Centre for Sustainable Delivery

NHS SCOTLAND

Modernising Patient Pathways Programme:

Cluster Headache Guidance

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Background

Cluster Headache is the most common of the Trigeminal Autonomic Cephalalgias (TAC). These are a group of primary headache disorders that are strictly unilateral, of severe intensity, and usually accompanied by Ipsilateral Cranial Autonomic symptoms. The presence of cranial autonomic features in headache or clustering does not necessarily indicate cluster headache or another TAC, as these features also occur in migraine.

Cluster Headache attacks last from 15 minutes to 3 hours. Autonomic symptoms may not always be present. Restlessness during attacks is very common, and can be used as an alternative symptom to aid the diagnosis.

Cluster attacks often wake patients from sleep, with some people only having nocturnal attacks.

In between attacks of pain, patients can experience a background dull ache in the same distribution area of the cluster attacks.

Acute treatment with subcutaneous Sumatriptan may be started in primary care, but referral to secondary care for specialist treatment is recommended. Medication Overuse Headache is rare in cluster headache, thus triptans may be taken up to twice daily if necessary.

Cluster Headache is differentiated into episodic and chronic. Episodic bouts usually last from weeks to months, with gaps of months to years in between. In chronic Cluster Headache, the attacks happen without break or with breaks lasting less than 3 months over a 1 year period.

Pathway recommendations

Diagnosis

Cluster Headache is much less common than migraine with a prevalence of about 0.1%. The duration and frequency of the attacks and the presence of cranial autonomic symptoms and restlessness help to differentiate it from other primary headache disorders.

Headache feature	Migraine (with or without aura)	Cluster headache	Tension-type headache
Frequency	Majority of patients presenting to both primary and secondary care (94% of people presenting in primary care with episodic headache will have migraine)	Rare - 1 in 1,000	Very common, but not often seen in primary or secondary care as usually mild and self-managed
Duration of untreated headache	4 to 72 hours in adults, 1 to 72 hours in young people	15 minutes to 3 hours	30 minutes to continuous
Pain location	Unilateral or bilateral (head, face or neck)	Unilateral (around the eye, above the eye and along the side of the head/face)	Bilateral (head, face or neck)
Pain quality	Pulsating in adults	Variable (can be sharp, boring,	Pressing/tightening

Headache feature	Migraine (with or without aura)	Cluster headache	Tension-type headache
	Throbbing or banging in young people	burning, throbbing or tightening)	(non-pulsating)
Pain intensity	Moderate or severe	Severe or very severe	Mild or moderate
Effect of activities	Aggravated by, or causes avoidance of, routine activities of daily living, e.g. prefer to stay still or go to bed	Restlessness or agitation	Not aggravated by routine activities of daily living

Other symptoms	• Photophobia (sensitivity to light)
	• Phonophobia (sensitivity to sound)
	• Nausea and/or vomiting
	• Allodynia (sensitivity to touch)
	• Cranial autonomic symptoms
	• Aura (lasts 5 to 60 minutes) can include:
	  ○ Flickering lights, spots or lines and/or partial loss of vision
	  ○ Sensory symptoms such as numbness and/or pins and needles
	  ○ Speech disturbance
		Cranial autonomic symptoms on the same side as the headache:
		• Red and/or watery eye
		• Nasal congestion and/or runny nose
		• Swollen eyelid
		• Forehead and facial sweating
		• Constricted pupil and/or drooping eyelid
		• Migrainous symptoms and aura
			None

The main difference from other TACs and Trigeminal Neuralgia is the duration and daily frequency of the attacks. The response to preventive treatment is also different.

