Clinical Priorities Advisory Group
20 May 2024

Agenda Item No	2.4
National Programme	Blood and Infection
Clinical Reference Group	Immunology and Allergy
URN	2270

Title
Human normal immunoglobulin for preventative treatment of Idiopathic Systemic Capillary Leak Syndrome following an acute episode (adults)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its relative prioritisation

Proposition
Human normal immunoglobulin is recommended to be available as a routine commissioning preventative treatment option for adults with idiopathic systemic capillary leak syndrome (SCLS) within the criteria set out in the policy proposition document. The policy proposition is for adults in line with the findings from the evidence review. If supported, this indication will be added to the existing NHS England Clinical Commissioning Policy for the use of therapeutic immunoglobulin (Ig) in England. Specialised immunology services are suitable and ready for delegation from April 2025.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Deputy Director of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.

2.	The Deputy Director of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Director of Clinical Commissioning confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In people with idiopathic SCLS, what is the clinical effectiveness and safety of human normal immunoglobulin preventative treatment compared with current standard care?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Survival **Certainty of evidence:** Low	Survival is important to patients because it reflects how long people live after treatment, although it does not provide information about their health and wellbeing during that time. One retrospective cohort study (n=65) provided evidence relating to survival in patients with idiopathic SCLS over a median follow-up of 5.1 years (interquartile range 2.5 to 9.7 years). The study compared survival rates in 48 people who received IV human normal immunoglobulin and 17 people who did not receive IV immunoglobulin. The retrospective cohort study (Pineton de Chambrun et al. 2017) found that, compared with patients who did not receive IV immunoglobulin, statistically significantly more patients who received IV immunoglobulin were alive after a median 5.1 years (5/17 [29.4%] versus 40/48 [83.3%]; p<0.0001). **(LOW)** Preventative treatment with IV immunoglobulin was an independent predictor of mortality (multivariate HR 0.27, 95% CI 0.10 to 0.70; p=0.007), suggesting that immunoglobulin improves survival compared with standard preventative care. **(LOW)**

	The 5-year survival rate was 91% in patients treated with IV immunoglobulin, compared with 47% in patients not treated with IV immunoglobulin. **(LOW)** The 10-year survival rate was 77% in patients treated with IV immunoglobulin, compared with 37% in patients not treated with IV immunoglobulin (log rank test p<0.0001). **(LOW)** **One retrospective observational study provided low certainty evidence that, compared with standard preventative care without immunoglobulin, IV immunoglobulin statistically significantly improves survival in patients with idiopathic SCLS for up to 10 years. The study suggests that, at 5 years, 9 out of 10 people receiving IV immunoglobulin are still alive, compared with 5 out of 10 people not receiving IV immunoglobulin.**
Frequency of acute episodes of any severity **Certainty of evidence:** Very low to low	The frequency of acute episodes of any severity is important to patients because SCLS is a relapsing condition and is characterised by acute episodes. These can be life threatening and require hospital admission. This outcome is a marker of overall disease activity and provides important information about disease severity, symptom control and thus quality of life. One retrospective cohort study (n=65) and 1 retrospective longitudinal study (n=21) provided evidence relating to the frequency of acute episodes of any severity in patients with idiopathic SCLS. The retrospective cohort study compared the rate of acute episodes in 48 people who received IV human normal immunoglobulin and 17 people who did not receive IV immunoglobulin over a median follow-up of 5.1 years (interquartile range 2.5 to 9.7 years). The longitudinal study compared the median frequency of acute episodes per year in 18 patients who started IV human normal immunoglobulin with outcomes in the study population while immunoglobulin was not being administered (n=21) over a median follow-up of 7 years (range 2.4 to 25 years). The retrospective cohort study (Pineton de Chambrun et al. 2017) found that, compared with patients who did not receive IV immunoglobulin, statistically significantly fewer patients who received IV immunoglobulin had acute episodes over a median 5.1 years (16/17 [94.1%] versus 31/48 [64.6%] p=0.03). **(LOW)** In the longitudinal study (Xie et al. 2015), the median frequency of acute episodes per year was 2.6 per patient (range 0.25 to 15.4 episodes) from disease onset to initiation of IV immunoglobulin (median duration 3.75 years). The study found that the frequency of acute episodes per year was statistically significantly lower after IV immunoglobulin was started (0 per patient, range 0 to 3.3 episodes; p< 0.0001) **(VERY LOW).** In this study, 15/18 patients (83.3%) did not experience any significant episodes of SCLS while receiving IV immunoglobulin (mean duration 2.7 years). **Two retrospective observational studies provided very low to low certainty evidence that, compared with standard preventative care without immunoglobulin, preventative**

