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Management of status dystonicus in children and adolescents

Introduction

This guideline contains information regarding the identification and management of the potentially life-threatening condition of status dystonicus with the aim of improving the diagnosis and management of status dystonicus in children and adolescents.

Background

Dystonia is defined as the sustained involuntary contraction of muscles leading to abnormal postures and movements. It usually affects multiple muscle groups (generalised) but may be limited to a few (focal). Children with cerebral palsy (a static injury to the antenatal or infant brain) are the commonest group of children with dystonia. Children with any illness or injury affecting the brain are at risk of dystonia.

Status dystonicus is a severe and potentially life-threatening condition comprising of increasingly frequent and severe episodes of generalised dystonia which requires urgent (hospital) management. Status dystonicus usually occurs in a child who is already known to have dystonia, although new-onset cases are reported.

Status dystonicus may present with one or more of the following complications:

- Elevated body temperature
- Pain / discomfort
- Exhaustion from sleep deprivation and exertion
- Rhabdomyolysis leading to myoglobinaemia and raised Creatine Kinase (CK)
- Dehydration with electrolyte disturbance from excess sweating
- Acute renal failure because of myoglobinuria / dehydration
- Bulbar dysfunction with risk of aspiration
- Respiratory failure
- Death

Diagnosis

Status dystonicus is a clinical diagnosis based on the identification of severe, generalized dystonic movements. Diagnosis should also involve identification of associated comorbidity (bulbar and respiratory difficulties, metabolic derangements, exhaustion and pain).

Note: Creatinine kinase (CK) is an enzyme that is released by damaged muscle in status dystonicus and can be measured in blood samples. Presence of significantly elevated CK supports a diagnosis of status dystonicus. However, CK can take 24 hours to become elevated in blood, and therefore a normal CK value does not exclude status dystonicus. For the same reason, CK should not be used in isolation to grade severity of status dystonicus.

Investigations:

The following investigations are used to monitor complications of status dystonicus and should be conducted in every child presenting with grade 3 - 5 severity:

- Creatine Kinase (repeated 24 and 48 hours later as CK rise may take 24hrs)
- Renal function (urea and electrolytes)
- Liver function testing, Lactate
- Calcium, magnesium, phosphate
- Capillary blood Gas
    - Monitor urine output.
    - Daily weight

Status dystonicus is precipitated by a trigger in approximately 2/3 of cases. Identification (through history and relevant testing) and management of a trigger is helpful in managing symptoms. Triggers can include:

- Intercurrent illness (especially gastroenteritis with dehydration, upper and lower respiratory tract infections, urinary tract infection)
- Pain / discomfort from any source, including constipation, urinary retention, gastro-oesophageal reflux, dental caries/ulcers, dislocated hip
- Recent anaesthesia
- Recent surgical procedures
- Change / omission of usual medication therapy
- Emotional factors such as stress

In children presenting with status dystonicus with no prior dystonia, investigations should be led by paediatric neurology advice and should include imaging of the brain.

Dystonia can be graded in terms of the following:

Principles of management are based on the level of severity as below (also see Appendix 2):

