NHS England evidence review:

Human normal immunoglobulin for preventative treatment of idiopathic systemic capillary leak syndrome

NHS England URN: 2270

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Human normal immunoglobulin for preventative treatment of idiopathic systemic capillary leak syndrome

Completed: March 2023

Prepared by NICE on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of human normal immunoglobulin for preventing further acute episodes in people with idiopathic systemic capillary leak syndrome (SCLS) compared with current standard care without immunoglobulin.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with immunoglobulin more than others, as well as the route of administration, dosage, frequency and duration of treatment.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of human normal immunoglobulin for preventing further acute episodes in people with idiopathic systemic capillary leak syndrome (SCLS) compared with current standard care without immunoglobulin. The searches for evidence published since January 2013 were undertaken on 26 January 2023 and identified 51 references. The titles and abstracts were screened and 8 full text papers were obtained and assessed for relevance. Two papers were selected for inclusion.

The evidence review included 2 retrospective observational studies that compared human normal immunoglobulin with standard preventative care without immunoglobulin for people with idiopathic SCLS. One study was a cohort study that compared outcomes in 48 people who received intravenous (IV) human normal immunoglobulin and 17 people who did not receive immunoglobulin over a median follow-up of 5.1 years (Pineton de Chambrun et al. 2017). The other study was a longitudinal study that compared outcomes in 21 people on and off treatment with IV human normal immunoglobulin over a median follow-up of 7 years. Eighteen of the 21 people received IV immunoglobulin at some stage during the study period (Xie et al. 2015). The cohort study was undertaken in 49 centres in 8 countries (France, Italy, Israel, Switzerland, Lebanon, Canada, Spain, and Turkey). The longitudinal study was undertaken in the United States.

In terms of clinical effectiveness:

Critical outcomes

- **Survival.** One retrospective cohort 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 5-year survival rate was 91% in patients treated with IV immunoglobulin, compared with 47% in patients not treated with IV immunoglobulin. 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 $p<0.0001$). Preventative treatment with IV immunoglobulin was an independent predictor of mortality ($p=0.007$), suggesting that immunoglobulin improves survival compared with standard preventative care.
- **Frequency of acute episodes of any severity.** Two retrospective observational studies suggested that, compared with standard 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 patients with idiopathic SCLS. The cohort study provided low certainty evidence that 65% of patients who received IV immunoglobulin had acute episodes over a median 5.1 years compared with 94% of patients who did not receive IV immunoglobulin ($p=0.03$). The longitudinal study provided very low certainty evidence that, on average, patients had 2.6 acute episodes of any severity each year from disease onset to initiation of IV immunoglobulin (median duration 3.75 years) whereas, on average, no acute episodes were seen each year after immunoglobulin was started ($p< 0.0001$).
- **Hospital admissions.** No direct evidence was identified for this outcome. See frequency of severe episodes for indirect evidence relating to this outcome.

Important outcomes

- **Health related quality of life.** No evidence was identified for this outcome.

- **Complication rate of SCLS.** No evidence was identified for this outcome.
- **Frequency of severe episodes.** One retrospective cohort study provided low certainty evidence that, compared with standard care without immunoglobulin, preventative treatment with IV immunoglobulin for 5 years statistically significantly reduces the frequency of severe episodes in people with idiopathic SCLS. In the study, 46% of patients who received IV immunoglobulin had severe episodes over a median 5.1 years compared with 94% of patients not treated with IV immunoglobulin ($p<0.0001$). 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.
- **Durability of remission.** No evidence was identified for this outcome.

In terms of safety:

- Very low certainty evidence from 1 retrospective longitudinal study suggests IV immunoglobulin is generally well tolerated in people with idiopathic SCLS. Most patients in the study did not experience significant adverse effects. A minority of patients reported minor post-infusion adverse effects, most commonly transient headache, rash and fatigue.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients that would benefit more from human normal immunoglobulin treatment.

In terms of doses, frequency and route of administration, and duration of treatment

- IV human normal immunoglobulin was used in both studies.
- The dosage in the cohort study was 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.
- Most patients (16/18) in the longitudinal study received 1-2 g/kg monthly, but 2 patients received half the standard dose (0.5-1 g/kg) every 2 weeks.
- The average duration of immunoglobulin treatment was 4.3 years (median) in the cohort study and 2.7 years (mean) in the longitudinal study.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

The studies included in the evidence review are small retrospective, observational studies, with no blinding of interventions or outcomes. Observational studies are subject to bias and confounding, and cannot prove that an intervention (such as immunoglobulin) caused an

outcome, only that it is associated with that outcome. This limits their application to clinical practice. However, idiopathic SCLS is a rare condition and, therefore, conducting prospective comparator studies may be unrealistic. Taking this into account, the cohort study appears to be appropriately designed and well reported, and the outcomes considered are relevant to patients.

The overall quality of the cohort study was assessed as good, and outcomes were considered to have low certainty using modified GRADE. The overall quality of the longitudinal study was assessed as poor and outcomes were considered to have very low certainty. The limitations of the longitudinal study include lack of a concurrent control group and use of a retrospective patient-reported questionnaire to assess outcomes, which is subject to recall bias.

Patients were recruited over 2 decades in the cohort study; therefore, treatment regimens were heterogeneous as management of SCLS changed. In the longitudinal study, apart from IV immunoglobulin, it is not known if changes in treatment pathways and clinical management were taken into account. This is a potential source of bias.

Patients in both studies received immunoglobulin treatment intravenously: no patients received it subcutaneously. No children were included in the studies, and all patients in the cohort study had monoclonal gammopathy. Most people (82%) in the longitudinal study were male, although the male to female ratio of people with SCLS is around 1.4 to 1 (Dhir et al. 2007).