TAC	Hemicrania Continua	Cluster Headache	Paroxysmal Hemicrania	SUNCT/ SUNA	Trigeminal Neuralgia
Male / Female tendency	Female	2.5 to 1	Equal	Male	Female
Attack duration	Constant	15 minutes to 3 hours	5 to 30 minutes	1 to 600 seconds	A few seconds to 2 minutes
Attack frequency	Not applicable	Up to 8 a day	Up to 5 an hour	Up to 30 an hour	1 to 50 a day
Circadian features	-	++	+	-	-
Restlessness	±	++	±	±	-
Other differentiating features	Typically more migrainous features	Strongest association with circadian rhythm,	Spontaneous, shorter and more frequent	Attacks are spontaneous and triggered.	Patients will always have some triggered attacks, some

TAC	Hemicrania Continua	Cluster Headache	Paroxysmal Hemicrania	SUNCT/ SUNA	Trigeminal Neuralgia
	than other TACs. Can worsen with acute medication overuse	restlessness, attacks from sleep, alcohol triggering	attacks than cluster.	Pain is always primarily in the area supplied by first division of trigeminal nerve	may be spontaneous. Pain is always primarily in the area supplied by the 2nd and 3rd division of the trigeminal nerve. No autonomic features
Episodic or chronic tendency	Chronic Continuous pain, without remission	Episodic Bouts lasting from weeks to month	Chronic Attacks occurring for more than 1 year without remission	Chronic	Currently undefined
Acute attack treatment	None Prone to worsen with medication overuse	Subcutaneous Sumatriptan 6mg High Flow Oxygen	None	None – too short	None – too short
First line preventive treatment	Indometacin	Verapamil	Indometacin	Lamotrigine	Carbamazepine

Adapted from BASH

Certain ophthalmological conditions may mimic Cluster Headache. These may include conditions such as trochleitis, scleritis, uveitis, orbital inflammatory disease, and intermittent angle closure glaucoma and may present with recurrent pain, lacrimation, conjunctival injection, periorbital oedema, ptosis, and pupillary abnormalities.

In inflammatory ophthalmological conditions, the changes would usually be continuous rather than short lasting. In intermittent angle closure glaucoma, vision is often reduced, a third of patients describe halos around bright light and the pupil tends to be dilated rather than constricted.

Investigations

It is recommended to consider Magnetic Resonance Imaging (MRI) neuroimaging in patients presenting with new onset Trigeminal Autonomic Cephalalgia or in those with chronic symptoms. The risk of a secondary cause in an individual with long history of episodic Cluster Headache and normal neurological examination is extremely low, so investigations in these patients is not required.

A possible association between pituitary adenoma and Cluster Headache has been reported, but the association is not proven and recent case series refute this association. Dedicated pituitary MRI is not necessary in patients with cluster headache unless the clinical presentation or standard MRI suggests a pituitary abnormality.

Treatment:

Acute

Subcutaneous Sumatriptan 6mg is the acute treatment of choice in a cluster attack.

Patients who have cluster headache rarely develop Medication Overuse Headache, however when migraine coexists, they may develop exacerbation of their migraine disorder whilst using a triptan effectively for their cluster attacks.

In patients who do not tolerate subcutaneous Sumatriptan, intranasal Zolmitriptan or Sumatriptan are alternative options.

Adverse effects: Patients should be warned that triptan sensations and/or sedation may occur. Symptoms may include tightness in the jaw, throat, or chest, and pins and needles in the face.

Cautions and contraindications: Triptans are contraindicated in coronary heart disease, peripheral vascular disease, or those with a history of stroke, and are cautioned in those with Raynaud's phenomenon. They should not be used in patients with a history of moderate or severe hypertension. Do not prescribe if blood pressure measurements are consistently above 140/90mmHg. While triptans are not licensed for adults over 65 years, there is no reason they can't be used. Vascular risk factors are more common and should be actively looked for in this age group.

High Flow Oxygen 100% at 10 to 15 litres/minute for 15 to 20 minutes, using a non-rebreathable mask, is effective in aborting acute attacks of Cluster Headache. An on demand valve is available for those not tolerating a non-rebreathable mask. Oxygen is prescribed from secondary care following established pathways.

There is no limit to the use of High Flow Oxygen, however cautions around nearby smoking, flames and fire hazards need to be considered/addressed. Oxygen is often used together with triptans in patients with multiple attacks.

