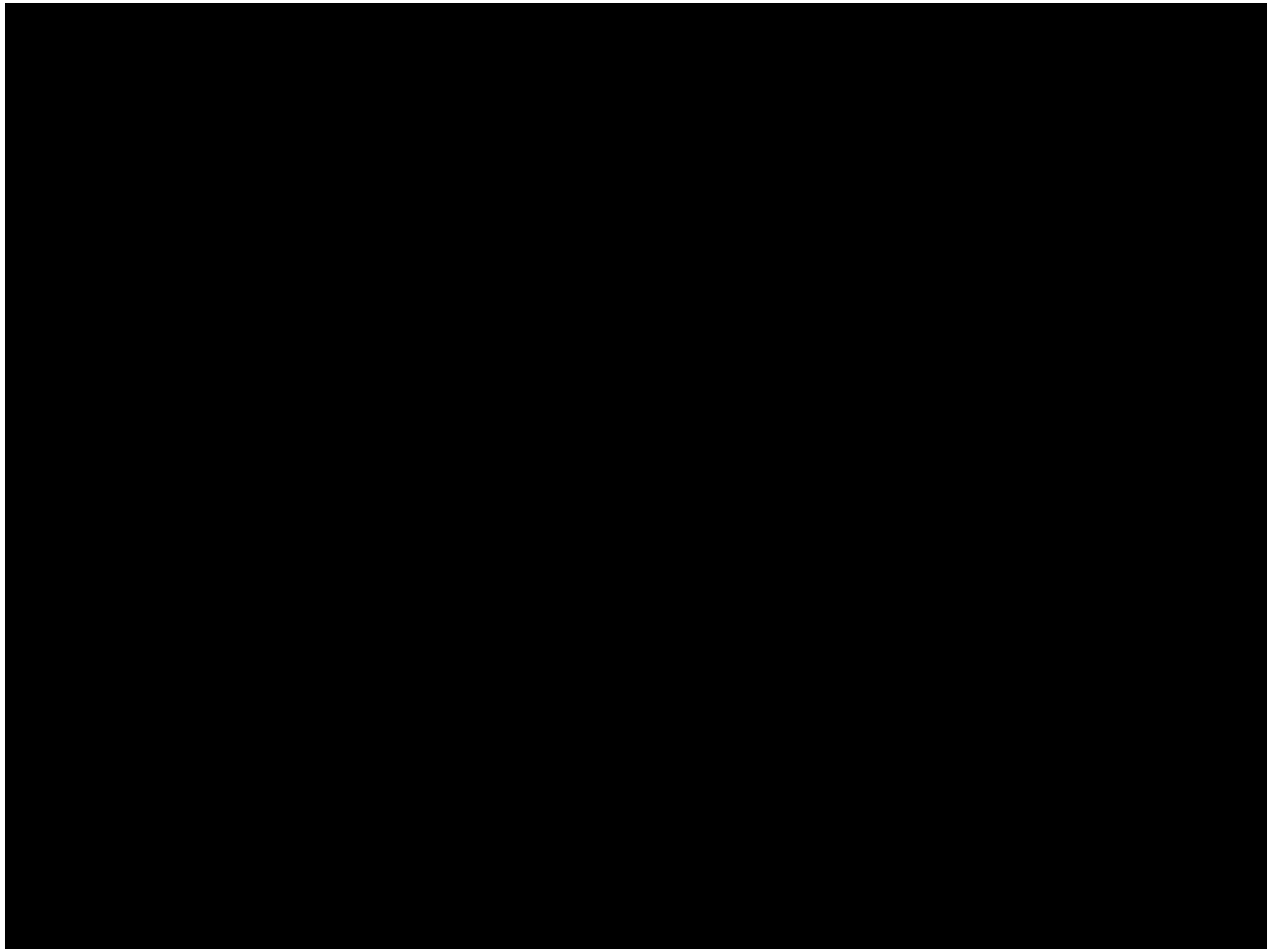
Royal College of Physicians

Spasticity in adults: management using botulinum toxin

National guidelines 2018

2nd edition

Pattern	Muscle involved	Benefits
Lower limb		
Thumb in palm, intrinsic muscles[5]	• Opponens pollicis, adductor pollicis, flexor pollicis brevis, lumbricals, interossei	• Improve grasp and hand opening
Hip adductor[6]	• Adductor magnus, longus and brevis	• Improve 'scissor gait' • Ease of perineal hygiene and urinary catheterisation • Easier sexual intercourse
Hip and knee flexion[7]	• Psoas major, iliacus, medial hamstring group (gracilis, semi-tendinosus, semi-membranosus), biceps femoris	• Improve weight bearing • Improve gait pattern and seating posture
Knee extension[8]	• Quadriceps group	• Seating posture (note potential to worsen sit to stand and standing)
Plantar flexed and inverted foot[9]	• Gastrocnemius, soleus and posterior tibialis	• Correct equinus deformity, and foot inversion to allow heel strike
Toe clawing[10]	• Flexor hallucis longus, flexor digitorum longus	• Ease of donning footwear and comfort
Hyperextension of great toe[11]	• Flexor hallucis longus • Extensor hallucis longus	• Ease of donning footwear and comfort



Identificazione dei muscoli da iniettare:

Spalla addotta, intraruotata

- pettorali
- latissimus dorsi
- teres maior
- subscapularis

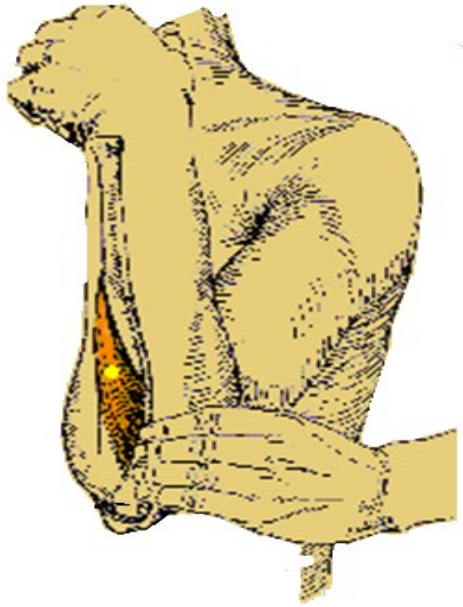
Identificazione dei muscoli da iniettare:

Gomito flesso

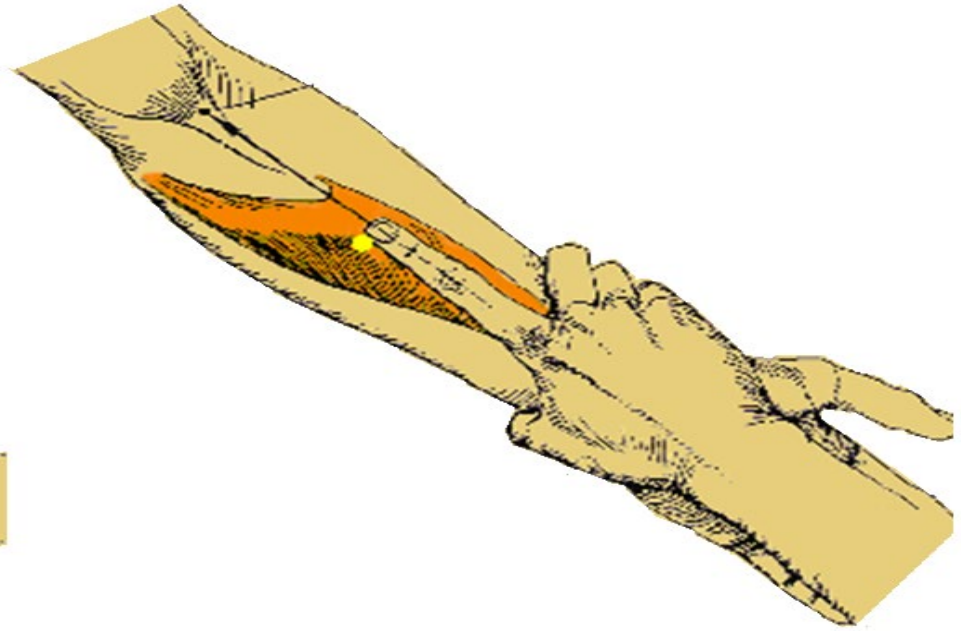
- brachioradialis
- biceps
- brachialis

Identificazione dei muscoli da iniettare:

Mano a pugno



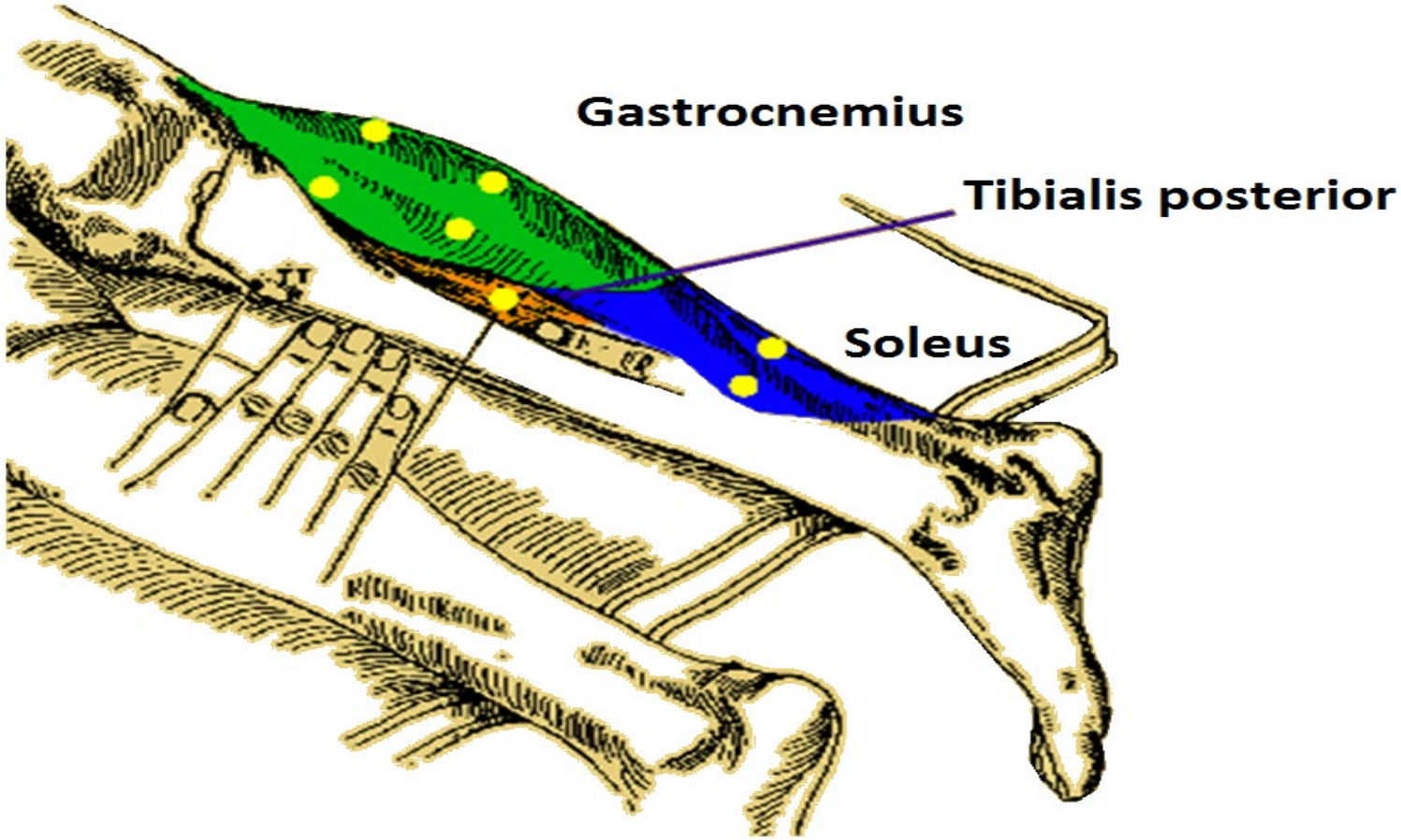
Flexor digitorum profundus



Flexor digitorum sublimis

Identificazione dei muscoli da iniettare:

Equino-varo

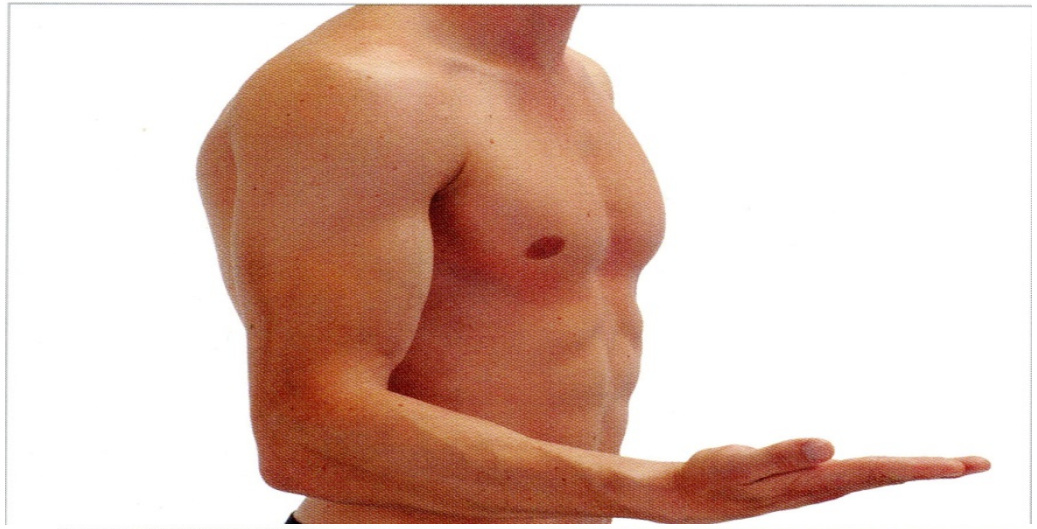


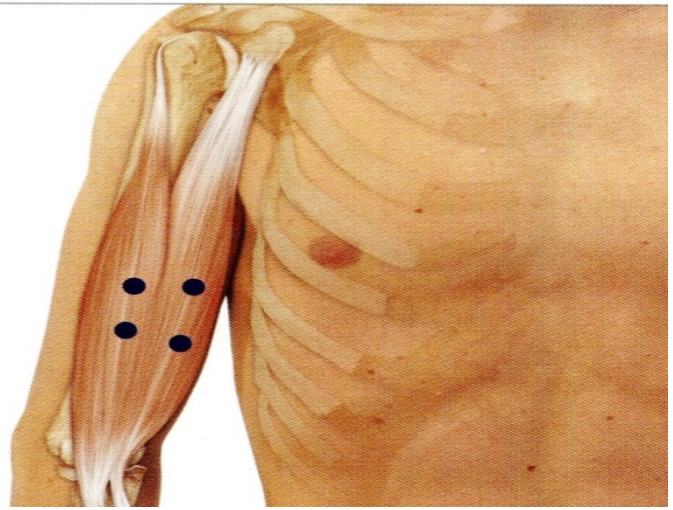
Identificazione dei muscoli da iniettare:

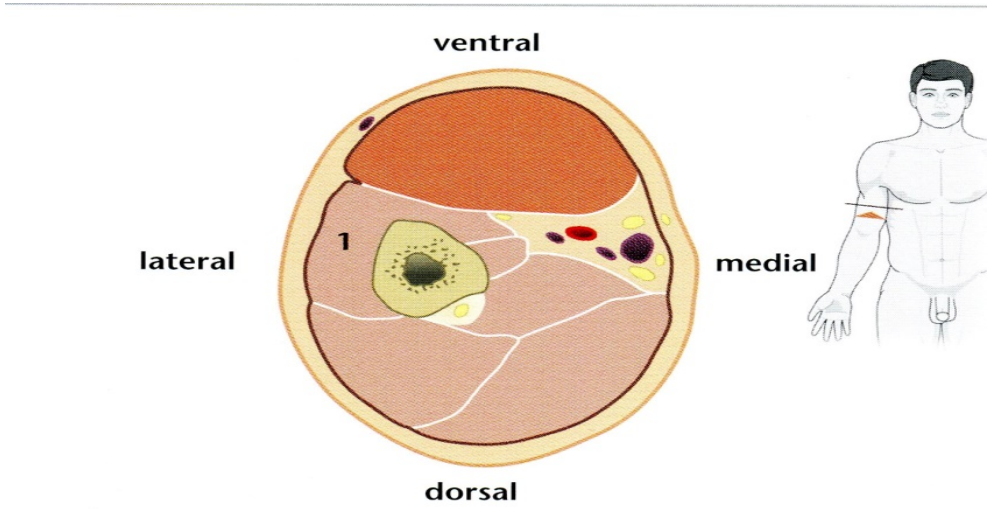
- Iliacus
- Psoas
- Rectus femoris
- Gastrocnemius
- Hamstrings

