NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Post stroke spasticity service Use of Botulinum Toxin A

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Does this version include changes to clinical advice:	N/A
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Approval Group:	Medicines Utilisation Subcommittee of ADTC

Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

NHS Greater Glasgow and Clyde		**NHS Greater Glasgow and Clyde** **Post stroke spasticity service** **Protocol for use of Botulinum toxin A**
Background:		Spasticity is part of the upper motor neurone syndrome and is common in conditions affecting the brain and spinal cord such as cerebral palsy (CP), acquired brain injury (ABI), stroke (CVA), multiple sclerosis (MS), hereditary spastic paraparesis (HSP) and spinal cord injury (SCI). Botulinum toxin A is a recognised treatment for focal spasticity as well as dystonia. It may be required to prevent loss of function, secondary complications, help manage pain or before rehabilitation goals can be met.
Agent and route:		Three preparations are available: • Botulinum toxin A – Botox® • Botulinum toxin A – Xeomin® • Botulinum toxin A – Dysport® Botulinum toxin A is given via an intramuscular injection using Electromyography (EMG), ultrasound or clinical anatomy.
License status:		All three brands of Botulinum toxin A are licensed for hand and wrist disability, associated with stroke spasticity. Dysport and Botox are licensed for ankle disability due to lower limb spasticity associated with stroke but this is not recommended for routine use by the Scottish Medicines Consortium (SMC) and is out with the scope of this guideline. Xeomin is not licensed for lower limb use. None of the brands of Botulinum toxin A are licenced for muscles around the elbow, shoulder, knee, and hip that are affected with post stroke spasticity and therefore use is “off label” or unlicensed. These “off label” uses, however, are very well established in clinical practice over many years. This protocol has been devised to cover the use of Botulinum toxin A in unlicensed indications in the stroke spasticity service and in the rare occasion a patient presents with spasticity resulting from comorbidities e.g., someone with stroke and multiple sclerosis where the use of botulinum toxin is unlicensed.
Indications for use		People with persistent or progressive focal spasticity after stroke affecting one or two areas for whom a therapeutic goal can be identified should be offered intramuscular botulinum toxin (RCP, 2016). Botulinum toxin A has been shown to provide a sustained reduction in post stroke spasticity (RCP, 2018).

		Intramuscular botulinum toxin A injections are the pharmacological treatments of choice for focal spasticity. It is not uncommon to have a mixed pattern of both focal and generalised spasticity and in practice interventions are often combined e.g., botulinum toxin A may be given to target a specific problem while baclofen is prescribed to manage a background of spasticity (RCP, 2018)
Treatment goals:		Patients will have a thorough and detailed assessment documented prior to receiving treatment. Outcome measure and SMART goals are recorded and reviewed within a month of treatment. Future treatment will be planned in accordance to goals. Treatment will be discontinued if goals are not achieved or if no response (as below).
Authorised and designated areas applicable to:		Patients may be treated within inpatient or outpatient settings in NHS GGC under the stroke spasticity service.
Dose, duration, dilution and administration:		The total maximum dose, as suggested by RCP guidelines or SPC for each preparation per treatment session in is as follows: **Xeomin**: Upper limb: 500 units Lower limb*: 500 units **Botox:** Upper limb: Botox 360 units Lower limb*: 400 units **Dysport:** Upper limb: 1000 units Lower limb*: 1500 units Dysport and Botox are licensed for ankle disability due to lower limb spasticity associated with stroke but this is not recommended for routine use by the Scottish Medicines Consortium (SMC) and is out with the scope of this guideline. Xeomin is not licensed for lower limb use. Treatment should be started at a low dose to minimise side effects. If an inadequate response is observed, consider a higher dose at next treatment. If a higher dose fails to produce an adequate response, consider switching to alternative brand if treatment is still appropriate. If there are 2 failed responses then the failure protocol as described by Kessler et al (1997) or Hanna et al (1999) (See under references). Injections should be given in one session and re-injections should occur no sooner than 12 weeks after the previous session.