The demand-valve oxygen system is a valve that allows oxygen to flow when the patient inhales and closes after inhalation. There is no evidence that it is better than a standard non-rebreathable mask, but some patients will find it beneficial and it can be requested when ordering oxygen.

When triptans are contraindicated, non-invasive vagal nerve stimulation can also be used. It is prescribed from secondary care following established pathways.

Treatment	Formulation	Strength	Maximum daily dose
Oxygen	Inhalation, non-rebreathable mask	7-15 L/min	No maximum
Sumatriptan	Subcutaneous injection	6mg	12mg
Zolmitriptan	Nasal spray	5mg	10mg
Sumatriptan	Nasal spray	20mg	40mg
Non-invasive vagal nerve stimulator	Transcutaneous	2 minutes stimulation	3 times a day as a preventative treatment, with additional stimulations as required for acute treatment

Transitional

Patients may use interim measures while waiting for a preventive treatment to have therapeutic effect. Such measures can also be used instead of preventative treatment in patients with episodic Cluster Headache with short bouts. Although oral Prednisolone is often used, this should be given with caution because of its many side effects and the cyclical pattern of Cluster Headache.

Oral steroids

Oral steroids (60mg Prednisolone for 5 days then reduced by 10mg every 2 days until stopped) may be given at the beginning of the bout at the same time as preventive medication is started. Repeated courses of oral steroids or prolonged use in chronic Cluster Headache is not recommended.

Peripheral Nerve Blocks

Peripheral Nerve Blocks may be used as bridge treatment in episodic Cluster Headache or as rescue treatment in chronic Cluster Headache. Greater Occipital Nerve (GON) is the main target but when the effect is insufficient with a GON block alone, multiple cranial nerves may be blocked with greater effect.

Peripheral nerve blocks are safe. The main reported side effects include dizziness, nausea, vasovagal prodromes or syncope, injection site tenderness, neck pain and transient worsening of headaches. All adverse events were transient and resolved fully without treatment. Repeated GON blocks with steroids may cause skin atrophy and alopecia of the injected area.

A mixture of Lidocaine and Methylprednisolone is often used for the GON block. A mixture of Lidocaine and Levobupivacaine is preferred for the lesser occipital nerve and trigeminal nerve branches.

Peripheral Nerve Blocks may be repeated as required but repeated steroid use has been associated with focal skin atrophy, alopecia and systemic steroid complications. We recommend restricting steroids to no more than 4 times a year.

Dihydroergotamine

Dihydroergotamine (DHE) is used in specialist centres for patients with refractory headache, including Cluster Headache. Its use is limited due to the potential cardiovascular, gastrointestinal, and pro-emetic effects of the treatment. Long term treatment can lead to fibrosis (pericardic, retroperitoneal and interstitial) and requires cardiac and Computed Tomography (CT) body monitoring. This limits its long term use in chronic Cluster Headache. (Prescrire Int. 2002 Dec;11(62):186-9. PMID: 12472101.)

DHE is given in a pulse regimen, usually as an intravenous (IV) infusion over 3 to 5 days as an inpatient. Initial doses are often given IV, pre-treating patients with metoclopramide or ondansetron, followed by 0.5mg DHE (in 100 mL of normal saline) infusion. If side effects are tolerable, an additional 0.5mg may be given, followed by 1mg doses in 250ml of normal saline) every 8 to 12 hours to a maximum total dose of 9mg. The effect can last from weeks to months and the treatment can be repeated after a few months.

Prophylactic

Verapamil

Verapamil is widely accepted as the first line preventive treatment for Cluster Headache. It is the most effective preventative treatment, but often has to be used at high doses. The standard release formulation is more effective than the slow release formulation in most patients. The main concern with Verapamil is the development of heart block. Minor first degree atrioventricular block is acceptable as long as the PR interval does not continue to increase. If second or third degree

heart block develops, Verapamil must be stopped and a cardiology referral may be considered if changes do not reverse. Regular ECG monitoring is required while on Verapamil to ensure heart block does not develop.