Dystonia Severity Scale[ii]	Assessment	Plan
Grade 1: **The child sits comfortably and has regular periods of uninterrupted sleep. Child stable on medication.**	Nil needed	Continue as normal
Grade 2: **The child is irritable and cannot settle.** **Dystonic posturing interferes with sitting activities.** **The child can only tolerate lying despite usual baseline medication.**	R/V in next few days	Treat underlying causes. Adjust their usual dystonia medications
Grade 3: **Child unable to tolerate lying and/ or unable to get to sleep or sleep disturbed** **No evidence of metabolic decompensation, with creatinine kinase (CK) <1000 IU/L.**	Urgent assessment, including finding triggers	Treat underlying causes. Further adjustments to their usual dystonia medication. Blood screen required to look for signs of decompensation (including renal function, CK); Observe in hospital; be prepared to escalate management. Ensure adequate hydration (commence intravenous hydration if in doubt). Failure to improve despite above escalations warrants management in HDU setting.
Grade 4: **Early multi-organ failure:** **Clinically as above with:** **- Pyrexia** **- Evidence of metabolic compromise (e.g. acidosis, elevated potassium, low calcium, evidence of rising creatinine and/or urea)** **- Evidence of myoglobinuria, CK >1000 IU/L.**	Emergency hospital admission for organ support and to prevent renal failure and other complications. Need HDU and prepare for PICU if worsening.	Treat underlying causes. Regular (4hourly at least) bloods for CK, renal and liver function Nasogastric, gastrostomy or rectal medication (see below) if tolerated and working, otherwise intravenous medication. Intravenous fluid support. **It is essential that all children in grade 4 are discussed with PICU as soon as possible**
Grade 5: **Immediate life-threatening: as above with:** **Full metabolic decompensation** **Respiratory, cardiovascular or renal compromise.** **Requires intensive care.**	Need HDU or PICU	Treat underlying causes. Consider need for : >IV Infusion of clonidine and/or midazolam >Dialysis/ haemofiltration > Invasive ventilation

		>Intrathecal baclofen LP dose or infusion

Management of Status Dystonicus in Childhood

Definition of SD: Increasingly frequent or continuous of generalised dystonic spasms requiring urgent hospital management. Represents the severe end of a spectrum of worsening dystonia. Early recognition of deterioration and timely intervention likely to improve outcomes.

Dystonia Severity Action Plan (DSAP): Staging the severity of worsening dystonia

Stages	Description	Suggested Action
1	Sits comfortably, Regular sleep, Stable on Medication	No assessment or change in medications required
2	Irritable and cannot settle Posturing interferes with seating activity Cannot tolerate sitting down despite baseline medication	Assessment (within days) Adjust medication or dystonia plan
3	Cannot tolerate lying down Sleep disturbed No signs of metabolic disturbance or airway compromise	Urgent assessment Exclude metabolic decompensation Escalate management +/- hospital admission
4	Clinically as in Grade 3, but with metabolic disturbance: fever, dehydration, abnormal electrolytes, CK >1000 IU/L, myoglobinuria	Emergency hospital admission for multisystem support
5	Severe generalised dystonia. As Grade 4 with full metabolic decompensation or respiratory-cardiovascular compromise requiring organ support	Child requires HDU/PICU care

Status Dystonicus – DSAP Grade 4-5

Supportive Care

- Urgent admission to High Dependency Area
- Identify and treat triggers
- IV hydration/hyperhydration
- Antipyretics
- Analgesia (opioids may be required)
- Close biochemical Monitoring (CK, renal, other parameters)
- General comfort and sleep•
- Respiratory/Airway support (elective Intubation may in extreme cases be required)
- Cardiovascular support (dysautonomia common feature)
- Psychological/Counseling support for child and carers

Temporising Measures

1st Line:

- Sedative hypnotic (sleep)e.g. enteral chloral hydrate 30-100mg/kg q 3–6 hourly to achieve sleep
- Non-respiratory depressant e.g. enteral or IV clonidine

Additional Agents:

- IV midazolam 30 to 100µg/kg/hr (tolerance may develop quickly)

General anaesthesia in extreme cases

See page 5 for more detailed information.

Dystonia-Specific

Pharmacological:

Choice of agent depends upon child's background medication.

Medications to consider include: Trihexyphenidyl, baclofen, benzodiazepine, gabapentin, l-dopa, Tetrabenazine, haloperidol

Polypharmacy may be required

Neurosurgical:

Considered in refractory presentations or when sedative medication weaning is not possible **ITB. DBS, Pallidotomy**

References:
Allen N, et al "Status Dystonicus: A Practice Guide" Dev Med Child Neurol 2014:56:105-112

Dr Daniel E Lumsden – Sept 2015

Treatment/Management

In any patient who has an intrathecal baclofen (ITB) pump, ITB withdrawal should be presumed to be the cause of an acute presentation with status dystonicus (pump malfunctioning / empty reservoir). Discuss with the on-call paediatric neurology consultant at the earliest oppurtunity.

