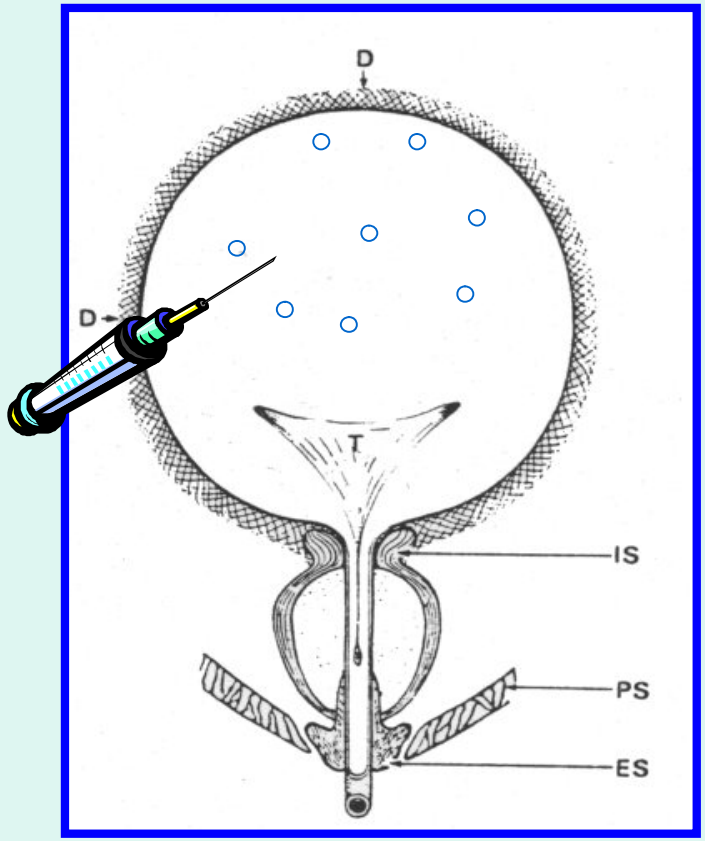
La terapia endoscopica con Botulino nella vescica iperattiva

Dott. G. P. Daniele
U.O UROLOGIA Ferrara



Alterazioni funzionali del complesso vescico-sfinteriale

SOCIETA' MEDICO CHIRURGICA DI FERRARA

FERRARA 18 giugno 2011

EVIDENCE SYNTHESIS:

The use of ***botulinum toxin*** type A is recommended in the treatment of intractable sypmtoms of **neurogenic detrusor overactivity** or **idiopathic detrusor overactivity** in adults (grade A)

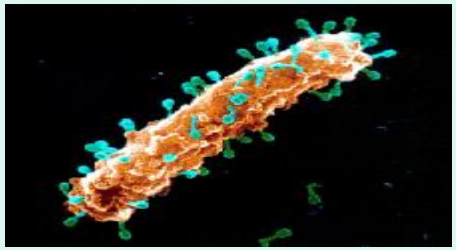
EAU guidelines 2008

Campi di utilizzo della tossina botulinica:

- Oculistica
- Neurologia
- Dermatologia
- Iperidrosi
- Urologia

un po' di storia:

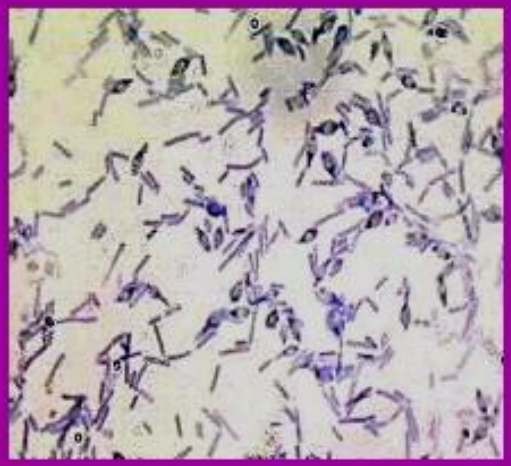
- **J. Kerner, prima descrizione di botulismo o "veleno delle salsicce". Ipotizzò il suo utilizzo nella danza di San Vito (Germania, 1822)**
- **E. P. van Ermengem, primo isolamento Clostridium Botulinum da cibi e tessuti post-mortem (Belgio, 1895)**
- **Inizio studi utilizzo bellico della tossina botulinica. Un grammo di tossina inalata capace di uccidere 1 milione di persone (Gran Bretagna, 1916)**
- **E. Schantz sviluppò forme cristalline della tossina ma escluse un suo uso militare USA, 1946)**
- **Dal 1972 formulazione per uso militare in USA e URSS ed Iraq poi**
- **A Scott, primo uso terapeutico nello strabismo (USA, 1980)**
- **J Carruthers, utilizzo nel blefarospasmo (Canada, 1987)**
- **sua moglie, Alastair, dermatologa la utilizza in campo cosmetico**
- **D. Dykstra , utilizzo nella dissinergia vescico-sfinterica (USA, 1988)**
- **B. Schurch, utilizzo nell'iperattività detrusoriale (USA, 2000)**