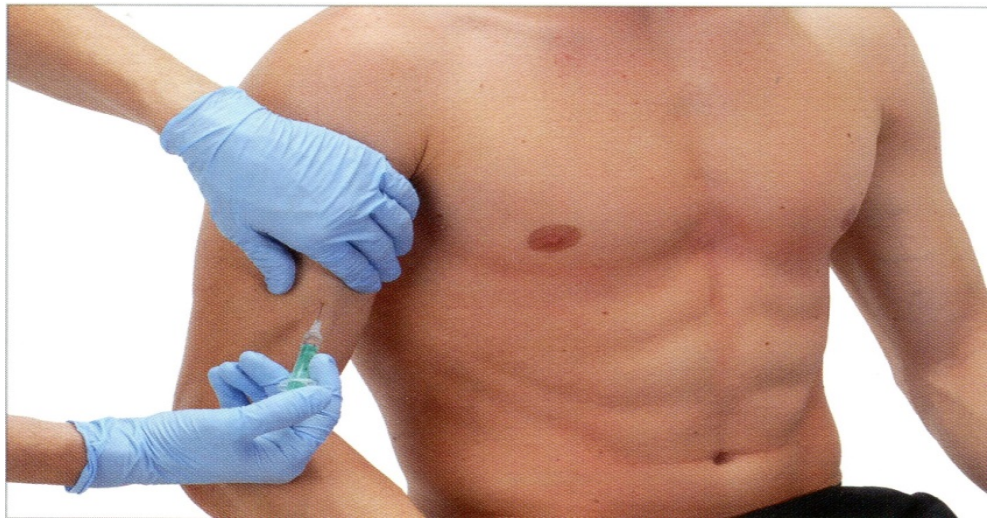
Anca e ginocchio flessi

Tecnica infiltrazione manuale: palpazione-punti di repere

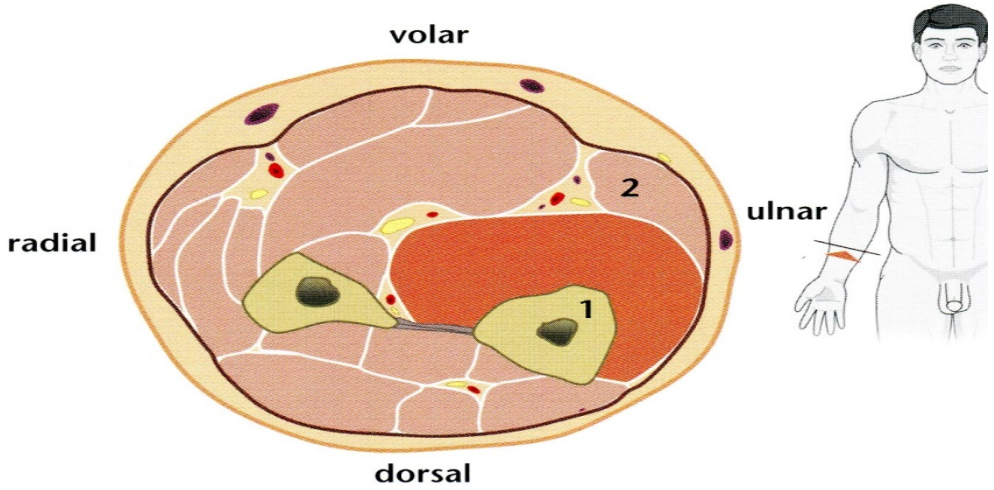


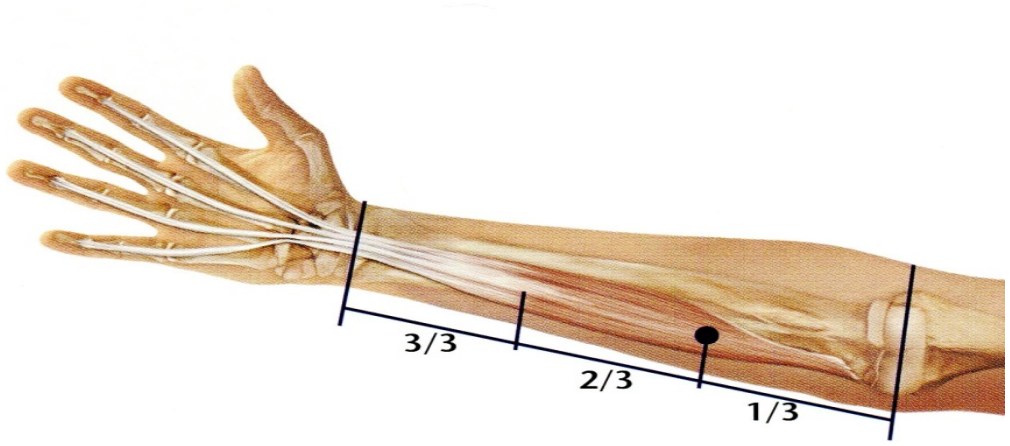


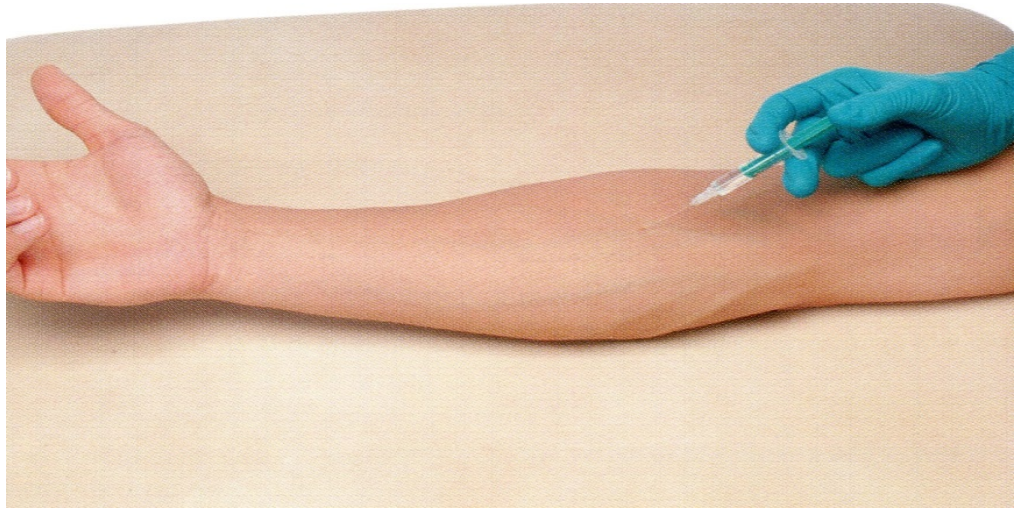




Tecnica infiltrazione manuale: palpazione-punti di repere







Ausilio per l’infiltrazione
Guida EMG - Ecografia

Muscoli “difficili”

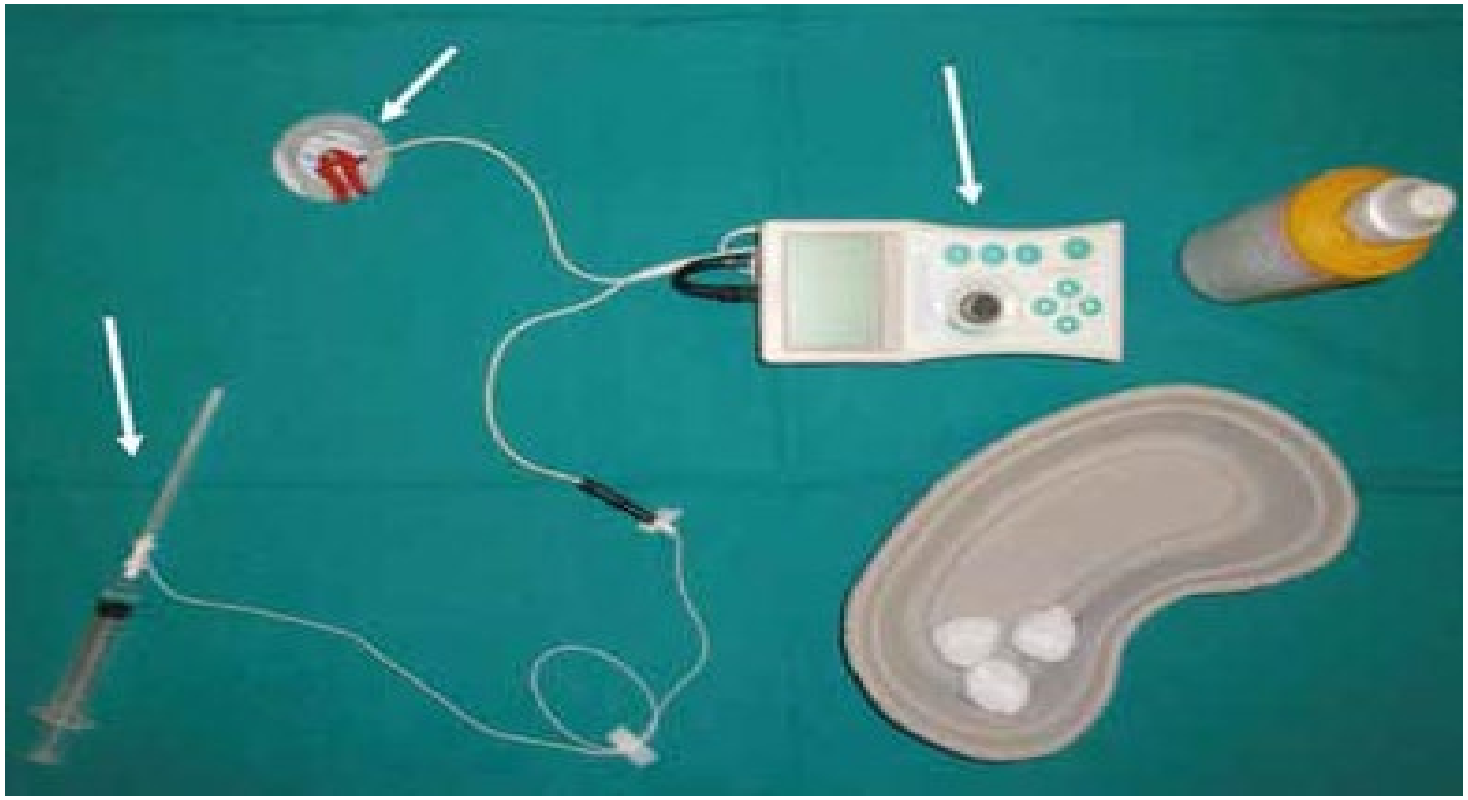
Muscoli profondi

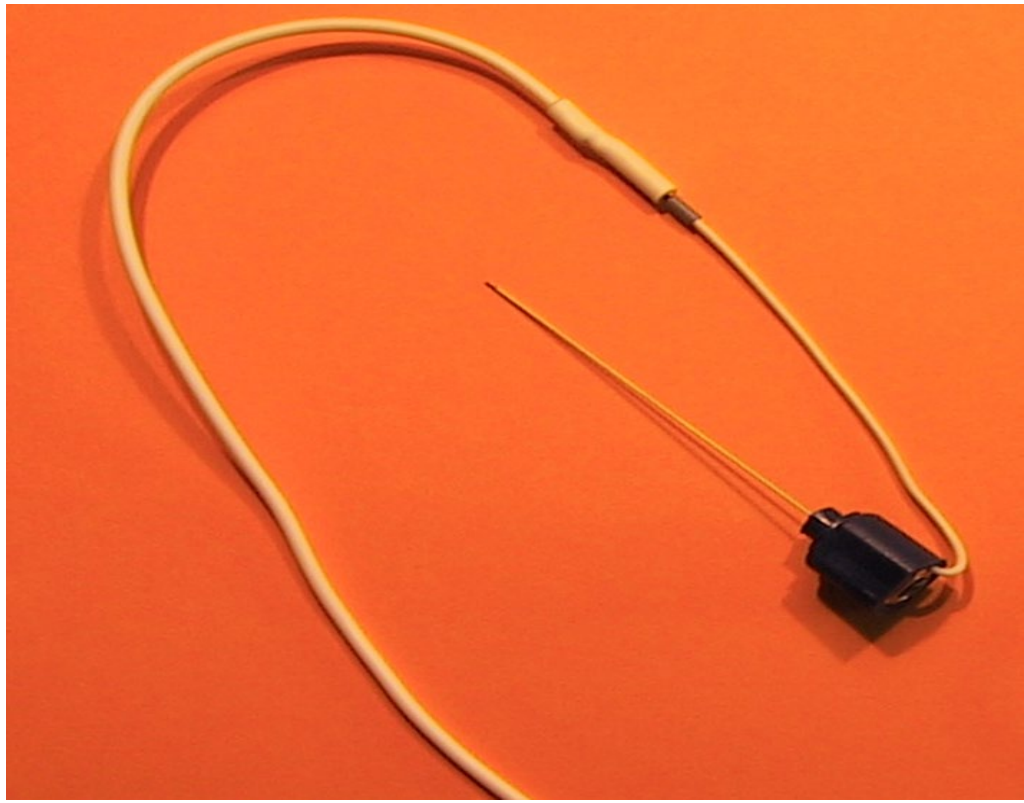
Muscoli non facilmente individuabili col solo esame clinico