Additional notes with reference to the management:

- **IV fluids**

Increased insensible losses through sweating can rapidly lead to dehydration and maintenance fluids may need to be increased by an additional 5-20% each day to compensate for increased insensible losses. Electrolytes should be measured regularly.

- **Positioning and handling**

Positioning (especially adopting a 'flexed' posture) can be useful in 'breaking' the spasms in some children and nursing and physiotherapy input may provide additional strategies to improve spasm-free periods and sleep. In some children, dystonia may be exacerbated by handling and this should be minimised to necessary cares.

- **Address emotional / behavioural /psychological contributing factors**

Many children with dystonia may be quite physically disabled but with intact cognition. In some of these children psychological / emotional factors can further aggravate their underlying dystonia. This should be considered and appropriate support provided.

- **Specific therapy for severe and or progressive rhabdomyolysis**

Consider the following: urine alkalinization, dantrolene, neuromuscular paralysis, and/or dialysis in acute renal failure

- **Intrathecal Baclofen (ITB) and Deep Brain Stimulation (DBS)** should be discussed as potential options of treatment in refractory status dystonicus.

Remember:

- Different children may have greater / lesser response to certain agents so often have a tailored management plan
- If in doubt about any of the above discuss with a senior and/or the on call paediatric neurology consultant

- Please be aware that once a child or young person has had successful treatment for severe (grade 4/5) status dystonicus they remain acutely unwell with a high risk of respiratory, cardiovascular and renal instability and re-emergence of status dystonicus. It is vital that these individuals are very closely monitored and there is a low threshold for transfer to HDU / PICU

Appendix 1:

Name of Medication	Comments
Baclofen	GABAnergic agent. Poorly crosses the blood brain barrier (BBB), and so higher doses may be required. Side effects commonly include sedation and nausea. Has additional beneficial effect in reducing spasticity (more common usage). Bulbar function may also be adversely affected by baclofen. Can be delivered intrathecally to bypass issues with crossing BBB.
Benzodiazepines (e.g. diazepam, midazolam, lorazepam)	GABAnergic agent. Depending on preparation, can be given enterally, rectally, bucally and intravenously. Acute side effects include sedation, respiratory suppression and increased drooling. Dependency develops with regular use, and so slow wean required to avoid symptoms of withdrawal. Tolerance to dosage also builds over time. Most useful as short term treatment around acute worsening of dystonia (e.g. around time of orthopaedic surgery).
Chloral Hydrate	Acute sedative agent, used as a PRN agent for troublesome dystonia. Can be delivered enterally or rectally (though rectal use rapidly results in mucosal irritation) Side effects include drowsiness, gastric irritation, respiratory depression. Dependency develops with regular use, and so slow wean required to avoid symptoms of withdrawal. Tolerance to dosage also builds over time.
Clonidine	Centrally acting adrenergic agent. Can be delivered enterally, intravenously or transdermally (1:1:1 dose ratio). Role in acute dystonia as benzodiazepine sparing sedative agent. Side effects include dizziness, sedation, headaches and bradycardia (particularly) with higher doses. If used for >2 weeks, weaning required (over 5 days)