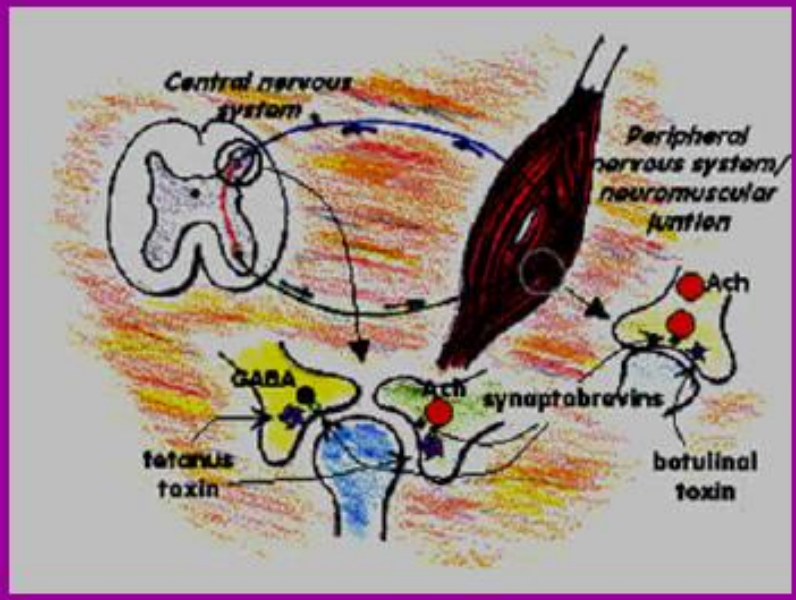


7 sottotipi di tossina botulinica
Il *sottotipo A* è il più importante
dal punto di vista clinico
e la maggior parte degli studi
riguardano il Botox® e poi il
Dysport®
Piccolo e recente utilizzo anche
del *sottotipo B*

E' possibile ottenere alte concentrazioni vescicali dell'agente terapeutico evitando inadeguati livelli in altri organi

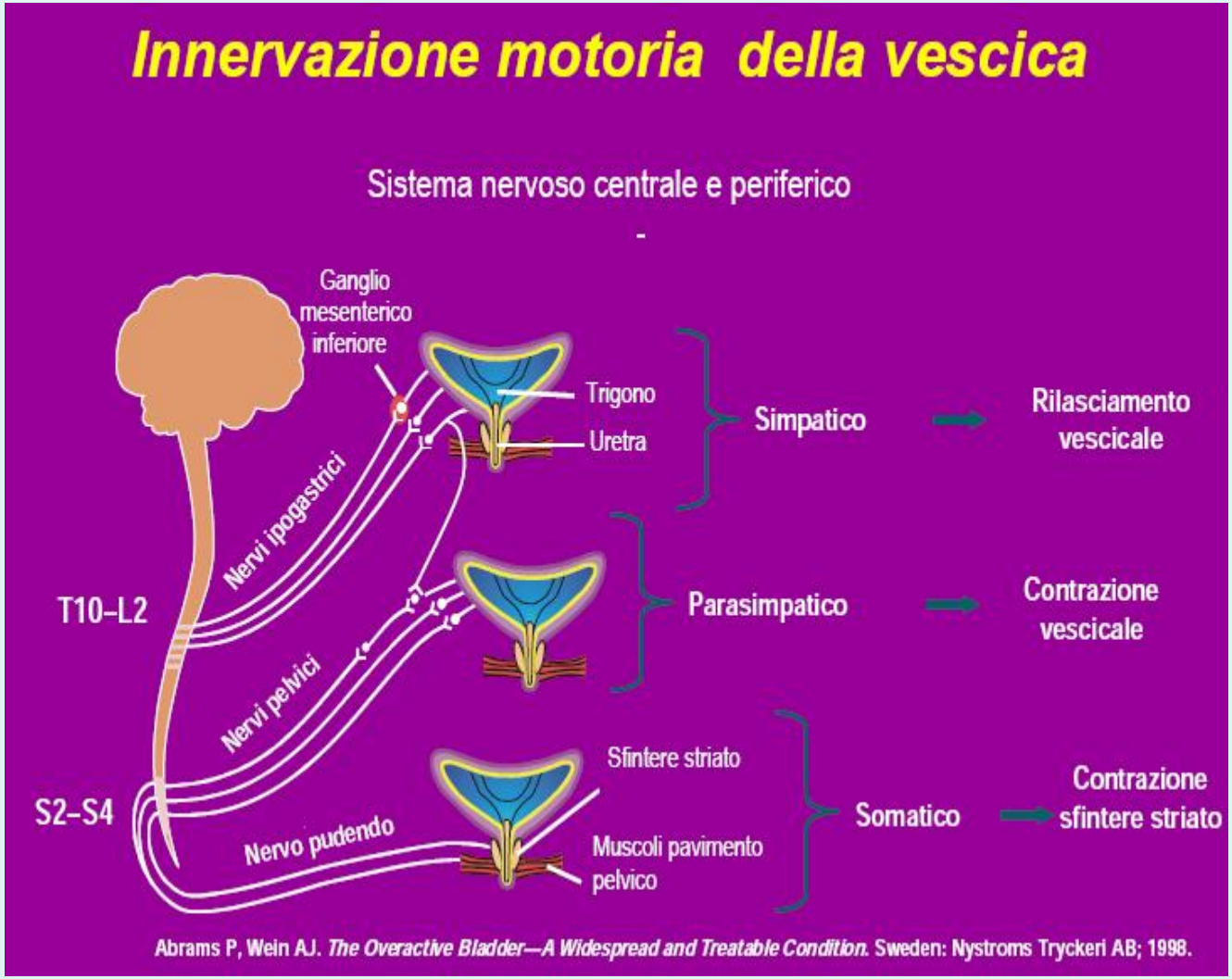
BOTULINUM-A TOXIN





BTx A inhibits calcium mediated release of Acetylcholine vesicle at neuromuscular junction, which results in reduced muscle contractility and atrophy at injection site. BTx-A has catalytic zine finger motif that may blok activity of SNAP-25, protein important in synaptic vesicle fusion.