Conclusion

Overall, 2 retrospective observational studies provided evidence for the clinical effectiveness and safety of human normal immunoglobulin preventative treatment compared with current standard care without immunoglobulin in people with idiopathic SCLS. Retrospective observational studies cannot prove cause and effect and should be considered hypothesis generating only because unknown or unmeasured factors may have influenced the findings.

A retrospective cohort study provided low certainty evidence that, compared with standard preventative care without immunoglobulin, IV immunoglobulin statistically significantly improves survival in people with idiopathic SCLS for up to 10 years. In the study, 9 out of 10 people receiving IV immunoglobulin were still alive after 5 years, compared with 5 out of 10 people receiving standard care.

Both studies in the evidence review suggest that immunoglobulin treatment reduces the frequency of acute episodes of any severity in people with idiopathic SCLS compared with standard preventative care without immunoglobulin. In the cohort study, 6 out of 10 people receiving IV immunoglobulin had at least 1 acute episode over 5 years, compared with 9 out of 10 people receiving standard care (low certainty evidence). In the longitudinal study, most people (15/18, 83.3%) did not experience any significant episodes of SCLS while receiving IV immunoglobulin (mean duration 2.7 years, very low certainty evidence).

The cohort study also provided low certainty evidence that IV immunoglobulin statistically significantly reduces the frequency of severe episodes of SCLS compared with standard preventative care without immunoglobulin. In the study, 5 out of 10 people receiving IV immunoglobulin had at least 1 severe episode over 5 years, compared with 9 out of 10 people receiving standard care.

The studies provided no evidence to determine whether immunoglobulin treatment improves the important outcomes, health related quality of life, complication rates and durability of remission compared with current standard preventative care without immunoglobulin. Indirect evidence for the critical outcome of hospital admission is available under frequency of severe episodes. No direct evidence was identified for this outcome.

Only limited information was available for adverse effects of immunoglobulin, with no data or statistical analyses reported in either study. Nevertheless, very low certainty evidence from the longitudinal study suggests that IV immunoglobulin is well tolerated by people with idiopathic SCLS.

No evidence was identified regarding the cost effectiveness of immunoglobulin treatment compared with standard preventative care without immunoglobulin. Also, no evidence was identified regarding subgroups of patients that may benefit from immunoglobulin treatment more than the wider population of interest.

The findings of this evidence review are important for people with idiopathic SCLS because they suggest that IV immunoglobulin treatment reduces the frequency of acute episodes (including severe episodes, such as those requiring hospital admission) and improves survival compared with current standard preventative care without immunoglobulin. Any potential benefits of treatment must be balanced against the unclear adverse event profile of immunoglobulin in this population.

3. Methodology

Review questions

1. In people with idiopathic SCLS, what is the clinical effectiveness of human normal immunoglobulin preventative treatment compared with current standard care?
2. In people with idiopathic SCLS, what is the safety of human normal immunoglobulin preventative treatment compared with current standard care?
3. 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?
4. 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?
5. 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?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 26 January 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Two papers were selected for inclusion (Pineton de Chambrun et al. 2017 and Xie et al. 2015). Table 1 provides a summary of these included studies and full details are given in Appendix E. One study was a retrospective cohort study (Pineton de Chambrun et al. 2017) and the other was a longitudinal study (Xie et al. 2015).

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Pineton de Chambrun et al. (2017) Retrospective cohort analysis of all patients in the European Clarkson disease (EurêClark) registry 49 centres in 8 countries	65 patients with Clarkson disease (SCLS) defined as: • monoclonal gammopathy • 1 or more episodes that met certain criteria (signs of acute hypovolaemia and interstitial oedema) • haemoconcentration with paradoxical hypoproteinaemia No children were included because none had monoclonal gammopathy Baseline characteristics: • 49.3% male • mean age at disease onset 52 years (±12 years)	**Interventions** Preventative treatment with IVIg 2 g/kg monthly (n=48, 73.8%), 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 4.3 years (interquartile range 2.3 to 7.5 years) **Comparators** No IVIg (n=17) It is unclear which treatments these patients were taking, if any Other preventative treatments were: • theophylline 400-1600 mg daily (n=22, 34%) • terbutaline 15-25 mg daily (n=22, 34%), and • thalidomide 50-100 mg daily (n=5, 7.7%) 9 patients received no preventative treatment	**Critical outcomes** • Survival (5- and 10-year survival rates) • Frequency of acute episodes of any severity during follow-up (median 5.1 years, interquartile range 2.5 to 9.7 years) **Important Outcomes** • Frequency of severe episodes during follow-up (median 5.1 years, interquartile range 2.5 to 9.7 years)
Xie et al. (2015) **Study location** Retrospective longitudinal study United States	21 patients aged over 16 years of age who met certain criteria for SCLS, including: • oedema with >1 kg of weight gain in <1 week or acute hypotension • haemoconcentration with hypoproteinaemia or hypoalbuminemia (Gousseff et al. 2011) Baseline characteristics: • 82% male • median age at disease onset 46 years (range 32 to 66 years)	**Interventions** Preventative treatment with IVIg 1-2 g/kg monthly at some stage during the study period (n=18, 85.7%) 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 IVIg treatment 2.7 years (range 10 months to 4.9 years) **Comparators** Outcomes were compared in the study population while IVIg was not being administered (n=21) 19 patients (90.5%) received theophylline as a preventative treatment after diagnosis, alone or in combination with terbutaline or albuterol	**Critical outcomes** • Frequency of acute episodes of any severity per year **Safety** • Complications of immunoglobulin treatment Median overall follow-up was 7 years (range 2.4 to 25 years)

Abbreviations

IVIg, intravenous human normal immunoglobulin; SCLS, systemic capillary leak syndrome, also known as Clarkson disease

5. Results

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 well-being 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

CI, confidence interval; HR, hazard ratio; IV, intravenous; SCLS, systemic capillary leak syndrome

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, 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.**

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	

6. Discussion

The evidence review included 2 retrospective observational studies that compared human normal immunoglobulin with standard preventative care without immunoglobulin for people with idiopathic SCLS. One study was a cohort study with 65 participants (Pineton de Chambrun et al. 2017) and the other was a longitudinal study with 21 participants (Xie et al. 2015). There was no blinding of interventions or outcomes in the studies. Retrospective observational studies are subject to bias and confounding, meaning unknown or unmeasured factors may have influenced the findings. Observational studies cannot prove that an intervention (such as immunoglobulin) caused an outcome, only that it is associated with that outcome, which limits their application to clinical practice.