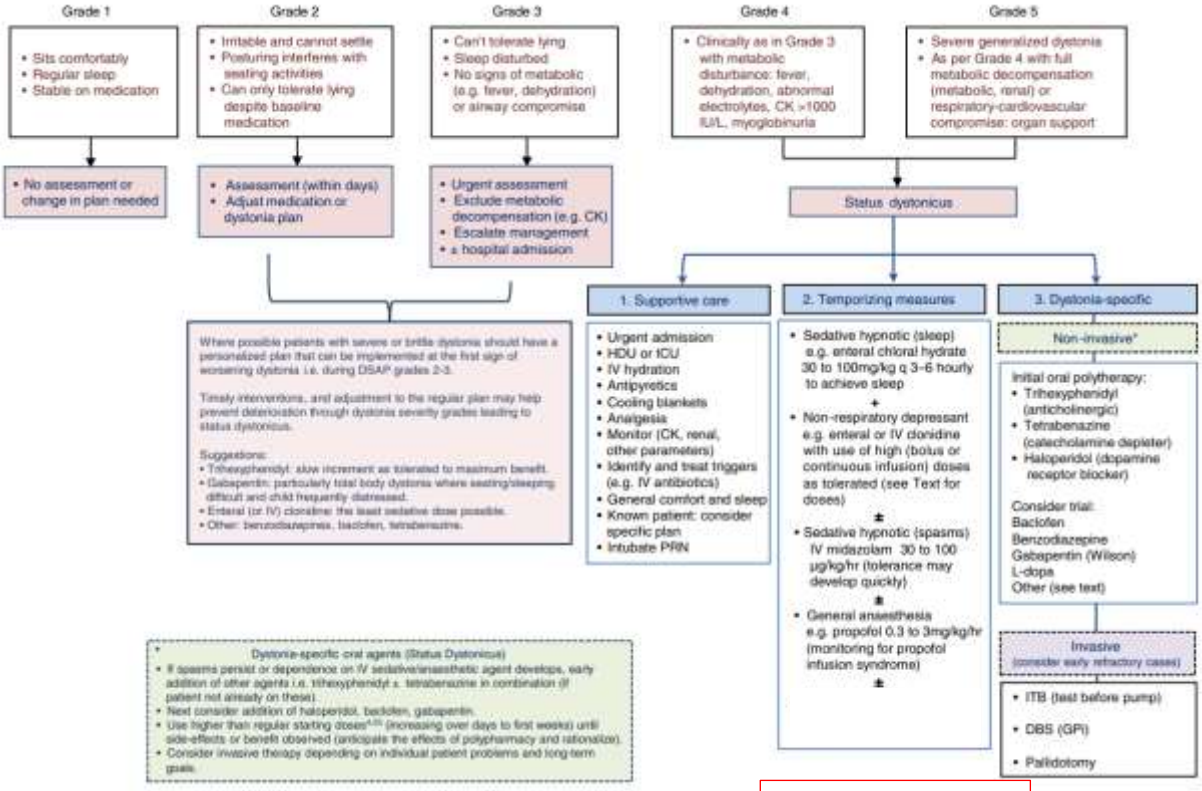
Gabapentin	GABAnergic agent. Can be delivered enterally. Potentially most useful when pain significant feature of dystonia (with particular evidence of efficacy in neuropathic pain). Side effects include tiredness, dizziness, GI upset, behavioural change, respiratory depression with high doses. Class C substance in UK from 2019.
Trihexyphenidyl	Anticholinergic agent. Strongest evidence base for use in childhood dystonia. Side effects include dry mouth, blurred vision, constipation and urinary retention. May be better tolerated in younger children and with slower dose escalation. Depression may also be seen. Once maximum dose reached, maintain for 3 months and review response.
L-DOPA	Precusor of dopamine, central neurotransmitter. Significant side effects include nausea, which may limit dosage. Must be stopped for a minimum of 72 hours prior to CSF neurotransmitter metabolite analysis, unless analysis aimed at monitoring efficacy of treatment in children, e.g. with a diagnosis of tyrosine hydroxylase deficiency. More limited benefit in other causes of dystonia, e.g. DCP

Note - the below is a combination of BNF dosing + GOSH status dystonicus guideline dosing regime, however in acute setting on-call paediatric neurologist may chose to escalate at a quicker rate)