la tossina botulinica A agisce a livello di numerosi trasmettitori sensoriali oltre che sul rilascio di ACH, come ATP, sostanza P, CGRP, glutammato, NGF (considerare la degenerazione assonale..)



RECETTORI

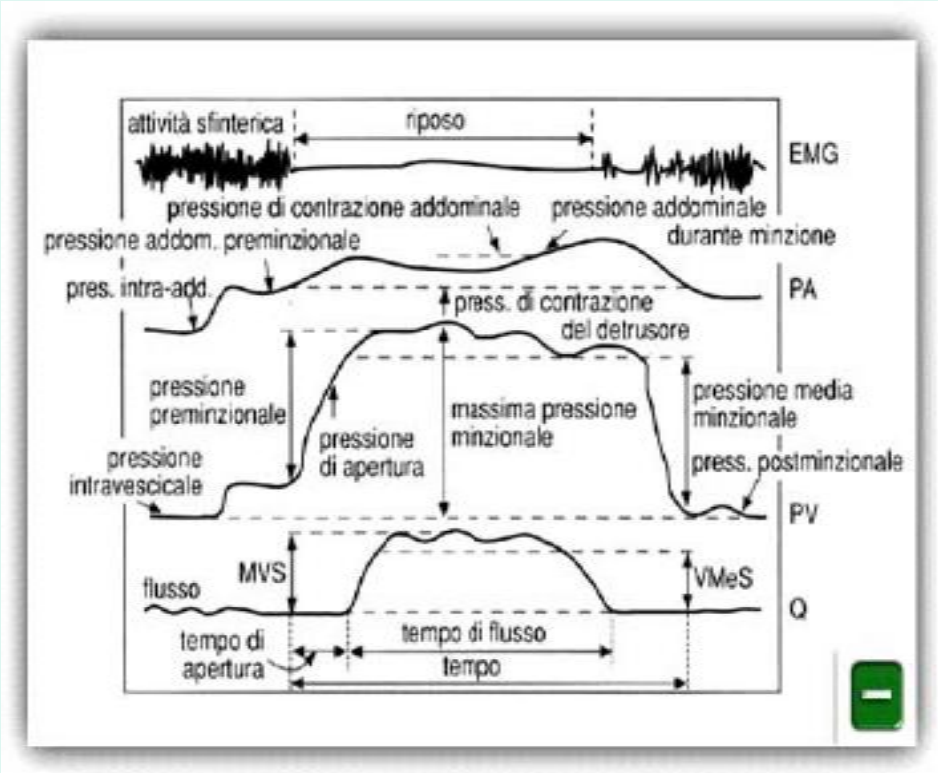
SIMPATICO

- Alfa-recettori: contrazione della muscolatura liscia, collo vescicale e uretra prossimale
- Beta-recettori: rilasciamento della muscolatura liscia, corpo vescicale

PARASIMPATICO

- Recettori colinergici: contrazione della muscolatura liscia, detrusore

- Iperattività destrusoriale (diagnosi urodinamica)
  - → **neurogena**
  - → **idiopatica**
- Vescica iperattiva (diagnosi clinica)



LESIONI CORTICO-SOTTOCORTICALI COMPLETE

assenza del controllo volontario della minzione
minzione coordinata
assenza di attività sfinterica volontaria

LESIONE MIDOLLARE ALTA COMPLETA (superiore a D10)

assenza del controllo volontario della minzione
iperattività detrusoriale
dissinergia detrusore-sfintere liscio e striato (“doppia dissinergia”)
assenza di attività sfinterica volontaria

BASSA COMPLETA

assenza del controllo volontario della minzione
iperattività detrusoriale
dissinergia detrusore-sfintere striato
assenza di attività sfinterica volontaria

LESIONE DEI CENTRI MIDOLLARI

acontrattilità detrusoriale
assenza di attività sfinterica volontaria
attività dello sfintere liscio conservata

Che cos'è la vescica iperattiva

La vescica iperattiva è una "sindrome sintomatica" indicativa di una disfunzione delle vie urinarie inferiori

In particolare si definisce come:

Urgenza, con o senza incontinenza da urgenza, di solito associata a frequenza aumentata e nicturia

Standardisation Subcommittee of the International Continence Society (ICS)

Abrams P, Cardozo L, Fall M et al Neurourol Urodyn 2002;21:167-178

OBIETTIVI:

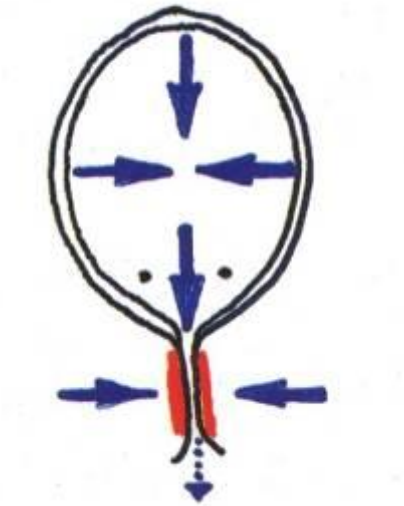
- **CONSENTIRE *UN ADEGUATO SVUOTAMENTO VESCICALE* MANTENENDO BASSA LA PRESSIONE ALL'INTERNO DEL SERBATOIO DETRUSORIALE, RICERCANDO NEL CONTEMPO UNA ACCETTABILE CONTINENZA URINARIA**

TRATTAMENTO

- **(cateterismo intermittente)**
- **TERAPIA FARMACOLOGICA CON:**
  - **anticolinergici ossibutinina, tolterodina, trospium**
  - **capsaicina, resinferatossina intravescicale**
  - **tossina botulinica a livello detrusoriale**
- **RIZOTOMIA SACRALE POSTERIORE (e stimolazione delle radici sacrali anteriori)**
- **AMPLIAMENTO VESCICALE**

Vescica neurologica-

Iperattività vescicale



- **Elevate pressioni**
- **Rischio vie superiori**
- **Incontinenza/Ritenzione**
- **Qualità vita**

Iperattività detrusoriale neurogena

Via endoscopica

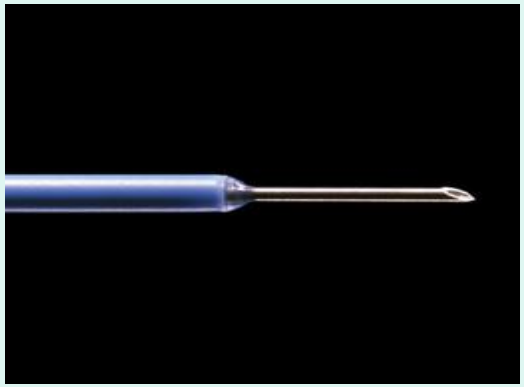
- **200-300 U Botox**
- **500-1000 U Dysport**