	treatment with IV immunoglobulin for up to 5 years statistically significantly reduces the frequency of acute episodes of any severity in people with idiopathic SCLS. Low certainty evidence suggests that, over 5 years, 9 out of 10 people not receiving IV immunoglobulin will have at least 1 acute episode, compared with 6 out of 10 people receiving IV immunoglobulin.
Hospital admissions **Certainty of evidence:** Not applicable	This outcome is important to patients because severe acute episodes often require hospital admission, including intensive care. However, not all acute episodes require hospital admission and if they do not, this signifies reduced severity. The definitions of severe or significant acute episodes in both studies included hospital admission. These are reported in the evidence review under frequency of acute episodes of any severity (both studies) and frequency of severe episodes (the cohort study only). **No direct evidence was identified. See frequency of severe episodes for indirect evidence relating to this outcome.**
Important outcomes	
Health related quality of life **Certainty of evidence:** Not applicable	This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment. **No evidence was identified for this outcome.**
Complication rate of SCLS **Certainty of evidence:** Not applicable	This outcome is important to patients as it reflects how effective the treatment is compared with current standard of care and is a surrogate for control of symptoms and quality of life. **No evidence was identified for this outcome.**
Frequency of severe episodes **Certainty of evidence:** Low	SCLS is a relapsing condition which is characterised by acute episodes, and when these are severe, they lead to admission, including to intensive care. Severe episodes are life threatening and contribute to mortality in these patients. One retrospective cohort study (n=65) provided evidence relating to the frequency of severe episodes in patients with idiopathic SCLS over a median follow-up of 5.1 years (interquartile range 2.5 to 9.7 years). The study compared the rate of severe episodes in 48 people who received IV human normal immunoglobulin and 17 people who did not receive IV immunoglobulin. Severe episodes were defined as systolic blood pressure less than 80 mm Hg, mean blood pressure less than 65 mm Hg, loss of consciousness, admission to intensive care or a combination of these.

	The retrospective cohort study (Pineton de Chambrun et al. 2017) found that, compared with patients who did not receive IV immunoglobulin, statistically significantly fewer patients who received IV immunoglobulin had severe episodes over a median 5.1 years (16/17 [94.1%] versus 22/48 [45.8%]; p<0.0001). **(LOW)** **One retrospective observational study provided low certainty evidence that, compared with standard preventative care without immunoglobulin, preventative treatment with IV immunoglobulin for 5 years statistically significantly reduces the frequency of severe episodes in people with idiopathic SCLS. The study suggests that, over 5 years, 9 out of 10 people not receiving IV immunoglobulin will have at least 1 severe episode, compared with 5 out of 10 people receiving IV immunoglobulin.**
Durability of remission **Certainty of evidence:** Not applicable	This outcome is important to patients because it gives an indicator of how long the effect of this intervention may last, and how long they can expect to be treated for. **No evidence was identified for this outcome.**
Safety	
Complications of human normal immunoglobulin therapy **Certainty of evidence:** Very low	Safety is important to patients as it reflects the risks involved in what is likely to be a long-term prophylactic treatment. This allows a risk benefit assessment to be undertaken. One retrospective longitudinal study (n=21) provided evidence relating to complications of human normal immunoglobulin treatment in patients with idiopathic SCLS. The study did not compare the adverse effects of immunoglobulin with other preventative treatments and no data or statistical analyses were reported. Most patients in the longitudinal study (Xie et al. 2015) did not experience significant adverse effects during IV immunoglobulin infusions. A minority of patients reported minor post-infusion adverse effects, most commonly transient headache, rash and fatigue. **Very low certainty evidence from 1 retrospective observational study suggests IV immunoglobulin is generally well tolerated in people with idiopathic SCLS. However, no firm conclusions can be drawn from the limited information reported.**
Abbreviations IV, intravenous; SCLS, systemic capillary leak syndrome	

From the evidence selected, are there any subgroups of patients that may benefit from human normal immunoglobulin preventative treatment more than the wider population of interest?