Considering idiopathic SCLS is a rare disease, the observational study (Pineton de Chambrun et al. 2017) was relatively large, appropriately designed and well-reported. The overall quality of this study was assessed as good, and outcomes were considered to have low certainty using modified GRADE. The overall quality of the longitudinal study (Xie et al. 2015) was assessed as poor and outcomes were considered to have very low certainty. The limitations of the longitudinal study include lack of a concurrent control group and use of a retrospective patient-reported questionnaire to assess outcomes. Such questionnaires are subject to recall bias because they rely on patients understanding the questions and accurately remembering information. Response rate is another limitation and 17% of patients did not return their questionnaire in this study.

Only patients with monoclonal gammopathy were included in the cohort study (Pineton de Chambrun et al. 2017). Children were not excluded but none were included because none had monoclonal gammopathy. The mean age of participants in this study was 52 years. It is not known how many people in the longitudinal study (Xie et al. 2015) had monoclonal gammopathy. This study included people aged 16 years or over only and the median age of participants at disease onset was 46 years. These average ages are consistent with the mean age of onset of SCLS reported in the literature (Dhir et al. 2007). Most people (82%) in the longitudinal study were male, although the male to female ratio of people with SCLS is around 1.4 to 1 (Dhir et al. 2007).

Patients in both studies received immunoglobulin treatment intravenously: no patients received it subcutaneously. The average duration of immunoglobulin treatment was 4.3 years (median) in the cohort study and 2.7 years (mean) in the longitudinal study, which may not be long enough to study outcomes that are infrequent. Median total follow ups were 5.1 years and 7 years, respectively. It is unclear whether the improvements seen with immunoglobulin treatment are maintained longer term.

In the cohort study (Pineton de Chambrun et al. 2017), outcomes in patients receiving immunoglobulin treatment (n=48) were compared with outcomes in patients not receiving immunoglobulin treatment (n=17). Patients were recruited over 2 decades; therefore, treatment regimens were heterogeneous as management of SCLS changed. It is unclear which preventative treatments patients in the standard care group were taking, if any, and whether any patients receiving immunoglobulin were also taking another preventative treatment.

In the longitudinal study (Xie et al. 2015), apart from IV immunoglobulin, it is not known if other changes over the study period were considered (for example, other changes in treatment pathways and clinical management). This is a potential source of bias.

7. Conclusion

Overall, 2 retrospective observational studies (Pineton de Chambrun et al. 2017 and Xie et al. 2015) provided evidence for the clinical effectiveness and safety of human normal immunoglobulin preventative treatment compared with current standard care without immunoglobulin in people with idiopathic SCLS. Retrospective observational studies cannot prove cause and effect and should be considered hypothesis generating only because unknown or unmeasured factors may have influenced the findings.

The cohort study (Pineton de Chambrun et al. 2017) provided low certainty evidence for the critical outcomes, survival and frequency of acute episodes of any severity and the important outcome, frequency of severe episodes. The longitudinal study (Xie et al. 2015) provided very low certainty evidence for the critical outcome, frequency of acute episodes of any severity and the safety outcome, complications of human normal immunoglobulin treatment.

The studies provided no evidence to determine whether immunoglobulin treatment improves the important outcomes, health related quality of life, complication rates and durability of remission compared with current standard preventative care without immunoglobulin. Indirect evidence for the critical outcome of hospital admission is available under frequency of severe episodes. No direct evidence was identified for this outcome.

No evidence was identified regarding the cost effectiveness of immunoglobulin treatment compared with standard preventative care without immunoglobulin. Also, no evidence was identified regarding subgroups of patients that may benefit from immunoglobulin treatment more than the wider population of interest.

The cohort study (Pineton de Chambrun et al. 2017) provided low certainty evidence that, compared with standard preventative care without immunoglobulin, IV immunoglobulin statistically significantly improves survival in people with idiopathic SCLS for up to 10 years. The 5-year survival rate was 91% in patients treated with IV immunoglobulin, compared with 47% in patients not treated with IV immunoglobulin. 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 $p<0.0001$). Preventative treatment with IV immunoglobulin was an independent predictor of mortality ($p=0.007$), suggesting that immunoglobulin improves survival compared with standard preventative care.

Both studies in the evidence review suggest that immunoglobulin treatment reduces the frequency of acute episodes of any severity in people with idiopathic SCLS compared with current standard preventative care without immunoglobulin. The cohort study (Pineton de Chambrun et al. 2017) provided low certainty evidence that 65% of patients who received IV immunoglobulin had acute episodes over a median 5.1 years compared with 94% of patients who did not receive IV immunoglobulin (statistically significant difference, $p=0.03$). The longitudinal study (Xie et al. 2015) provided very low certainty evidence that, on average, patients had 2.6 acute episodes of any severity each year from disease onset to initiation of IV immunoglobulin (median duration 3.75 years) whereas, on average, no acute episodes were seen each year after immunoglobulin was started (statistically significant difference, $p< 0.0001$: only 3/18 patients receiving immunoglobulin treatment had an acute episode over a mean 2.7 years).

The retrospective cohort study (Pineton de Chambrun et al. 2017) provided low certainty evidence that, compared with standard preventative care without immunoglobulin, IV immunoglobulin statistically significantly reduces the frequency of severe episodes. In the study,

46% of patients who received IV immunoglobulin had severe episodes over a median 5.1 years compared with 94% of patients not treated with IV immunoglobulin ($p<0.0001$).