Diluizione

in 20-30 siti (0,5-1 ml per sito)
a 10-30 ml

Catetere

per 24 ore



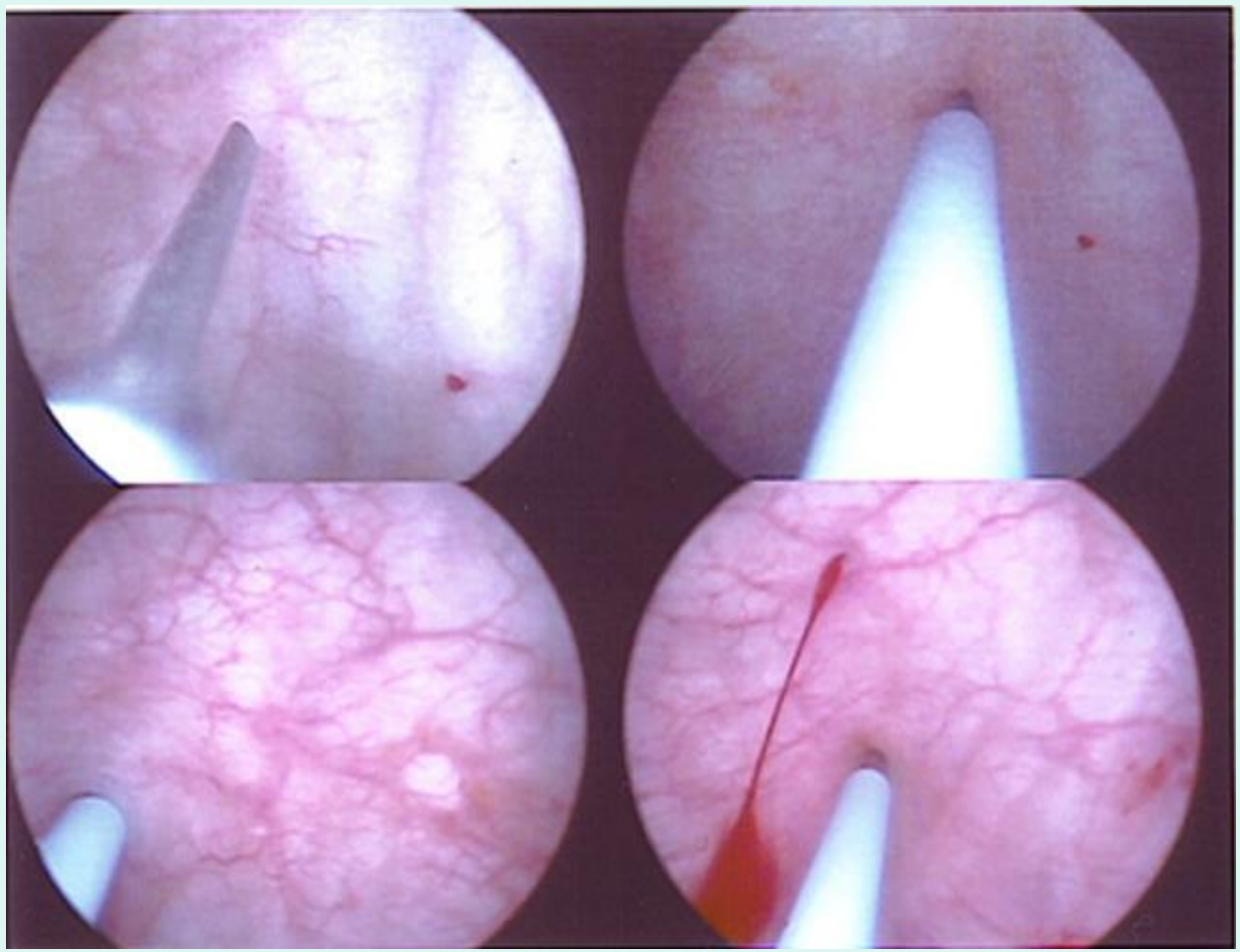
Terapia anticolinergica

per 1-3 settimane, poi scalare fino a sospendere

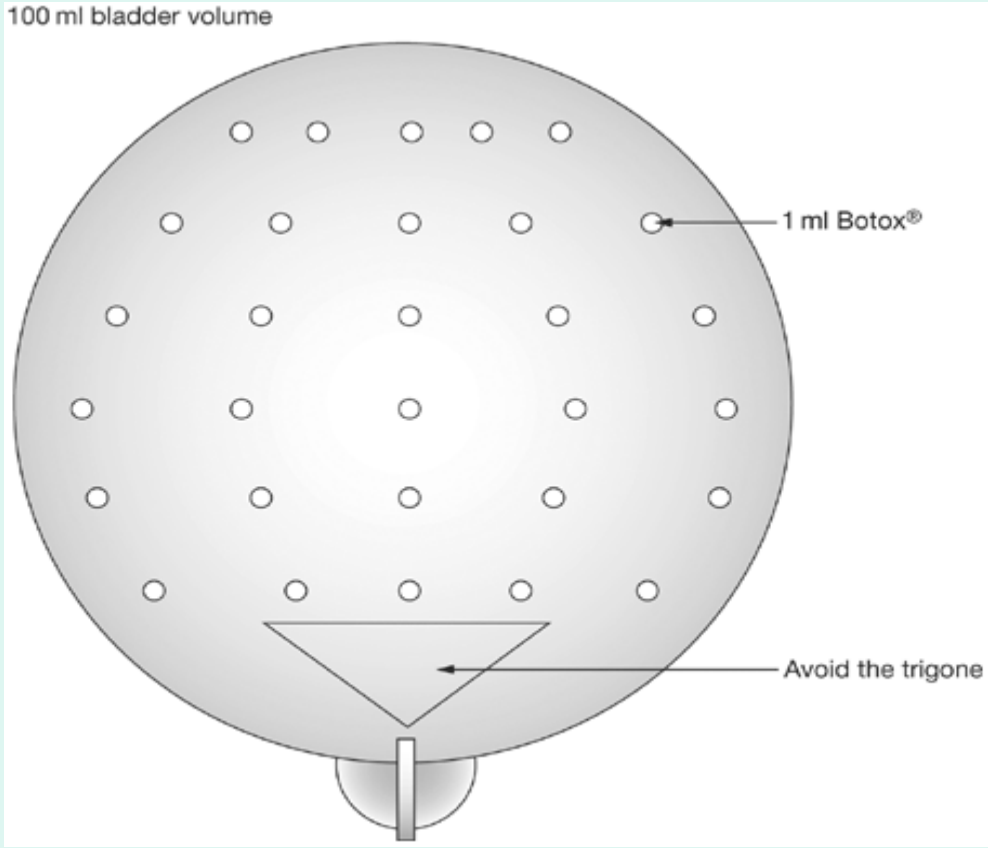
Reinfiltrazione

alla ricomparsa dell'incontinenza riflessa (4 -12 mesi)

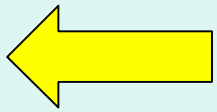
Nella vescica iperattiva *idiopatica* le dosi di attacco sono nettamente inferiori (100-200 U Botox)



Schema di somministrazione



Preoperatorio

- *Urine sterili*
- *Esame urodinamico*
- *Certezza che il paziente abbia compreso la possibilità di ricorrere al cateterismo intermittente*
- *Verificare la destrezza manuale e la presenza di familiari in grado di cateterizzare*
- *Consenso informato* 

Postoperatorio

- *Antibiotico per alcuni giorni*
- *Catetere per 24 ore*
- *Alla rimozione può verificarsi un'aumento temporaneo della urgenza e delle perdite*
- *Possibilità di dover ricorrere al cateterismo intermittente per vari mesi o anni*
- *Efficacia circa 4-14mesi*

European Association of Urology

Review – Neuro-urology

Recommendations on the Use of Botulinum Toxin in the Treatment of Lower Urinary Tract Disorders and Pelvic Floor Dysfunctions: A European Consensus Report