		Refer to RCP guidelines (see under references and Appendix 1) or Delphi Panel guidance for suggested muscle dosing regimes (see under references and Appendix 2).
Potential side effects:		<u>Local and distant spread of toxin effect</u> Spread of toxin distant from the site of administration has been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility. Patients treated with therapeutic doses may also experience exaggerated muscle weakness. Dysphagia has also been reported following injection to sites other than the cervical musculature. <u>Patients with pre-existing neuromuscular disorders</u> May have an increased sensitivity to agents such as Botulinum Toxin A, which may result in excessive muscle weakness and an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise. <u>Hypersensitivity reactions</u> If serious (e.g., anaphylactic reactions) and/or immediate hypersensitivity reactions occur, appropriate medical therapy should be instituted. <u>Antibody formation</u> Too frequent doses may increase the risk of antibody formation, which can result in treatment failure. The potential for antibody formation may be minimised by injecting with the lowest effective dose at the longest intervals between injections as clinically indicated. <u>Procedure-related injury</u> Could occur such as localised infection, pain, inflammation, paraesthesia, hypoesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g., syncope, hypotension, etc. Flu like symptoms have also been reported in some patients.
Contraindications for use:		•The presence of infection or inflammation at the proposed injection site. • Under active treatment with antibiotic therapy due to infection. • If the tissue is contracted with no spasticity. • Avoid use in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. Myasthenia Gravis or Lambert-Eaton Syndrome.

		• Patients who are currently breast feeding.
Cautions for use:		<u>General</u> Should be used with caution: • in pregnancy (the benefit must outweigh the risks) • if bleeding disorders of any type occur If the patient is taking warfarin then the INR should be taken prior to the day of treatment and be ≤2.5 on day of injection. If patients target INR needs to be higher than this then liaise with anticoagulation clinic/Haematology. If the patient is taking other anticoagulants (such as apixaban, rivaroxaban, dabigatran), they would continue to take their normal dose. For these patients and those on warfarin with a satisfactory INR, half the volume of saline should be used to dilute the mixture i.e., 100 units mixed with 1 ml saline and the minimal number of injection sites used. <u>Pre-existing neurological conditions</u> Should only be used with extreme caution and under close supervision in patients with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy) and in patients with underlying neurological disorders. Patients with a history of dysphagia, aspiration or breathing difficulties should be treated with extreme caution. In these patients, treatment must be administered only if the benefit of treatment outweighs the risk. Caution is warranted when injecting in proximity to the lung (particularly the apices) or other vulnerable anatomic structures. Elderly and debilitated patients should be treated with caution. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range. Careful consideration should be given before the injection of patients who have experienced a previous allergic reaction to a product containing botulinum toxin type A. The risk of a further allergic reaction must be considered in relation to the benefit of treatment.
Authorised users:		Dr Niall Hughes, Stroke Consultant Patricia Creelman, Advanced Practitioner Physiotherapist / NMP