Only limited information was available for adverse effects of immunoglobulin, with no data or statistical analyses reported in either study. Nevertheless, the longitudinal study (Xie et al. 2015) reported that most patients did not experience significant adverse effects during IV immunoglobulin infusions, although a minority of patients experienced minor post-infusion adverse effects.

The dosage in the cohort study (Pineton de Chambrun et al. 2017) was immunoglobulin 2 g/kg monthly initiated after resolution of an acute attack. Lower dosages could also be used in the longitudinal study (Xie et al. 2015): 16 patients received 1-2 g/kg monthly and 2 patients received half the standard dose (0.5-1 g/kg) every 2 weeks. Doses could be tapered in the cohort study if there was no recurrence after at least a year.

The included studies are small observational studies, which are subject to bias and confounding, and the quality of the evidence for all outcomes was assessed as low or very low certainty. However, idiopathic SCLS is a rare condition and, therefore, conducting prospective comparator studies may be unrealistic. Taking this into account, the cohort study appears to be appropriately designed and well reported, and the outcomes considered are relevant to patients.

The findings of this evidence review are important for people with idiopathic SCLS because they suggest that IV immunoglobulin treatment reduces the frequency of acute episodes (including severe episodes, such as those requiring hospital admission) and improves survival compared with current standard preventative care without immunoglobulin. Any potential benefits of treatment must be balanced against the unclear adverse event profile of immunoglobulin in this population.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with idiopathic SCLS, what is the clinical effectiveness of human normal immunoglobulin preventative treatment compared with current standard care?
2. In people with idiopathic SCLS, what is the safety of human normal immunoglobulin preventative treatment compared with current standard care?
3. 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?
4. 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?
5. From the evidence selected, what doses, frequency and route of administration human normal immunoglobulin preventative treatment were used?

P – Population and Indication	People with idiopathic systemic capillary leak syndrome who have recovered or are recovering from an acute episode. [Synonyms for idiopathic systemic capillary leak syndrome include Clarkson's syndrome, monoclonal gammopathy-associated systemic capillary leak syndrome, systemic capillary leak syndrome, idiopathic capillary leak syndrome, Clarkson's disease, Clarkson disease, or unexplained primary anasarca] [Patients with systemic capillary leak syndrome that is secondary to a known causative agent of the condition, including but not limited to, haematological malignancy, certain medications, certain viral infections, should be excluded. These patients may be referred to as having secondary systemic capillary leak syndrome] [Patients described as having chronic idiopathic SCLS and appropriate abbreviations of all terms e.g. CISCLS should be included in this review]
I – Intervention	Human normal immunoglobulin every 4-6 weeks, with or without standard preventative care. Standard preventative care may include immunosuppressants such as theophylline, or may involve best supportive care [IVIg at a dose of 1-2 g/kg or SCIg at equivalent doses] [Treatment is usually commenced at, or during, the resolution of an acute episode to prevent further acute episodes and therefore may be termed as treatment or prevention/prophylaxis. Phrases such as preventative treatment, maintenance treatment, secondary prevention, secondary prophylaxis, long term treatment, are all relevant and should be included]

C – Comparator(s)	Standard preventative therapy [The term maintenance therapy may be used interchangeably with terms including preventative treatment, long-term treatment, secondary prevention or secondary prophylaxis]
O – Outcomes	**<u>Clinical Effectiveness</u>** *Unless stated for the outcome, minimum clinically important differences (MCIDs) are unknown. Outcomes ideally measured at 6, 12, 24 months as well as long-term outcomes.* ***<u>Critical to decision making</u>*** **Survival** *This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about their health and well-being during that time.* [Other terms used to describe or indicate survival include but are not limited to, overall survival, survival rate, death] **Frequency of acute episodes per year of any severity** *This outcome is important to patients because this is a relapsing condition and is characterised by acute episodes. These can be life threatening and require hospital admission. Frequency of acute episodes of any severity is a marker of overall disease activity and would provide important information about disease severity, symptom control and thus quality of life.* **Hospital admissions** *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.* [Admissions may be to secondary care, or intensive care] [Terms used to describe or indicate admissions include but are not limited to; total hospital bed days, total admission duration, total intensive care bed days, total intensive care admission duration, number of admissions to hospital, number of admissions to intensive care] ***<u>Important to decision making:</u>*** **Health related quality of life (HRQL)** *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.* [Other terms used to describe or indicate quality of life include but are not limited to; patient-reported quality of life outcomes, health related quality of life. Examples of metrics

	to assess quality of life include but are not limited to: Short Form (SF-36), EuroQuality of Life Five Dimensions (EQ-5D) Other methods of assessing quality of life include but are not limited to subjective/self-reported/carer reported quality of life experiences.] **Complication rate of SCLS** *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.* [Complications include but are not limited to; limb compartment syndromes requiring fasciotomies and/or limb amputations, pulmonary oedema, pleural effusions, pericardial effusions, acute renal failure, need for dialysis or other forms of renal replacement therapy, acute cardiac injury, and deep venous thrombosis] **Frequency of severe episodes per year** *This 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.* [Definition of a severe episode includes but is not limited to the presence of any of the following criteria; systolic blood pressure <80 mm Hg, mean blood pressure <65 mm Hg, loss of consciousness, admission to the intensive care unit] **Durability of remission** *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.* [Terms used to describe or indicate durability of remission include, but are not limited to; time to recurrence, remission duration, time to relapse] <u>Safety</u> **Complications of human normal immunoglobulin (IVIg/SCIg) therapy** *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* [Other terms used to describe or indicate safety include, but are not limited to; adverse events, serious/ major adverse events. This may include but is not limited to; death, aseptic meningitis, myocardial infarction, need for intensive care admission, haemolysis, fever, chills, rash, headache] **<u>Cost effectiveness</u>**
Inclusion criteria	

Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013 – 2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, preprints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search date: 26 January 2023. Results earlier than 2013 were excluded.