Apostolos Apostolidis [a,], Prokar Dasgupta [b], Pierre Denys [c], Sohier Elneil [d], Clare J. Fowler [e], Antonella Giannantoni [f], Gilles Karsenty [g], Heinrich Schulte-Baukloh [h], Brigitte Schurch [i], Jean-Jacques Wyndaele [j]*

Study	No. of patients	BoNT type, dosage	Continence % completely dry/% Δleak episodes	MCC change, %	$Pdet_{max}$ mean % change vs base line	QoL mean % change vs base line	Duration of follow-up	Duration of benefit	LoE
Kalsi et al [40]	16	Botox 300 U	NA/–88 (result at day 4)	NA	NA	NA	4 wk	≥4 wk	3
Kalsi et al [39]	43	Botox 300 U	NA/–77	+303	–33.5	+78 (UDI6-IIQ7)	16 wk (per injection) 1 reinjection	9.7 mo	3
Reitz et al [41]	20	Botox 300 U	85/NA	+130	–83	NA	35 mo (4 reinjections)	≥28 wk (per injection)	3
Del Popolo et al [42]	199	Dysport 500 U, 750 U, 1000 U	95/–95*	+80	NA	+40 (VAS)	75 mo (up to 8 reinjections)	44–52 wk (per injection)	3
Ehren et al* [21]	31	Dysport 500 U	NA/–48	+37.5	–69	NA	26 wk	26 wk	1b
Kalsi et al [35]	63	Botox 300 U	NA/–47	+178	–22	NA	≥15 mo	10 mo	3
Giannantoni et al [27]	23	Botox 300 U	78/–68	+86	–61	NA	12 wk	≥12 wk	3
Karsenty et al [38]	17	Botox 300 U	NA/–100	+43 (first) +32 (last)	–62 (first) –65 (last)	NA	208 wk	39 wk	3
Schulte-Baukloh et al [33]	16	Botox 300 U	NA/NA	+36	–57	35 (UDI-6) 50 (SSI)	24 wk	≥12 wk	3
Kalsi et al [34]	32	Botox 300 U	NA/–85	+166	–54	65 (UDI-6)	16 wk	≥16 wk	3
Ruffion et al [37]	45	Dysport 500 U	30/NA	+74	–20	NA	88 wk	16–17	3
		Dysport 1000 U	75/NA	+82	–49	NA	88 wk	40–44	
Schurch et al [12]	59	Botox 200 U	74/–32	+67	–50	61	24 wk	≥24 wk	1b
		Botox 300 U	53/–58	+32	–38	56 (I-QoL)			
Kuo [36]	24	Botox 200 U	8/NA (CVA 42/NA (SCI)	+28 +45	–27 –34	NA	12 wk	12 wk	3
Khaphajone et al [30]	10	Botox 300 U	50/NA	+23	–34	NA	36 wk	≥16 wk	3
Popat et al [13]	44	Botox 300 U	55/–68	+181	–42	NA	16 wk	≥16 wk	3
Kessler et al [28]	11	Botox 300 U	73/NA	+196	–40	NA	1 wk	22 wk	3
Hajebrahimi et al [32]	10	Botox 400 U	86/NA	+74	–56	NA	12 wk	≥12 wk	3
Smith et al [29]	42	Botox 100–300 U	NA/NA	+61	–30	NA	24 wk	≥24 wk	3
Grosse et al [31]	66	Botox 300 U	73/NA	+40	NA	NA	NA	36–44 wk	3
		Dysport 750–1000 U							
Giannantoni et al [22]	12	Botox 300 U vs RTX	73/–77	+54	–44	NA	112 wk	35 wk (per injection)	1b
Bagi et al [24]	15	Botox 300 U	87/NA	+31	–59	NA	6 wk	30 wk	3
Kuo [26]	30	Botox 200 U	8/NA	+11		51 (IPSS)	12 wk	21 wk	3
Reitz et al [11]	200	Botox 300 U	73/NA	+54 (week 12) +29 (week 36)	–51 (week 12) –28 (week 36)	NA	36 wk	≥36 wk	3
Kennelly et al [23]	10	Botox 300 U	80/NA	+23	–5	NA	24 wk	12–24 wk	3
Schurch et al [2]	21	Botox 200 or 300 U	64/NA	+54	–44	NA	36 wk	≥36 wk	3

Despite heterogeneous designs, all single-injection studies showed significant improvements in a variety of outcomes concerning symptomatology, urodynamics, and quality of life. The LoE for a beneficial effect of BoNTA in NDO is 1b. There is LoE 3 for efficacy of repeat treatments.

MCC = maximum cystometric capacity; $Pdet_{max}$ = maximum detrusor pressure; QoL = quality of life; LoE = levels of evidence; DO = detrusor overactivity; NA = not applicable; UDI6-IIQ7 = Urinary Distress Inventory and Incontinence Impact Questionnaire short forms; VAS = Visual Analogue Scale; UDI-6 = Urinary Distress Inventory short form; SSI = Symptom Severity Index; I-QoL = Urinary Incontinence Quality of Life scale; IPSS = International Prostate Symptom Score; CVA = cerebrovascular accident; SCI = spinal cord injury; RTX = resiniferatoxin.