		Susie Hughes, Specialist Orthotist under a Patient Group Direction (PGD).
Authorised for storage in clinical areas:		Botulinum toxin A should be signed out via the toxin register stored within the controlled drugs cupboard in Day Hospital, Langlands Building, QEUH.
References:		ROYAL COLLEGE OF PHYSICIANS 2018. *Spasticity in adults: management using botulinum toxin*. London. [viewed 21st February 2021]. Available from: http://www.rcplondon.ac.uk ROYAL COLLEGE OF PHYSICAINS 2016. National clinical guideline for stroke. London. [viewed 21st February 2021]. Available from: https://www.strokeaudit.org/Guideline/Full-Guideline.aspx ESQUENAZI, A., ALFARO, A., AYYOUB, Z., CHARLES, D., DASHTIPOUR, K., GRAHAM, G., McGUIRE, J., ODDERSON, I., PATEL, A. & SIMPSON, D., 2017. OnabotulinumtoxinA Injections for Lower Limb Spasticity: Guidance From a Delphi Panel Approach. *American Academy of Physical Medicine and Rehabilitation*. **9,** pp. 960-968. [viewed 15 July 2020]. Available from: http://dx.doi.org/10.1016/j.pmrj.2016.06.016 SIMPSON, D., PATEL, A., ALFARO, A., AYYOUB, Z., CHARLES, D., DASHTIPOUR, K., ESQUENAZI, A., GRAHAM, G., McGUIRE, J. & ODDERSON, I., 2017. OnabotulinumtoxinA Injection for Poststroke Upper-Limb Spasticity: Guidance for Early Injectors From a Delphi Panel Process. *American Academy of Physical Medicine and Rehabilitation.* **9,** pp. 136-148. [viewed 15 July 2020]. Available from: http://dx.doi.org/10.1016/j.pmrj.2017.02.014 TRUONG, D., HALLETT, M., ZACHARY, C. & DRESSLER, D., 2014. *Manual of Botulinum Toxin Therapy second edition.* Cambridge: Cambridge University Press. HARDING, P., HICKLIN, D., LINDSAY, C., MAYBURY, M., JONES, C., MASON, S. 2013. *Botulinum Toxin injections workbook*. Edition 1, First Printing, UK. WOLFGANG, J., 2012. *Pictorial Atlas of Botulinum Toxin injection: dosage, localisation , application. Second edition,* Quintessence Publishing Co. Ltd, UK. HANNA, P., JANKOVIC, J., & VINCENT, A.,1999. Comparison of mouse bioassay and immunoprecipitation assay for botulinum toxin antibodies. *Journal of Neurology and Neurosurgical Psychiatry*. **66**, pp. 612-616. KESSLER, K. & BENECKE, R., 1997. The EBD test- a clinical test for detection of antibodies to Botulinum Toxin type A. *Movement Disorders*. **12**(1), pp. 95-99. Botox, Xeomin and Dysport SPC https://www.medicines.org.uk/emc/
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Appendix 1 - RCP guidelines dosing

Upper Limb	Botox/Xeomin* (U)	Dysport (U)
Pectoral girdle		
Trapezius	50-75	200-300
Rhomboid	50-60	200-250
Supraspinatus	40-50	160-200
Infraspinatus	50-60	200-200
Subscapularis	50-80 (B)	200-320
	15-100 (X)	
Deltoid	50-75 (B)	200-300
	20-150 (X)	
Shoulder		
Pectoralis major	75-100 (B)	300-400
	20-200 (X)	
Pectoralis minor	40	150-160
Latissimus dorsi	60-80 (B)	240-320
	25-150 (X)	
Teres major	30-50 (B)	120-200
	20-100 (X)	
Teres minor	30-50	120-200
Serratus anterior	60-70	250-270
Coracobrachialis	30-50	120-200
Elbow flexors		
Biceps brachii	75-100	100-300
Brachialis	50-75	200-400
Brachioradialis	50-60	200-240
Forearm		
Pronator quadratus	20-30	75-120
Pronator teres	30-40	120-160
Supinator	30-40	120-160
Wrist flexors		
Flexor carpi radialis	30-40	120-160

Flexor carpi ulnaris	30-40	120-160
Finger flexors		
Flexor digitorum superficialis	25-30	100-120
Flexor digitorum profundus	30-40	120-160
Thumb flexors		
Flexor pollicus longus	20-30	75-120
Flexor pollicus brevis	(SPC 5-30)	-
Opponens pollicis	(SPC 5-30)	-
Adductor pollicis	20-40	75-100
Elbow extensors		
Triceps	75-100	300-400
Wrist extensors		
Extensor carpi ulnaris	30-40	120-160
Extensor carpi radialis longus	30-40	120-160
Extensor carpi radialis brevis	20-30	75-120
Finger extensors		
Extensor digitorum communis	30-40	120-160
Extensor digiti minimi	30-40	120-160
Extensor indicis	20-30	75-120
Thumb extensors		
Extensor pollicis longus	20-30	75-120
Extensor pollicis brevis	20-25	75-100

*Dysport and Botox are licensed and ankle disability due to lower limb spasticity associated with stroke but this is not recommended for routine use by the Scottish Medicines Consortium (SMC) and is out with the scope of this guideline. Xeomin is not licensed for lower limb use. Botox and Xeomin have the same dose range.