Other side effects include nausea, fatigue, constipation, and ankle oedemas. Rarely gynaecomastia and gum hypertrophy occur with long term use. Hypotension may be a limiting factor.

Different authors suggest different starting regimes.

A gradual increase of the dose with regular Electrocardiogram (ECG) monitoring to ensure no significant prolongation of PR.

An ECG should be performed before Verapamil is started and before every dose increase. If normal, the dose can be increased after 2 weeks until the optimal or maximum is reached.

Two regimens are recommended. Both regimens are equivalent. Regimen 1 has a slower titration schedule and may be more appropriate in patients where side effects are an issue or where the clinician would prefer a slower titration schedule.

Regime 1:

	Morning	Midday	Evening
An ECG should be performed before Verapamil is started. If normal:			
Starting dose **For 2 weeks take:**	**80mg**	**80mg**	**80mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**80mg**	**80mg**	**160mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**80mg**	**160mg**	**160mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**160mg**	**160mg**	**160mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**160mg**	**160mg**	**240mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**160mg**	**240mg**	**240mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**240mg**	**240mg**	**240mg**
An ECG should be performed before each dose increase. If normal:			

	Morning	Midday	Evening
For 2 weeks take:	**240mg**	**240mg**	**320mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**240mg**	**320mg**	**320mg**
An ECG should be performed before each dose increase. If normal:			
Maximum dose:	**320mg**	**320mg**	**320mg**

From Neurology. 2007;69:668-75

Regime 2:

	Morning	Midday	Evening
An ECG should be performed before Verapamil is started. If normal:			
Starting dose For 2 weeks take:	**120mg**		**120mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**120mg**	**120mg**	**120mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**120mg**	**120mg**	**240mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**240mg**	**120mg**	**240mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**240mg**	**240mg**	**240mg**
An ECG should be performed before each dose increase. If normal:			
For 2 weeks take:	**240mg**	**240mg**	**360mg**
An ECG should be performed before each dose increase. If normal:			
Maximum dose:	**360mg**	**240mg**	**360mg**

Courtesy of Prof. Matharu

Anti-seizure medication

Several open-label trials have shown some efficacy for Topiramate, Gabapentin, Valproic Acid, and Levetiracetam for Cluster Headache, and represent an alternative or add-on treatment options.

Topiramate, Gabapentin and Valproate are not recommended during conception, pregnancy or lactation. For management of cluster in pregnancy, please see section 5 of this document.

Children exposed to Topiramate and Sodium Valproate in utero are at high risk of serious developmental disorders and congenital malformations. There is also a risk of transient impaired fertility in men taking Sodium Valproate. Patients who may become pregnant should be appropriately counselled and be on highly-effective contraception before commencing either treatment. Advice on contraception is available from the Royal College of the Obstetricians and Gynaecologists Faculty of Sexual and Reproductive Healthcare, https://www.fsrh.org/standards-and-guidance/fsrh-guidelines-and-statements/. At the time of writing the Medicines and Healthcare products Regulatory Agency (MHRA) is reviewing the risks of Topiramate in pregnancy. The Commission on Human Medicines recommends that no patients (male or female) under the age of 55 years should be initiated on Sodium Valproate unless 2 specialists independently consider and document that there is no other effective or tolerated treatment.

For current contraceptive advice on patients prescribed Topiramate or Sodium Valproate, check the MHRA website, www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency.

Melatonin

The use of Melatonin in Cluster Headache is unlicenced. Evidence for the use of Melatonin in cluster is limited, but this may be due to the timing and doses used in the different trials. The relatively mild side effect profile makes it a good choice for patients with Cluster Headache who are unable to tolerate other options. Melatonin may be used as adjunctive therapy. Somnolence (sleepiness or drowsiness for long periods) is the main side effect.

Due to abnormalities in the release of endogenous melatonin in patients with Cluster Headache, timing of supplementation is essential and it should be given 2 hours before bedtime.