* Results not included in analysis of means.

studi su trattamento con tossina botulinica nella *iperattività detrusoriale neurogena* (Eur Urol 2009; 55:100-120)

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Recommendations on the Use of Botulinum Toxin in the Treatment of Lower Urinary Tract Disorders and Pelvic Floor Dysfunctions: A European Consensus Report

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Study	No. of patients	BoNT type, dosage	% improvement or success	Continence % completely dry/% Δ leak episodes	Frequency change, %	Urgency change, %	MCC change, %	$Pdet_{max}$ change, %	DO resolution, %	QoL ↑ reinjection/improvement, %	Duration of study or benefit	LoE
Jeffery et al [59]	25	Dysport 500 U	–	32/NA	–22	–22	+19	–	40	37	9 mo (study) 6 mo (benefit)	3
Lee et al[b] [52]	10	Purified toxin 50–200 U	89	50/–58	–26	–	+125	–56	–	22	3 mo (study) 6 mo (benefit)	3
Sahai et al [44]	32	Botox 200 U vs placebo	–	70/NA	–40	–53	+45	–49	25	52	6 mo (study)	1b
Kuo [46]	45	Botox 100 U detrusor	80/3 mo	60/NA	–48	–34	+27	–20	–	93	9 mo (study)	2b
		Botox 100 U suburo	42/6 mo	47/NA	+24	–28	+51	+10		80	6 mo (benefit)	
		Botox 100 U base	16/9 mo	53/NA	–40	–50	+12	+9		87		
Ghoniemi and Al-Ghoro [53]	16	Dysport 500 U	–	75/NA	–55	–	+36	–26	–	Satisfied: 87.5	5 mo (benefit)	3
Karsenty et al [54]	11	Botox 100 U including trigone	36.4	33.3/NA	–33.3	–	+128	–20	75	–	6 wk (study)	3
Kuo [45]	35	Botox 100 U vs Botox 150 U vs Botox 200 U	77.1	40/NA	–	–	+36, 100 U* +36, 150 U* +47, 200 U*	+6, 100 U* –29, 150 U* –21, 200 U*	–	–	3 mo (study) Benefit: 6.7 mo, 300 U* 5.5 mo, 200 U* 3.5 mo, 100 U* Duration shorter with 100 U*	2b
Lucioni et al [51]	40	Trigone vs nontrigone	63	–/–	–	–	–	–	–	26.5 trigone 23 nontrigone	3 mo (study)	3
Schmid et al [15]	100	Botox 100 U	88	NA/–86	–50	82, no urgency	+56	–	–74	–	9 mo (study)	3
Kalsi et al [34]	16*	Botox 200 U	–	NA/–83	–33	–68	+242	–89	–	72	4 mo (study)	3
Kalsi et al [35]	38	Botox 200 U	73 (ITT analysis)	NA/–35	–18.2	–28.1	+46	–9	–	–	4 mo (study) 10.4 mo (benefit)	3
Popat et al [13]	31*	Botox 200 U	–	57.3/NA	–36.3	–50.7	+111	–24.5	–	–	4 mo (study)	3
Smith et al [29]	17	Botox 100–300 U	50 excellent	NA/–87	–40	–	+61	0	–	–	6 mo (study)	3
Smith et al [58]	10	Botox 100 U	80	NA/NA	–	–	–	–	–	–	3–6 mo (benefit)	3
Schulte-Baukloh et al [56]	44	Botox 200–300 U	86	NA/–43	–13	–	+34	–	–	UDI-6: 28	9 mo (study) 6 mo (benefit)	3
Kessler et al [28]	11	Botox 300 U	–	91/NA	–63.6	–	+54.5	–35.5	–	–	5 mo (benefit)	3
Rajakumar et al [49]	15	Botox 300 U	–	54.5/NA	–60	–	+16.8	–	40	32	9 mo (study) 6 mo (benefit)	3
Schulte-Baukloh et al [57]	7	Botox 300 U	71.4	NA/–64	–18	–	+14	–	–	42	6 mo (study)	3
Kuo et al [30]	20	Botox 200 U	85	45/NA	–	–	+40	–28	–65	–	6 mo (study)	3
Werner et al [55]	26	Botox 100 U	60	80/NA	–35	–	+58	–	–60	–	9 mo (study)	3
Rapp et al [14]	35	Botox 300 U	58	–54 (pads: no)		–		–	–	24	6 mo (study)	3
Kuo [26]	18	Botox 200 U	78 excellent or improved	39/NA	–	–	+11*	–35*	–	51*	5.3 mo (benefit)	3
Flynn et al [48]	7	Botox 150 U	64	NA/NA	–12	–	–	–	–	77	6 mo	3
Mean			69	58/–65	–35.5	–49.9	+65.5	–32.4	54.1	47.9	6.2 mo (benefit)	–

Despite heterogeneous designs, all single-injection studies showed significant improvements in a variety of outcomes concerning symptomatology, urodynamics, and QoL. The LoE for a beneficial effect of BoNTA in idiopathic DO (IDO) is at 1b.

MCC = maximum cystometric capacity; $Pdet_{max}$ = maximum detrusor pressure; DO = detrusor overactivity; QoL = quality of life; LoE = levels of evidence; NA = not applicable; suburo = suburothelium; UDI-6 = Urinary Distress Inventory short form; ITT = intent to treat.

* Results not analysed separately for IDO or NDO and not included in analysis of means.