Lower limb	Botox/Xeomin* (U)	Dysport (U)
Hip flexors		
Psoas major	100-200	600-800
Iliacus	75-150	200-400
Lateral verterbral column flexion		
Quadratus lumborum	100	400

Hip adductors		
Adductor magnus,	100-200	400-750
Adductor longus,	(between whole	(between whole
Adductor brevis	Adductor group)	Adductor group)
Gracilis	80-120	300-400
Pectineus	50-100	200-400
Internal rotation of hip		
Gluteus maximus	-	-
Gluteus medius	100	400
Gluteus minimis	-	-
Knee flexors		
Semitendinosus,	100-150	400-600
Semimembranosus	100-150	400-500
Biceps femoris long head and short head	100-150	400-600
Popliteus	25-30	100-120
Knee extensors		
Rectus femoris	100-150	400-500
Vastus medialis, intermedius and vastus lateralis	100-150	400-500
Sartorius	-	-
Foot		
Tibialis anterior	75-120	300-400
Peroneus tertius	30-40	120-150
Peroneus longus	50-80	200-320
Peroneus brevis	30-40	120-160
Extensor digitorum longus*	50-75 (B) 50-80 (X)	200-300

Extensor hallucis longus	50-60	200-250
Flexor hallucis brevis	10-20	40-80
Adductor Hallucis	10-20	40-80

* Xeomin doses same as Botox unless stated

Appendix 2

Delphi panel approach to treating most common UL postures:

UL posture;	Muscles	Dose range (U)	Total dose used (U)
Adducted	**Pectoral complex**	75-100	100-200
and IR shoulder	**Latissimus Dorsi**	75	
	Teres Major	50-75	
	Deltoid	20	
	Brachialis	75	
	Levator scapulae	30	
Flexed elbow	**Brachioradialis**	25-50	100-150
	Biceps	0-50	
	Brachialis	50-100	
	Pronator teres	38-100	
Pronated forearm	**Pronator quadratus**	0-25	50-100
	Pronator teres	45-60	
	Flexor carpi radialis	20	
	Brachialis	100	
	Brachioradialis	25	
Flexed wrist	**Flexor carpi radialis**	50-75	60-100

	Flexor carpi ulnaris	25-50		
	Palmaris longus	13-50		
	Flexor pollicis longus	20-75		
	Flexor digit superficialis	25-75		
	Flexor digit profundus	25-75		
Flexed fingers	**Flexor digit superficialis**	20-60	50-100	
	Flexor digit profundus	25-75		
	Flexor carpi radialis	30		
	Flexor carpi ulnaris	30		
	Lumbricals	30		
Thumb-in-palm	**Flexor pollicis longus**	40-50	50-75	
	Adductor pollicis	10-20		
	Flexor pollicis brevis	12.5-20		
	Flexor digit profundus	35		

Delphi panel approach to treating most common LL postures:

LL posture;	Muscle	Dose range (U)	Total dose (U)
Adducted thigh	**Adductor magnus**	75-150	150-200
	Adductor longus	75-80	
	Adductor brevis	20-25	
	Gracilis	25-40	
	Iliopsoas	25-150	
	Medial hamstrings	50	
Flexed knee	**Medial hamstrings**	125	100-200
	Lateral hamstrings	75	
	Iliopsoas	40-150	
	Tensor fascia lata	25-150	
	Medial Hamstrings	50	
Extended knee	**Rectus femoris**	80-125	125-200
	Vastus lateralis	50-70	
	Vastus medialis	50	
	Vastus intermedialis	35-75	
	Gluteus maximus	40	
Equinovarus foot	**Tibialis posterior***	100	250-300
	Tibialis anterior	75	
	Extensor hallucis longus	13-50	
Plantar flexed foot			
	Long toe flexors	20	
Striated toe	Extensor hallucis longus	50	50

	Extensor hallucis longus (motor point)	38
	Flex digit longus*	25-30
Flexed toes		
	Flexor hallucis brevis*	13