Punto motore

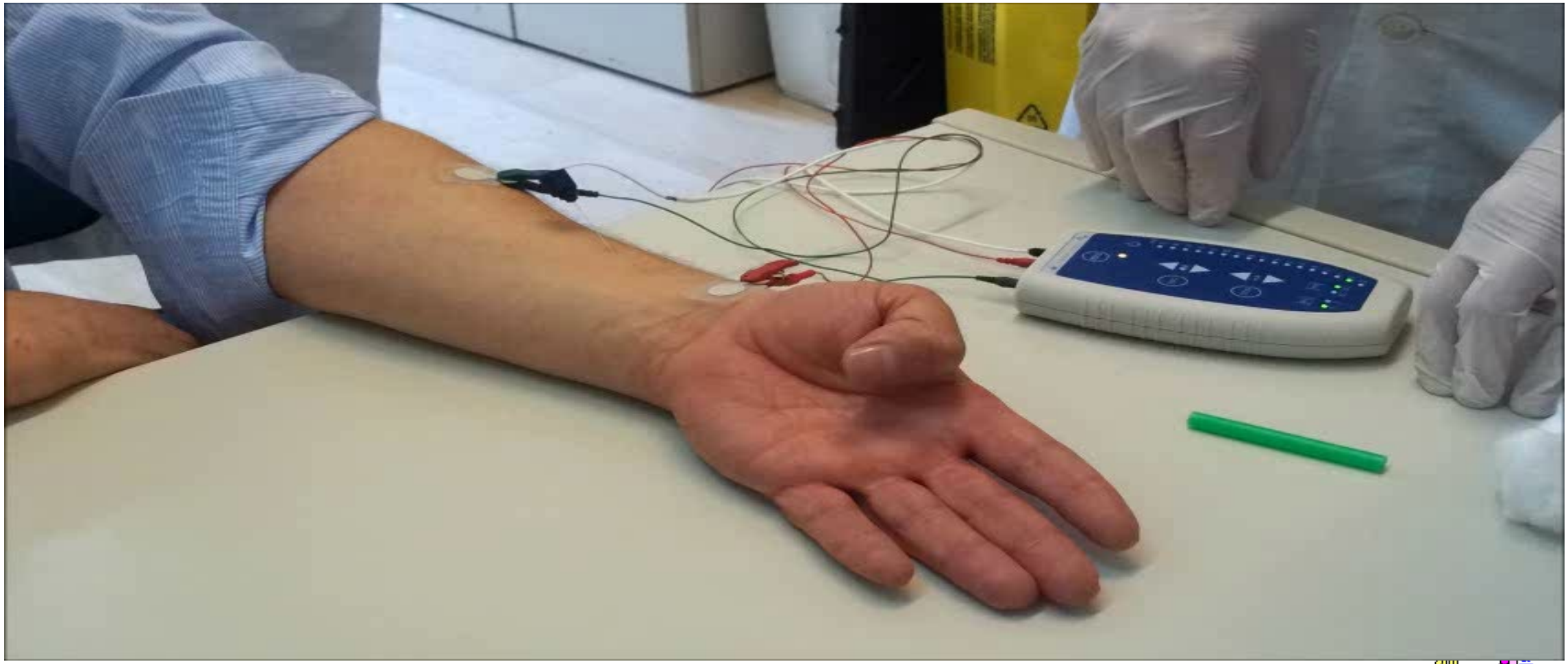
Infiltrazione guidata mediante EMG – Stim. elettrica

1) **Localizzazione dei muscoli iperattivi durante attivazione muscolare attiva o passiva.**
2) **Stimolazione elettrica con localizzazione del punto motorio tramite ago ipodermico utilizzato per iniettare e registrare l'EMG simultaneamente.**