† Patients included in Kalsi et al [35].

studi su trattamento con tossina botulinica nella *vescica iperattiva*
(Eur Urol 2009; 55:100-120)

Criticità

- ***Efficacia a lungo termine?***
- ***Tossicità?***
- ***Detrusore?***
- ***Compliance?***
- ***Costi***
- ***Farmaco con indicazioni diverse***

Use in the lower urinary tract

- *Detrusor –sphincter dyssynergia*
- *Bladder pain syndrome/i.c.*
- *BPH associated with LUTS*
- *Pelvic-floor disorders*
- *Detrusor injection in children*
- *Prostatitis*
- *Urethral stricture*

La terapia endoscopica con Botulino nella vescica iperattiva

Recommendations on the use of BoNTs in the treatment of intractable symptoms of LUT and pelvic-floor disorders	Grade
NDO	
Use BoNTA to treat refractory NDO in patients willing to use CISC.	A
The aim of the treatment is to improve symptoms, urodynamic risk factors for renal impairment, or quality of life in patients with spinal NDO.	A
The diagnosis of NDO should follow the EAU guidelines (ie, urodynamic assessment is mandatory).	A
Patients should be told the treatment does not last indefinitely but should have a mean duration of 8 mo.	A
Repeated treatment has been shown to be efficacious.	B
IDO/OAB	
Use BoNTA to treat refractory IDO in patients willing to use CISC.	A
Use caution because the risk of voiding difficulty as well as the duration of effect has not been accurately evaluated to date. Future studies should address the benefit–risk ratio for the best minimal dosage.	
All patients should accept in writing the possible need to perform CISC following treatment.	A
Residual volumes should be measured regularly for the first month starting at the first week.	A
Patients should be told that the treatment does not last indefinitely but has a mean duration of 6 mo.	A
Comparison of injection techniques	
The dilution of Botox should be 10 U/ml per site; thus, the number of injection sites depends on the total dosage being administered (ie, 30 sites for a dosage of Botox 300 U in NDO). The optimum dose for dilution of Dysport has yet to be established.	B
The choice of flexible or rigid cystoscope should be left to local expertise.	C
The depth and location for injections should be within the detrusor muscle outside the trigone.	C
Detrusor injections in children	
Dose range should be determined by body weight: 5–10 U/kg body weight up to a maximum dosage of Botox 300 U has been shown to be effective and safe. Caution is recommended for the total dosage in children also treated for spasticity.	B
A minimum age of 3 yr is suggested because there are little data for younger ages.	C
Other recommendations follow adult NDO indications.	A
BoNTA sphincter injections	
There is LoE 1b for the use of BoNTA in DSD in neurogenic patients, but the clinical value of this has to be studied further before a recommendation can be made.	–
If injection is done, Botox 100 U in 4 ml should be used.	C
Further studies in adults with voiding dysfunction of non-neurogenic origin are needed.	A
Before its use in children is recommended, the longer term clinical value needs to be assessed.	–
BPS	
In the absence of placebo-controlled data in the indication of BPS, it is impossible to recommend the use of BoNTA despite results from open-label studies.	–
Patients should be warned of the possible need to perform CISC or of worsening pain.	C
BPH associated with LUTS	
Currently, there is insufficient data to recommend this promising treatment for use of BoNTA for bladder-outlet obstruction due to BPH indication.	–
Further placebo-controlled studies are needed.	A
Pelvic-floor disorders	
Insufficient evidence exists on which to base clinical advice.	–
There is a need for robust clinical trials to prove that this agent is truly efficacious in this disparate group of patients.	A
Safety in urological applications	
BoNT can be used in the LUT with the current dosages and techniques; the clinical results show that it is safe overall. Side-effects have been reported, mostly at a low incidence.	A
Further follow-up of safety is necessary because BoNT in other applications has been shown to have histologic, autonomic, and other secondary effects. Similar studies are also needed in urologic treatment.	A
Patients treated for DO should accept beforehand the possible need to perform CIC because increase of residual/retention is the most frequent complication.	A

The highest grade of recommendation was given for the use of BoNTA in NDO and IDO refractory to oral pharmacotherapy in patients willing to perform CISC if needed as well as for the overall clinical safety of the treatment under the currently used dosages and techniques. No recommendations could be made for the use of BoNTs in urethral sphincter disorders, BPS, benign prostate diseases, and pelvic-floor disorders, as the available data were considered inconclusive. Large placebo-controlled and comparative trials are needed in all aspects of BoNT use in the LUT and the pelvic floor.

NDO = neurogenic detrusor overactivity; BoNTA = botulinum neurotoxin type A; DO = detrusor overactivity; CISC = clean, intermittent self-catheterisation; EAU = European Association of Urology; IDO = idiopathic detrusor overactivity; OAB = overactive bladder; LoE = level of evidence; DSD = detrusor-sphincter dyssynergia; BPS = bladder pain syndrome; BPH = benign prostatic hyperplasia; LUTS = lower urinary tract symptoms; CIC = clean intermittent catheterisation.

EVIDENCE SYNTHESIS:

The use of ***botulinum toxin*** type A is recommended in the treatment of intractable sypmtoms of **neurogenic detrusor overactivity** or **idiopathic detrusor overactivity** in adults (grade A)

grazie per l'attenzione!