Database: Medline All
Platform: Ovid
Version: Ovid MEDLINE(R) ALL <1946 to January 25, 2023>
Search date: 26th Jan 2023
Number of results retrieved: 241
Search strategy:
---
1 Capillary Leak Syndrome/ (675)
2 (Capillary Leak* or SCLS* or ISCLS* or CISCLS* or (clarkson* adj1 (syndrome* or disease*))).tw. (2411)
3 1 or 2 (2625)
4 exp immunoglobulins/ (970488)
5 (Immunoglobulin* or IVIg or SCIg or "immun* globulin*" or Subgam* or Cutaquig* or Gammanorm* or Hizentra* or "antibod* protein*" or endobulin* or flebogamma* or gamastan* or gamimmune* or gamimune* or "gamma globulin*" or gammagee* or gammaglobulin* or gammar* or gammimune* or gamulin* or globuman* or glovenin* or igam* or igc* or "serum globulin*" or immuno or immunogammaglobulin* or immunoprotein* or intraglobin* or isiven* or iveegam* or ivega* or ivig* or panglobulin* or sandoglobin* or tegelin* or veinoglobulin*).tw. (228060)
6 4 or 5 (1070887)
7 3 and 6 (288)
8 limit 7 to english language (273)
9 animals/ not humans/ (5052829)
10 8 not 9 (241)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2023 January 25>
Search date: 26th Jan 2023
Number of results retrieved: 351 (main search); 112 (conferences)
Search Strategy:
---
1 capillary leak syndrome/ (3608)
2 (Capillary Leak* or SCLS* or ISCLS* or CISCLS* or (clarkson* adj1 (syndrome* or disease*))).tw. (3578)
3 1 or 2 (5222)
4 exp immunoglobulin/ (572656)
5 (Immunoglobulin* or IVIg or SCIg or "immun* globulin*" or Subgam* or Cutaquig* or Gammanorm* or Hizentra* or "antibod* protein*" or endobulin* or flebogamma* or gamastan* or gamimmune* or gamimune* or "gamma globulin*" or gammagee* or gammaglobulin* or gammar* or gammimune* or gamulin* or globuman* or glovenin* or igam* or igc* or "serum globulin*" or immuno or immunogammaglobulin* or immunoprotein* or intraglobin* or isiven* or iveegam* or ivega* or ivig* or panglobulin* or sandoglobin* or tegelin* or veinoglobulin*).tw. (301161)
6 4 or 5 (707433)

7 3 and 6 (501)
8 limit 7 to english language (482)
9 nonhuman/ not human/ (5189955)
10 8 not 9 (463)
11 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5438279)
12 10 not 11 (351)
13 10 and 11 (112)

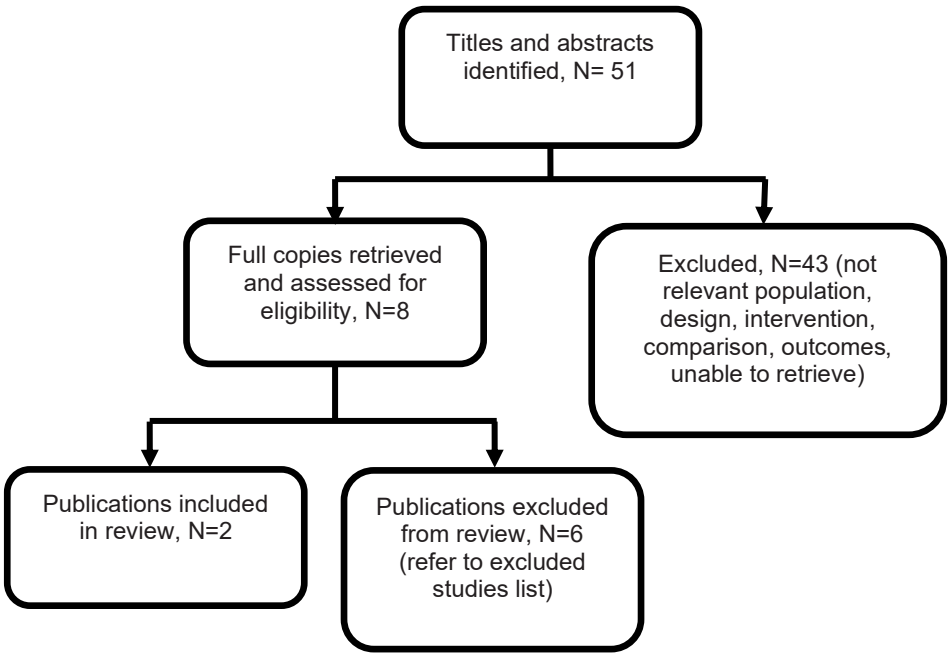
Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews
Platform: Wiley
Version:
CDSR - Issue 1 of 12, January 2023
CENTRAL – Issue 1 of 12, January 2023
Search date: 26th Jan 2023
Number of results retrieved: CDSR – 0; CENTRAL – 10.
Search strategy:

ID	Search	Hits
#1	MeSH descriptor: [Capillary Leak Syndrome] this term only	18
#2	(Capillary Leak* or SCLS* or ISCLS* or CISCLS* or (clarkson* near/1 (syndrome* or disease*))):ti,ab,kw	372
#3	#1 or #2	372
#4	MeSH descriptor: [Immunoglobulins] explode all trees	29711
#5	(Immunoglobulin* or IVIg or SCIg or "immun* globulin*" or Subgam* or Cutaquig* or Gammanorm* or Hizentra* or "antibod* protein*" or endobulin* or flebogamma* or gamastan* or gamimmune* or gamimune* or "gamma globulin*" or gammagee* or gammaglobulin* or gammar* or gammimune* or gamulin* or globuman* or glovenin* or igam* or igc* or "serum globulin*" or immuno or immunogammaglobulin* or immunoprotein* or intraglobin* or isiven* or iveegam* or ivega* or ivig* or panglobulin* or sandoglobin* or tegelin* or veinoglobulin*):ti,ab,kw	18089
#6	#4 or #5	39558
#7	#3 and #6	14
#8	"conference":pt or (clinicaltrials or trialsearch):so	658360
#9	#7 not #8	10
#10	"conference":pt	215178
#11	#7 and #10	0

Appendix C Evidence selection

The literature searches identified 51 references. These were screened using their titles and abstracts and 8 references were obtained in full text and assessed for relevance. Of these, 2 references are included in the evidence summary. The remaining 6 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Xie Z., Chan EC, Long LM et al. (2015). High-dose intravenous immunoglobulin therapy for systemic capillary leak syndrome (Clarkson disease). American Journal of Medicine 128(1): 91-5	Included
Pineton de Chambrun M, Gousseff M, Mauhin W et al. (2017). Intravenous immunoglobulins improve survival in monoclonal gammopathy-associated systemic capillary leak syndrome. American Journal of Medicine 130(10): 1219e19-1219e27	Included
Moyon Q, Pineton de Chambrun M, Gousseff M et al. (2022). Intravenous immunoglobulins tapering and withdrawal in systemic capillary leak syndrome (Clarkson disease). The Journal of Allergy and Clinical Immunology: In Practice 10(11): 2889-95	Excluded: incorrect population (looks at outcomes on stopping treatment, not during preventative treatment following an acute episode)

Appendix D Excluded studies table

Study reference	Reason for exclusion
Bozzini M-A, Milani GP, Bianchetti MG et al. (2018) Idiopathic systemic capillary leak syndrome in childhood: Systematic review of the literature. Swiss Medical Weekly 147 (supplement228): 64s	Incorrect study type (literature review)
Eo TS, Chun KJ, Hong SJ et al. (2018) Clinical presentation, management, and prognostic factors of idiopathic systemic capillary leak syndrome: a systematic review. The Journal of Allergy and Clinical Immunology. In Practice 6(2): 609-18	Incorrect study type (systematic review of case reports/series: higher quality evidence available)
Hsu P, Xie Z, Frith K et al. (2015) Idiopathic systemic capillary leak syndrome in children. Pediatrics 135(3): e730-5	Incorrect study type (case series: higher quality evidence available)
Moyon Q, Pineton de Chambrun M, Gousseff M et al. (2022). Intravenous immunoglobulins tapering and withdrawal in systemic capillary leak syndrome (Clarkson disease). The Journal of Allergy and Clinical Immunology: In Practice 10(11) 2889-95	Incorrect population (looks at outcomes on stopping treatment, not during preventative treatment following an acute episode)
Pecker MS, Hammudi M, Melchio R et al. (2022) Management of acute episodes of Clarkson disease (monoclonal gammopathy-associated systemic capillary leak syndrome) with intravenous immunoglobulins. Annals of internal medicine. Clinical cases 1(6)	Incorrect population (treatment of acute attacks, not preventative treatment)
Wan XC, Lai A, Kompala T et al. (2017) Mimicker of hereditary angioedema: Idiopathic systemic capillary leak syndrome successfully treated with intravenous immunoglobulin. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology 118(5): 631-2	Incorrect study type (single case report)

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Pineton de Chambrun M, Gousseff M et al. (2017). Intravenous immunoglobulins improve survival in monoclonal gammopathy-associated systemic capillary leak syndrome. American Journal of Medicine 130(10): 1219e19-1219e27 **Study location** 49 centres in 8 countries (France, Italy, Israel, Switzerland, Lebanon, Canada, Spain, and Turkey) **Study type** Cohort analysis of all patients included in the European Clarkson disease (EurêClark) registry using standardised forms **Study aim** 'This study was conducted to better describe the clinical characteristics, natural history, and long-term outcome of monoclonal gammopathy-associated systemic capillary leak syndrome' **Study dates** January 1997 to March 2016	**Inclusion criteria** Patients with Clarkson disease (SCLS) defined as: • monoclonal gammopathy • 1 or more episodes that met certain criteria (signs of acute hypovolaemia and interstitial oedema) • haemoconcentration with paradoxical hypoproteinaemia **Exclusion Criteria** • Any other cause of secondary capillary leak syndrome or hypoproteinaemia • No monoclonal gammopathy **Total sample size** 69 patients 4 patients died during their first episode and were not included in the follow-up analysis **No. of participants in each treatment group** 48 patients (73.8%) received IVIg **Baseline characteristics** • 49.3% male • Mean age at disease onset 52 years (±12 years) • All patients had IgG monoclonal gammopathy	**Interventions** Preventative treatment with IVIg 2 g/kg monthly (n=48, 73.8%), 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 IVIg treatment 4.3 years (interquartile range 2.3 to 7.5 years) **Comparators** No IVIg (n=17) Other preventative treatments were: • theophylline 400-1600 mg daily (n=22, 34%) • terbutaline 15-25 mg daily (n=22, 34%), and • thalidomide 50-100 mg daily (n=5, 7.7%) 23 patients (35.4%) received more than 1 preventative treatment 9 patients received no preventative treatment Median follow-up was 5.1 years (interquartile range 2.5 to 9.7 years)	**Critical outcomes** **Survival** Compared with patients who did not receive IVIg, statistically significantly more patients who received IVIg were alive at the end of follow-up (5/17 [29.4%] versus 40/48 [83.3%]; p<0.0001) Preventative treatment with IVIg was an independent predictor of mortality (multivariate HR 0.27, 95% CI 0.10 to 0.70; p=0.007) The 5-year survival rate was 91% in patients treated with IVIg, compared with 47% in patients not treated with IVIg. The 10-year survival rate was 77% in patients treated with IVIg, compared with 37% in patients not treated with IVIg (log rank test p<0.0001) Compared with non-survivors, survivors received IVIg statistically significantly more often (8/20 [40%) versus 40/45 [88.9%]; p<0.0001) **Frequency of acute episodes of any severity** Compared with patients who did not receive IVIg during follow-up, statistically significantly fewer patients treated with IVIg had acute episodes (16/17 [94.1%] versus 31/48 [64.6%] p=0.03) **Important outcomes** **Frequency of severe episodes** Compared with patients who did not receive IVIg during follow-up, statistically significantly fewer patients treated with IVIg had severe episodes (16/17 [94.1%] versus 22/48 [45.8%]; p<0.0001) Compared with patients who had severe episodes during follow-up, statistically significantly fewer patients without severe	This study was appraised using the Newcastle-Ottawa tool for cohort studies. Domain 1: Selection b) Truly representative c) Drawn from the same community as the exposed cohort a) Secure record b) Yes **Domain 2: Comparability** a) Study controls for age and sex b) Study controls for other factors (no statistically significant differences in univariate analyses for various demographic, clinical and biological characteristics) **Domain 3: Outcome** b) Record linkage a) Yes. Follow-up forms were completed every 6 months. Median follow-up was 5 years a) Complete follow-up **Overall quality is assessed as good** **Other comments:** considering idiopathic SCLS is a rare disease, the study is relatively large, appropriately designed and well-reported. However, it is a retrospective observational study with no blinding of interventions or outcomes and is, therefore, subject to bias and confounding. It cannot prove cause and effect and should be considered hypothesis generating only because unknown or unmeasured factors may have influenced the findings. In the study, patients were recruited over 2 decades; therefore, treatment regimens were heterogeneous. It is unclear which preventative treatments patients in the non-IVIg group were taking, if any, and whether any patients receiving IVIg were also taking another