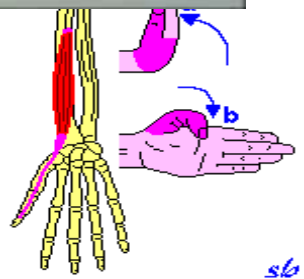




Infiltrazione guidata mediante EMG – Stim. elettrica

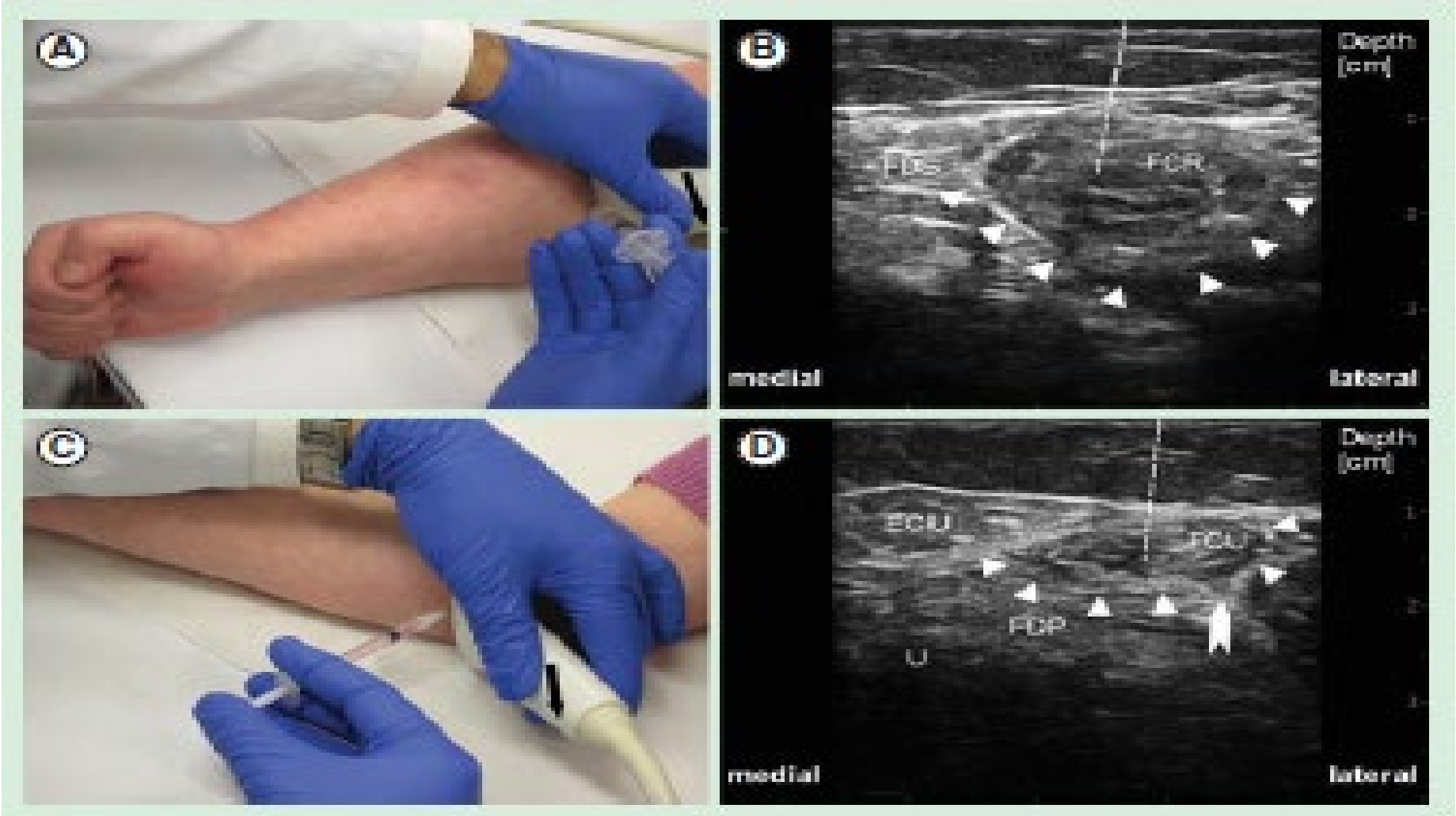


Flessore lungo del pollice

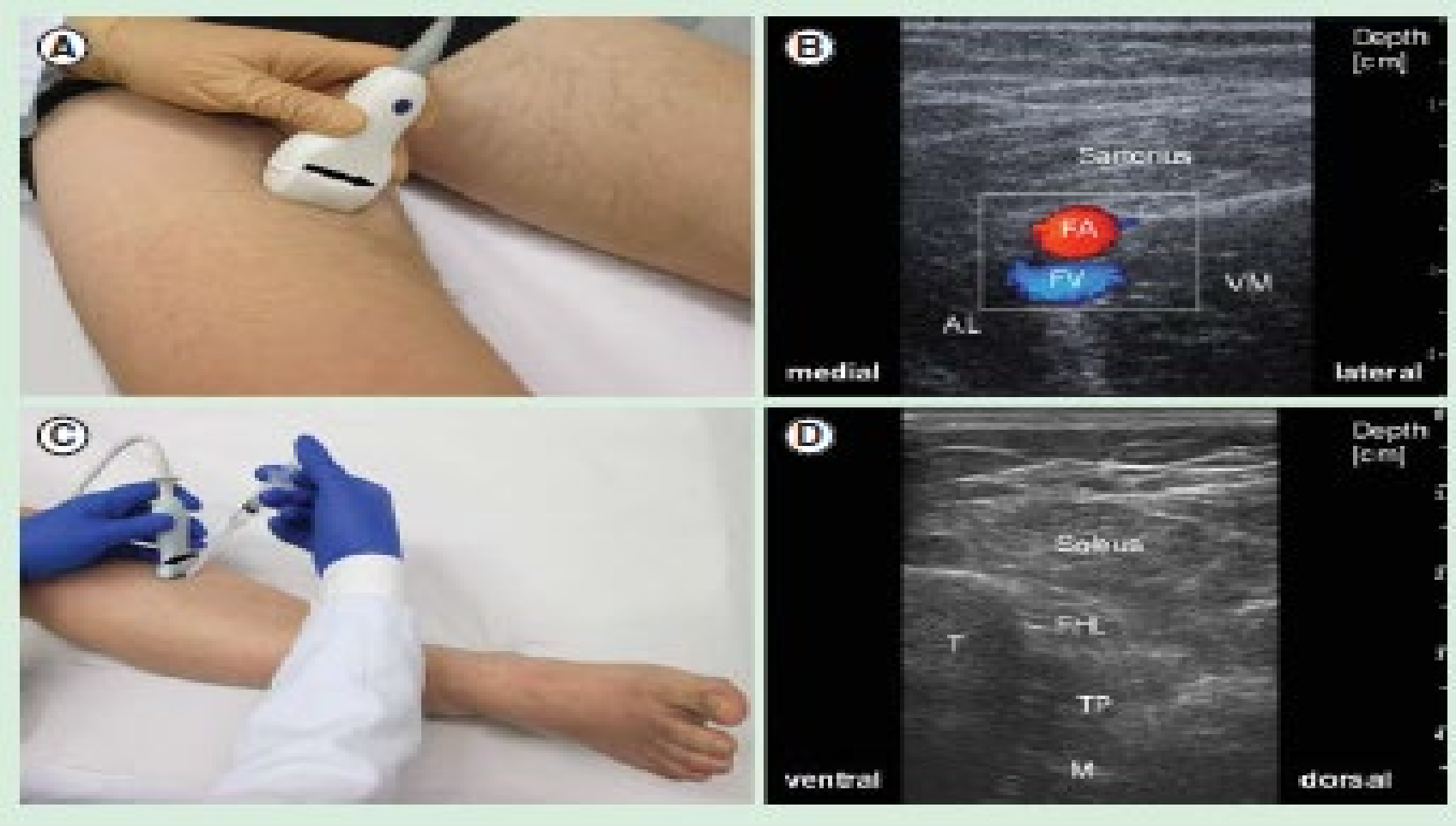


Infiltrazione eco-guidata

US della regione prossimale dell’avambraccio per guidare l’iniezione di tossina botulinica



US dei muscoli della coscia e della gamba per guidare l'iniezione di tossina botulinica



Misure di Outcome:

Modified Ashworth Scale; Tardieu Scale; wrist and fingers passive range of motion.

Risultati:

Alla valutazione ad 1 mese tutti gli score erano migliori nei gruppi infiltrati sotto guida rispetto all'infiltrazione manuale.

Nessuna differenza statistica tra gruppo US e gruppo ES.

Conclusioni:

La guida strumentale può migliorare l'outcome delle iniezioni di tossina botulinica nei muscoli spastici dell'avambraccio dei pazienti post-stroke.

(A) Pre-injection

(B) Post-injection

Key Points

After stroke, different muscles are responsible for spastic equinus foot; a careful clinical evaluation and an interdisciplinary approach is therefore required for optimal administration of botulinum toxin type A (BoNT-A) therapy.

In stroke survivors, it is important to differentiate between spasticity and weakness in leg muscles prior to treatment with BoNT-A.

Studies of high doses of BoNT-A showed a greater reduction of severe spasticity after stroke.

In stroke survivors with spasticity in the plantar-flexor muscles, a combined approach between surgery and BoNT-A should be considered.

Botulinum Toxin Type A for the Treatment of Lower Limb Spasticity after Stroke, Santamato et al., Drugs, 2019

Outcome measures

AQoL:	**Assessment of Quality of Life scale**
ARAT:	**Action Research Arm Test**
CBS:	**Carer Burden Scale**
CGI:	**Clinical Global Impression**
DAS:	**Disability Assessment Scale**
EQ-5D:	**EuroQol-5 dimensions**
FIM:	**Functional Independent Measure**
GAS:	**Global Assessment Scale**
MAS:	**Modified Ashworth Scale**
PAINAD:	**Pain Assessment in Advanced Dementia Scale**
PGA:	**Physician Global Assessment**
REPAS:	**Resistance to Passive Movement Scale**
ROM:	**Range Of Movement**
SF-36:	**Study 36-Item Short-Form Health Survey**
ADL:	**Activities of Daily Living**
VAS:	**Visual Analogue Scale**

Paralisi cerebrale infantile: AS

Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE) (Review)

Hoare BJ, Wallen MA, Imms C, Villanueva E, Rawicki HB, Carey L

THE COCHRANE COLLABORATION®

There is high level evidence to support the safety and effectiveness of BoNT-A)as an adjunct to managing the upper limb in children with cerebral palsy.
When injected into muscles BoNT-A reduces muscle tightness. When used in conjunction with occupational therapy, the aim of BoNTA injections in the arms and hands is to improve movement and function in treated limbs. In the absence of significant side effects, injection of BoNT-A has been identified as a safe and effective treatment for upper limb spasticity when used in combination with occupational therapy in children with cerebral palsy

Paralisi cerebrale infantile: AI

Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy (Review)

Ade-Hall R, Moore P

THE COCHRANE COLLABORATION®

This review found that published, controlled evidence was weak as they identified three controlled trials involving only a small number of children (2 to 11 years). Children receiving a single course of injections of BtA (Botox®, 3 to 8 µg/kg or Dysport®, 15 µg /kg) into the calf muscle tended to have an improved pattern of walking (gait) compared with inactive injections (placebo). Both BtA injections and lightweight walking plaster casts below the knee (for four to six weeks) produced similar significant improvements in gait.