Drug	**Doses**	**Side Effects to look for**
Baclofen	ORAL: initially 300 micrograms/kg daily in 4 divided doses, increased gradually at weekly intervals until satisfactory response; usual maintenance dose of 0.75–2 mg/kg daily in divided doses; Child up to 8 years max. total daily dose 40 mg/day, Child 8–18 years max. total daily dose 60 mg/day; review treatment if no benefit within 6 weeks of achieving maximum dose. (Baclofen is given intrathecally via an intrathecal pump in some patients).	Drooling, drowsiness, loss of head control, respiratory muscle weakness, urinary retention, constipation, irritability, weakness, sleep disturbance, appetite change
Chloral hydrate	ORAL or PR: 30-50mg/kg 4-6 times per day increasing if necessary up to 100mg/kg (max 1g/dose) tds (can be given rectally) Maximum daily dose 200mg/kg. In status dystonicus total daily dose can be divided and given 4-6hrly	Sedation, Respiratory depression, Gastric irritant, Rash, Headache Ketonuria Eosinophilia, low WCC
Clonidine	ORAL: Child 2–17 years Initially 0.2 –1microgram/kg 3 times a day, then increased if necessary up to 25 micrograms/kg daily in divided doses, increase dose gradually; maximum 1.2 mg per day Increased every 5-7 days as required IV: As an infusion (doses of 0.25–2.0 micrograms kg/hr), with consideration of higher or bolus doses as tolerated Transdermal patch: dosing is equivalent to enteral dosing. Patches changed weekly and available as following strengths: • 2.5mg (100microrgams/24hr) patch • 5mg (200micrograms/24hr) patch • 7.5mg (300micorgrams/24hr patch) Can apply multiple patches for higher doses. Can be converted from enteral or IV (please refer to APPM fomulary or seek guidance from pharmacist / neurologist) or can be started directly with option for gradual increasing dose by occluding a portion of the patch from contact with skin (e.g. ¼ in contact with skin, ¾ occluded)	Hypotension (monitor BP when starting and titrating), drowsiness. Avoid acute withdrawal. In addition, transdermal patches may cause skin irritation. May use budesonide spray or topical steroid cream before application and after patch removal to treat this. Rotating patch site is advised. Transdermal patch is not recommended for management of status dystonicus. Infusion only to be used in critical care environment

Diazepam oral and rectal	RECTAL (PRN: can repeat dose x1) Neonate 1.25–2.5 mg, then 1.25–2.5 mg after 10 minutes if required. Child 1 month–1 year 5 mg, then 5 mg after 10 minutes if required. Child 2–11 years 5–10 mg, then 5–10 mg after 10 minutes if required. Child 12–17 years 10–20 mg, then 10–20 mg after 10 minutes if required ORAL <1yr 250micrograms/kg BD 1-4 yrs 2.5mg BD 5-12 yrs 5mg BD >12 yrs 10mg BD (max 40mg per day)	Long half life Doses may be cumulative Drowsiness, irritability Respiratory depression Tolerance may occur
Gabapentin	ORAL: under 12 yrs 10 mg/kg once daily (max. per dose 300 mg) on day 1, then 10 mg/kg twice daily (max. per dose 300 mg) on day 2, then 10 mg/kg 3 times a day (max. per dose 300 mg) on day 3 (then can be slowly increased if needed up to max 70 mg/kg daily in 3 divided doses), >12yrs 300mg OD and increase by one dose every 3 days as tolerated until 300mg TDs is reached and can slowly increase further to max. 1.6 g 3 times daily	Drowsiness, emotional lability, headaches, dizziness, gastrointestinal disturbance, change in appetite / weight gain, tremor, ataxia, visual disturbance
Midazolam	BUCCAL: 300microgram/kg (max 10mg) IV: Slow iv injection of 100-200microgram/kg then infusion of 30microgram/kg/hr increasing according to response up to a maximum of 120micrograms/kg/hr for 6mth-11yr olds and to a maximum of 200micrograms/kg/hr for 12-17yr olds	Respiratory depression Cardiovascular depression (severe hypotension) Potentiated by erythromycin and other drugs Infusion only to be used in critical care environment
Lorazepam	IV: Used PRN 50 micrograms/kg/dose (max 4mg) Can repeat x1 if required Max dose of 100microgram/kg or 8mg in 12 hours	Respiratory depression Hypotension S/P Liver disease
Trihexyphenidyl (Benzhexol)	Start 1mg BD (<8yrs) or 2mg BD (>8yrs). Increase total dose by 1mg (<8yrs) or 2mg (>8yrs) every 7 days until clinical effect or side effects intervene or max dose 1mg/kg/dose BD. Only for use > 3 months of age.	Anti-cholinergic effects (urinary retention, dry mouth, dry eyes, blurred vision, Gi disturbance etc.)

Appendix 2:



See page 5 for more detailed information.

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