Proposed starting doses:

The dose should be increased every few days up until the optimal or maximum dose is reached:

- **3mg tablets should be increased by 3mg every 3 days.**
- **5mg tablets should be increased by 5mg every 5 days.**

Melatonin 3mg tablets	Evening (2 hours before going to sleep)
For 3 days take:	**3mg**
For 3 days take:	**6mg**
For 3 days take:	**9mg**
For 3 days take:	**12mg**
Maximum dose:	**15mg**

Melatonin 5mg tablets	Evening (2 hours before going to sleep)
For 5 days take:	**5mg**
For 5 days take:	**10mg**
Maximum dose:	**15mg**

Courtesy of Prof. Matharu

Lithium

Lithium is more commonly used in chronic Cluster Headache. Its narrow therapeutic range and undesirable side effect profile make it a less desirable choice.

Lithium therapy requires regular blood monitoring to maintain a serum concentration between 0.8 and 1.0 mEq/L. Toxicity is common and can present as gastrointestinal and neurological symptoms. The main side effects include somnolence, cognitive impairment, diabetes insipidus, and hypothyroidism.

Renal and thyroid function should be checked before starting Lithium and regularly thereafter. Lithium dosing starts at 300mg twice a day. Trough lithium levels should be obtained and the dose adjusted every 2 weeks until a stable dose is achieved (trough level of 0.8-1.0).

- If the trough lithium level is below 0.8 the dose should be increased by 100mg twice daily.
- If between 0.8 and 1.0 then the dose should not be changed.
  If above 1.0, the dose should be reduced.

Trough serum concentrations need to be checked 12 hours after dosing. Regular level monitoring is required once the dose is stable.

Suggestions on starting doses and titration for some preventative treatment for cluster headache

Medication	Topiramate	Valproate	Melatonin
Starting dose	25mg Please see contraceptive advice in the notes section	200mg twice daily Please see contraceptive advice in the notes section	3mg
Suggested increment	25mg every 1 to 2 weeks	200mg twice daily every week	3mg every week
Maximum dose	Initially to 100mg bd (twice a day), maximum 200mg bd (Most patients won't tolerate high doses.)	1000mg twice daily	15mg taken 2 hours before bed

Other treatments with some anecdotal evidence include gabapentin and levetiracetam.

Devices

Gammacore

Gammacore is a handheld external device. The Scottish Health Technologies Group recommended its use for acute and preventive treatment of cluster headaches in NHS Scotland.

The preventive effect may be achieved by 3 doses of 2-minute stimulation twice a day. On top of this, extra doses may be given as acute treatment for additional cluster attacks. It is prescribed from secondary care following established pathways.

Treatment in pregnancy

Ideally drugs are avoided in pregnancy. The advice of a headache specialist should be sought.

Acute treatment:

Pregnancy	Breastfeeding	
✓	✓	**Sumatriptan (Nasal Spray / Subcutaneous Injection)** Can be used up to twice a day without risk of Medication Overuse Headache.
✓	✓	**Oxygen therapy** High flow oxygen therapy through a non rebreathe mask is the preferred treatment of acute cluster headache.

Transitional treatment:

✓	✓	**Prednisolone** Risk of cleft palate in first trimester. Usually used as a steroid taper. 60mg for 7 days followed by a reducing course (reduce by 10mg per day).
✓	✓	**GON Blocks** (Depomedrone and Lidocaine/Lidocaine alone) Avoid corticosteroid use in the first trimester. Useful to break cycle of cluster headaches.
✓	✓	**Weak Opioids** Can be considered where other options are ineffective.

Preventive treatment:

Pregnancy	Breastfeeding	
✓	✓	**Verapamil – CONSULT SPECIALIST** Where preventative therapies are needed (continued only on specialist advice), Verapamil in the lowest effective dose remains first choice.
✗	✗	**Lithium** Known Teratogenicity
✗	✗	**Topiramate/Valproate** Known Teratogenicity

Verapamil use in pregnancy appears to be low risk with no evidence of foetal harm. Verapamil is excreted into breast milk and therefore may theoretically have effects in the infant but was rated as compatible by the American Academy of Paediatrics. Available information is for doses up to 360mg daily, with breastfeeding avoided at higher doses.

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