Outcome	Evidence statement
Subgroups	**No evidence was identified regarding subgroups of patients that may benefit from human normal immunoglobulin preventative treatment more than the wider population of interest.**

In people with idiopathic SCLS, what is the cost-effectiveness of human normal immunoglobulin preventative treatment combined with current standard care compared with current standard care alone?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified regarding the cost-effectiveness of human normal immunoglobulin preventative treatment combined with current standard care compared with current standard care alone.**

From the evidence selected, what doses, frequency and route of administration human normal immunoglobulin preventative treatment were used and what was the duration of treatment?

Study	Dosage
Pineton de Chambrun et al. 2017	IV immunoglobulin 2 g/kg monthly initiated after resolution of an acute attack. Treatment was given for at least 1 year but could then be tapered in the absence of recurrence. Median duration of treatment was 4.3 years (interquartile range 2.3 to 7.5 years).
Xie et al. 2015	IV immunoglobulin 1-2 g/kg monthly 2/18 patients (11.1%) received half the standard dose (0.5-1 g/kg) every 2 weeks, rather than being treated with the standard dose once a month. Mean duration of treatment was 2.7 years (range 10 months to 4.9 years).
Abbreviations IV, intravenous	

Patient Impact Summary
The condition has the following impacts on the patient's everyday life: • **mobility:** patients with idiopathic systemic capillary leak syndrome experience multiple life-threatening acute episodes of capillary leak. Admissions to hospital and intensive care, which are often required for

stabilisation, can cause significant deconditioning. Furthermore, as a direct result of an acute episode, patients can experience thromboembolism and compartment syndrome which may in some cases cause limb loss. They can also experience chronic peripheral cutaneous oedema with all the associated complications (i.e. cellulitis, reduced mobility).

- **ability to provide self-care:** as a result of the loss of mobility described above patients can rapidly lose their independence, become dependent on others for care and on the state for financial support. Multiple hospital admissions with acute episodes will also prevent usual self-care activities. Other complications of acute episodes can involve multi-organ failure which will further impact self care.
- **undertaking usual activities:** The reduced mobility and frequent prolonged hospital/ITU admissions experienced by these patients, especially those with more frequent episodes, will severely impact on their ability to carry out their usual activities, activities of daily living and employment. This is particularly relevant as patients are often of middle age and therefore may otherwise be in employment and/or have dependents.
- **experience of pain/discomfort:** Multiple prolonged admissions to hospital or intensive care will cause significant discomfort to patients. The more specific complications experienced by these patients including thromboembolism, organ failure and compartment syndrome may cause a variety of difficult symptoms from pain to shortness of breath.
- **experience of anxiety/depression:** The anxiety around having further episodes and the lack of known cause of these is significant. Frequent intensive care admissions are associated with post-traumatic stress. Multiple admissions can also directly cause isolation, stress and low mood for the patient and their families.

Further details of impact upon patients:

The condition severely impacts all areas of everyday life given the recurrent hospitalisations with life threatening acute episodes.

Once commenced, patients should remain on treatment continuously (if there is a response) until a complete clinical response is achieved as defined by a year without any acute episodes and without any associated hospital admissions. At this point the multi-disciplinary team (MDT) may consider, jointly with the patient, whether treatment can be stopped. The risk of stopping is that the condition will recur, and patients therefore must be appropriately counselled and understand this risk.

Further details of impact upon carers:

Those living with and caring for people with idiopathic SCLS risk becoming the main care provider. They may be required to help with activities of daily living, as well as hospital appointments and emergency attendances for acute episodes. The stress of not knowing when the patient may experience a sudden acute episode is likely to impact carers.

Considerations from review by Rare Disease Advisory Group
RDAG committee members supported the policy proposition on 19th October 2023.

Pharmaceutical considerations
This clinical commissioning policy proposition is for the use of human normal immunoglobulin as a treatment option for idiopathic systemic capillary leak syndrome (SCLS) in people of all ages. The recommendation is outside of the marketing authorisations for human normal immunoglobulin therapies so use is off-label and Trust policy regarding unlicensed medicines should apply. Human normal immunoglobulin therapies are on the NHS Payment Scheme Annex A, that is, they are excluded drugs. All use of human normal immunoglobulins is recorded on the national MDSAS human normal immunoglobulin database.

Considerations from review by National Programme of Care
The proposal received the full support of the Blood & Infection PoC on the 30th January 2024.