	No children were included because none had monoclonal gammopathy		episodes received IVIg (22/38 [57.9%] versus 26/27 [96.3%]; p<0.0001) Severe episodes were defined as systolic blood pressure <80 mm Hg, mean blood pressure <65 mm Hg, loss of consciousness, admission to intensive care or a combination of these	preventative treatment. Patients without monoclonal gammopathy were not considered for inclusion in the registry. No children were included in the study because none had monoclonal gammopathy Source of funding: none
Full citation Xie Z, Chan EC, Long LM et al. (2015). High-dose intravenous immunoglobulin therapy for systemic capillary leak syndrome (Clarkson disease). American Journal of Medicine 128(1): 91-5 **Study location** United States **Study type** Longitudinal study using a retrospective questionnaire **Study aim** 'Here, we evaluated the efficacy of IVIg as prophylactic therapy in a cohort of patients with the SCLS' **Study dates** 2008 to May 2014	**Inclusion criteria** Patients aged over 16 years of age who met certain criteria for SCLS, including: • oedema with >1 kg of weight gain in <1 week or acute hypotension • haemoconcentration with hypoproteinaemia or hypoalbuminemia (Gousseff et al. 2011) **Exclusion Criteria** Any other cause of secondary capillary leak syndrome or hypoproteinaemia (Gousseff et al. 2011) **Total sample size** 21 patients (29 patients were enrolled in the study, but only 22 returned the questionnaire. 1 patient was subsequently excluded because diagnosis was uncertain) **No. of participants in each treatment group** 18 patients (85.7%) received IVIg **Baseline characteristics** • 82% male • Median age at disease onset 46 years (range 32 to 66 years)	**Interventions** 18 people received preventative treatment with IVIg 1-2 g/kg monthly at some stage during the study period 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 2.7 years (range 10 months to 4.9 years) **Comparators** Outcomes were compared in the study population while IVIg was not being administered (n=21) 19 patients (90.5%) received theophylline as a preventative treatment after diagnosis, alone or in combination with terbutaline or albuterol for a median 2 years (range 3 months to 8 years) Median follow-up was 7 years (range 2.4 to 25 years)	**Critical outcomes** **Frequency of acute episodes of any severity per year** 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 IVIg (median duration 3.75 years, range 10 months to 23.8 years). Following IVIg prophylaxis, the frequency of acute episodes per year was statistically significantly lower (0 per patient, range 0 to 3.3 episodes; p<0.0001). 15/18 patients (83.3%) did not experience any significant episodes of SCLS while receiving IVIg Significant episodes were defined as requiring medical attention in a provider's office, emergency room and/or hospital admission **Safety** **Complications of immunoglobulin treatment** Most patients did not experience significant adverse effects during IVIg infusions. A minority reported minor post-infusion adverse effects, most commonly transient headache, rash and fatigue (data and statistical analyses not reported)	This study was appraised using the National Institutes of Health quality assessment tool for before-after [pre-post) study with no control group 1. Yes 2. Yes (via citation) 3. No 4. No 5. Cannot determine 6. Yes 7. Cannot determine 8. No 9. Yes 10. Cannot determine 11. No 12. Cannot determine **Overall quality is assessed as poor** Other comments: longitudinal studies have several limitations including, primarily the lack of a concurrent control group. Data are collected from different time periods and bias can occur if other changes over that period are not considered (for example, other changes in treatment pathways and clinical management). The study assessed outcomes using a retrospective questionnaire completed by patients. Questionnaires are subject to bias because they rely on patients understanding the questions and accurately remembering information. Response rate is another limitation: 17% of patients did not return their questionnaire in this study. There was no blinding of interventions or outcomes. The study included adults only. Source of funding: the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health

Abbreviations

CI, confidence interval; HR, hazard ratio; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; p, p value; SCLS, systemic capillary leak syndrome , also known as Clarkson disease