SM

J Neurol
DOI 10.1007/s00415-016-8304-z

ORIGINAL COMMUNICATION

Botulinum toxin therapy for treatment of spasticity in multiple sclerosis: review and recommendations of the IAB-Interdisciplinary Working Group for Movement Disorders task force

Dirk Dressler[1] · Roongroj Bhidayasiri[2] · Saeed Bohlega[3] · Abderrahmane Chahidi[4] · Tae Mo Chung[5] · Markus Ebke[6] · L. Jorge Jacinto[7] · Ryuji Kaji[8] · Serdar Koçer[9] · Petr Kanovsky[10] · Federico Micheli[11] · Olga Orlova[12] · Sebastian Paus[13] · Zvezdan Pirtosek[14] · Maja Relja[15] · Raymond L. Rosales[16] · José Alberto Sagástegui-Rodríguez[17] · Paul W. Schoenle[18] · Gholam Ali Shahidi[19] · Sofia Timerbaeva[20] · Uwe Walter[21] · Fereshte Adib Saberi[22]

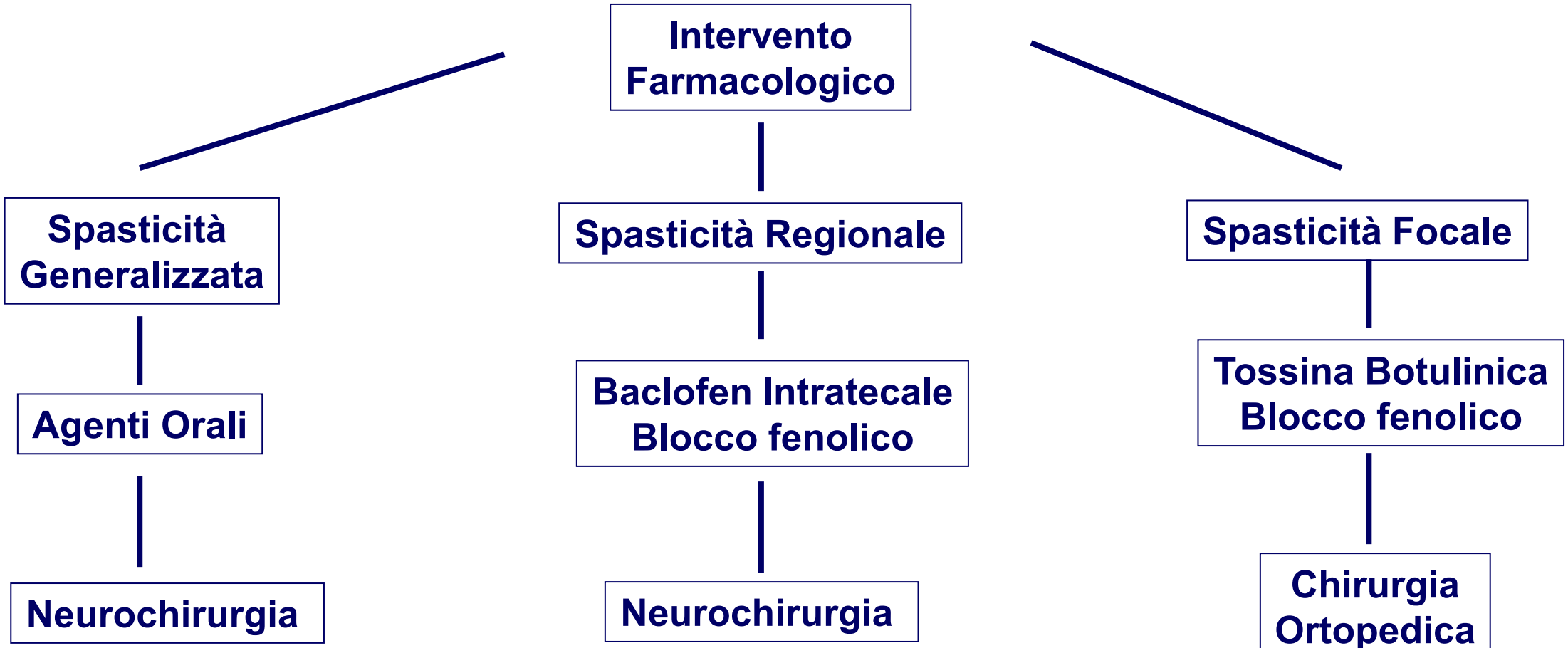
Botulinum toxin (BT) therapy is an established treatment of spasticity due to stroke. For multiple sclerosis (MS) spasticity this is not the case. IAB-Interdisciplinary Working Group for Movement Disorders formed a task force to explore the use of BT therapy for treatment of MS spasticity. A formalised PubMed literature search produced 55 publications (3 randomised controlled trials, 3 interventional studies, 11 observational studies, 2 case studies, 35 reviews, 1 guideline) all unanimously favouring the use of BT therapy for MS spasticity. There is no reason to believe that BT should be less effective and safe in MS spasticity than it is in stroke spasticity.

European Journal of Neurology 2002, 9 (suppl. 1): 48–52

A summary of spasticity management – a treatment algorithm

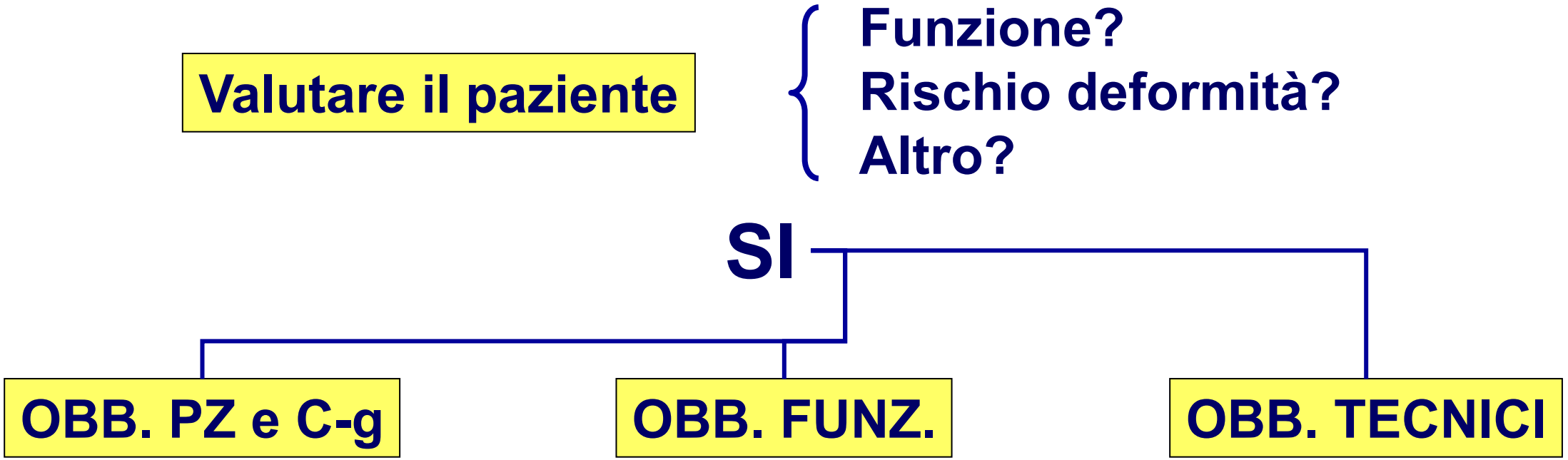
A. B. Ward

North Staffs Rehabilitation Centre, Haywood and Stanfield Hospital, Department of Rehabilitation Medicine, Stoke on Trent, UK



Algoritmo BTX-A Spasticità

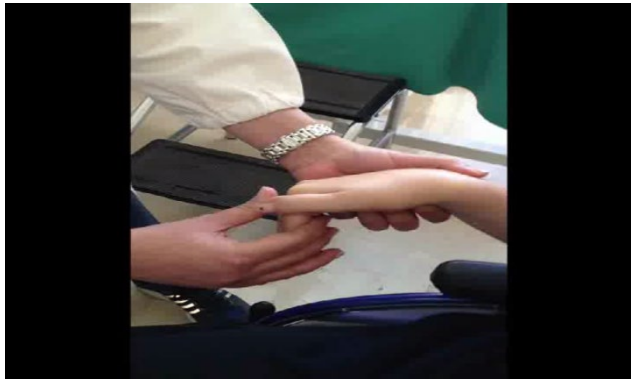
Paziente con spasticità per ictus, PCI, SM……



Obiettivi del trattamento

- ✓ Migliorare la mobilità
- ✓ Ridurre il dolore
- ✓ Ridurre gli spasmi
- ✓ Migliorare il range di movimento
- ✓ Migliorare l'adattamento alle ortesi
- ✓ Migliorare l'estetica
- ✓ Migliorare il posizionamento
- ✓ Ritardare o prevenire la chirurgia

...mancata individuazione dei muscoli coinvolti



The Upper Limbs

The Adducted/Internally Rotated Shoulder
pectoralis major
latissimus dorsi
teres major
subscapularis

The Flexed Elbow
brachioradialis
biceps
brachialis

The Pronated Forearm
pronator quadratus
pronator teres

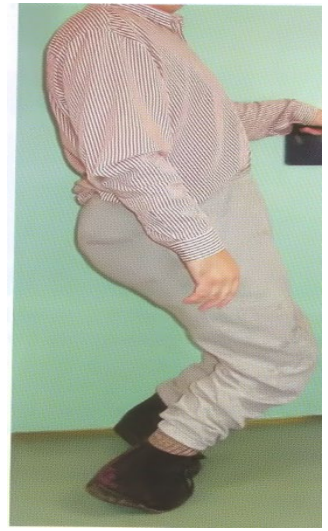
The Flexed Wrist
flexor carpi radialis and brevis
extrinsic finger flexors

The Clenched Fist
various muscle slips of FDP
various muscle slips of FDS

The Intrinsic Plus Hand
dorsal interossei

The Thumb-In-Palm Deformity
adductor pollicis
thenar group
flexor pollicis longus

…..mancata individuazione dei muscoli coinvolti



The Lower Limbs

The Equinovarus Foot (with Curled Toes or Claw Toes)
medial gastrocnemius
lateral hamstrings
soleus
tibialis posterior
tibialis anterior
extensor hallucis longus
long toe flexors
peroneus longus

The Valgus Foot
peroneus longus and brevis
gastrocnemius
soleus
tibialis anterior (weak)
long toe flexors (weak)

The Stiff (Extended) Knee
gluteus maximus
rectus femoris
vastus lateralis
vastus medialis
vastus intermedius
hamstrings
gastrocnemius
iliopsoas (weak)

The Flexed Knee
medial hamstrings
lateral hamstrings
quadriceps
gastrocnemius

Striatal Toe (Hitchhiker's Great Toe)
extensor hallucis longus

Adducted Thighs
adductor longus
adductor magnus
gracilis
iliopsoas (weak)
pectineus (weak)

The Flexed Hip
rectus femoris
iliopsoas
pectineus
adductors longus
adductor brevis (weak)
gluteus maximus (weak)

…..errori nell'infiltrazione

MANUAL NEEDLE PLACEMENT: ACCURACY OF BOTULINUM TOXIN A INJECTIONS

ALEXIS SCHNITZLER, MD,[1] NICHOLAS ROCHE, MD,[1] PHILIPPE DENORMANDIE, MD,[2] CHRISTINE LAUTRIDOU, MD,[2] BERNARD PARRATTE, MD, PhD,[3] and FRANÇOIS GENET, MD[1]

Muscle Nerve **46:** 531–534, 2012

Fifty-two injections were successful (43%), and 69 failed (57 %). This result was unrelated to injector experience ($P = 0.097$). *Conclusions:* Our findings show a poor success rate, regardless of injector experience.

FIGURE 2. Unsuccessful injection (superficial, ink in the fat).

Accuracy of Intramuscular Injection of Botulinum Toxin A in Juvenile Cerebral Palsy

Terence Y. P. Chin, MBBS, Gary R. Nattrass, MD, FRCS(C), FRACS,**
Paulo Selber, MD, SBOT (Br), FRACS, and H. Kerr Graham, MD, FRCS (Ed), FRACS*†‡*

J Pediatr Orthop • Volume 25, Number 3, May/June 2005

Accuratezza posizionamento ago mediante tecnica manuale vs stim. elettrica

1,372 iniezioni in 226 bambini con PCI

MUSCOLI	ACCURATEZZA
Gastroc-soleus	>75%
Hip adductors	67%
Medial hamstrings	46%
Tibialis posterior	11%
Biceps brachii	62%
Forearm and hand muscles	13% - 35%

NEUROLOGY

"Starfish" hand

Bryan K. Ho, John C. Morgan and Kapil D. Sethi

Neurology 2007;69;115

NEUROIMAGES

"Starfish" hand

Figure "Starfish" hand dystonia following a right middle cerebral artery stroke involving the caudate

Benchè con indicazioni in scheda tecnica leggermente diverse, dovute agli studi di registrazione, tutte le tossine di tipo A sono utilizzabili nella spasticità.

Per passare da una tossina ad un'altra vanno effettuate delle opportune conversioni:

1 U Onabotulinum/Incobotulinum: 3-4 U Abobotulinum.

La diluizione della tossina, quindi il volume iniettato, può variare a seconda delle esigenze.

Ogni passaggio del processo (conservazione, ricostituzione, iniezione) va effettuato con attenzione pena la ridotta efficacia della terapia.

Vantaggi della terapia con BoNT-A:

Possibilità di intervento precoce o in qualsiasi momento lo si ritenga opportuno nel contesto del programma riabilitativo

Individualizzazione del trattamento (!!)

Integrazione con altre terapie (elettrostimolazione?)

Ripetibilità

Sicurezza

Can the early use of botulinum toxin in post stroke spasticity reduce contracture development? A randomised controlled trial
Clin Rehab, 2021

Clinical message

- Early use of Botulinum toxin, in patients who have spasticity, is safe following stroke and is not detrimental to functional recovery.
- A single cycle of Botulinum toxin reduces the rate of contracture formation and reduced the need for concomitant contracture treatment such as splinting.
- Botulinum toxin does not improve function in people with severe stroke who have developed spasticity.

- **Criticità:**
- Disponibilità dei centri iniettori, con personale adeguatamente formato anche nell'uso delle tecniche attualmente utilizzate nell'ausilio dell'infiltrazione (EMG, ECO, ES, etc.)
- Accesso alla terapia: invio dagli specialisti/centri del territorio/mmg.
- Integrazione tra specialisti e creazione di Team multidisciplinari: creazione ambulatori spasticità/percorsi integrati (telemedicina?)
- Costi (eventuale tavolo tecnico Regione Sicilia)