Appendix F Quality appraisal checklists

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
    a) Truly representative (1 star)
    b) Somewhat representative (1 star)
    c) Selected group
    d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
    a) Drawn from the same community as the exposed cohort (1 star)
    b) Drawn from a different source
    c) No description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
    a) Secure record (e.g., surgical record) (1 star)
    b) Structured interview (1 star)
    c) Written self report
    d) No description
    e) Other
4) Demonstration that outcome of interest was not present at start of study
    a) Yes (1 star)
    b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
    a) The study controls for age, sex and marital status (1 star)
    b) Study controls for other factors (list) _____ (1 star)
    c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome
    a) Independent blind assessment (1 star)
    b) Record linkage (1 star)
    c) Self report
    d) No description
    e) Other
2) Was follow-up long enough for outcomes to occur
    a) Yes (1 star)
    b) No
    Indicate the median duration of follow-up and a brief rationale for the assessment above:_____
3) Adequacy of follow-up of cohorts
    a) Complete follow-up- all subject accounted for (1 star)
    b) Subjects lost to follow-up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (1 star)
    c) Follow-up rate less than 80% and no description of those lost
    d) No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):
Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

National Institutes of Health quality assessment tool for before-after (pre-post) study with no control group

Q. The National Institutes of Health quality assessment tool for before-after (pre-Post) study with no control group Website: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools			
Major Components	Response options		
1. Was the study question or objective clearly stated?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Yes	No	Cannot Determine/ Not Applicable/ Not Reported
Quality Rating	Good	Fair	Poor
Additional Comments (If Poor, please state why):			

Appendix G GRADE profile

Table 2: Question: In people with idiopathic SCLS, what is the clinical effectiveness and safety of human normal immunoglobulin preventative treatment compared with current standard care?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	IVIg	No IVIg (standard care)	Result (95%CI)		
Survival (1 retrospective cohort study)									
5-year survival rate									
Retrospective cohort study (Pineton de Chambrun et al. 2017)	No serious limitations	No serious indirectness	Not applicable	Not calculable	91% (n=48)	47% (n=17)	Log rank test p<0.0001	Critical	Low
10-year survival rate									
Retrospective cohort study (Pineton de Chambrun et al. 2017)	No serious limitations	No serious indirectness	Not applicable	Not calculable	77% (n=48)	37% (n=17)	Log rank test p<0.0001	Critical	Low
Number of patients (%) who survived (median follow-up 5.1 years, interquartile range 2.5 to 9.7 years)									
Retrospective cohort study (Pineton de Chambrun et al. 2017)	No serious limitations	No serious indirectness	Not applicable	Not calculable	40/48 (83.3%)	5/17 (29.4%)	p<0.0001 Preventative treatment with IVIg was an independent predictor of mortality (multivariate HR 0.27, 95% CI 0.10 to 0.70; p=0.007)	Critical	Low
Frequency of acute episodes of any severity (1 retrospective cohort study and 1 retrospective longitudinal study)									
Number of patients (%) who had an acute episode of any severity (median follow-up 5.1 years, interquartile range 2.5 to 9.7 years)									
Retrospective cohort study (Pineton de Chambrun et al. 2017)	No serious limitations	No serious indirectness	Not applicable	Not calculable	31/48 (64.6%)	16/17 (94.1%)	p=0.03	Critical	Low
Median frequency of acute episodes of any severity per year									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**IVIg**	**No IVIg (standard care)**	**Result (95%CI)**		
Retrospective longitudinal study (Xie et al. 2015)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	0 per patient, (range 0 to 3.3, n=21)	2.6 per patient (range 0.25 to 15.4, n=18)	p<0.0001	Critical	Very low
Number of patients (%) who had a severe episode (median follow-up 5.1 years, interquartile range 2.5 to 9.7 years)									
Retrospective cohort study (Pineton de Chambrun et al. 2017)	No serious limitations	No serious indirectness	Not applicable	Not calculable	22/48 (45.8%)	16/17 (94.1%)	p<0.0001	Important	Low
Safety (1 retrospective longitudinal study)									
Adverse effects									
Retrospective longitudinal study (Xie et al. 2015)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	Most patients did not experience significant adverse effects during infusions. A minority reported minor post-infusion adverse effects, most commonly transient headache, rash and fatigue	Not reported	No data or statistical analyses reported	Safety	Very low

Abbreviations

CI, confidence interval; HR, hazard ratio; IVIg, intravenous immunoglobulin; p, p value; SCLS, systemic capillary leak syndrome

1 Downgraded. Data in this study were collected from different time periods and it is not known if changes over that period have been taken into account (for example, other changes in treatment pathways and clinical management). The study assessed outcomes using a retrospective questionnaire completed by patients, which is subject to bias. Also, 17% of patients (5/29) did not return their questionnaire

Glossary

Idiopathic Systemic Capillary Leak Syndrome (SCLS)	Idiopathic SCLS (also known as Clarkson disease) is an extremely rare condition, the cause of which is unknown. It causes fluid and proteins to leak out of capillaries into surrounding tissues. This can lead to hypotension, hypoalbuminemia, and thickened blood due to a decrease in plasma volume (haemoconcentration). Complications include general swelling, compartment syndrome, kidney failure, and stroke, and the condition can be fatal. SCLS occurs in episodes which vary in frequency, with some people having several episodes per year.
Human normal immunoglobulin	Human normal immunoglobulin is used in a variety of conditions, many of which involve the immune system and reduce or stop antibody production. It is prepared using donated human plasma and contains immunoglobulin G (IgG) and antibodies to various viruses. It is generally given intravenously (IVIg) or subcutaneously (SCIg).

References

Included studies

- Pineton de Chambrun M, Gousseff M et al. (2017). Intravenous immunoglobulins improve survival in monoclonal gammopathy-associated systemic capillary leak syndrome. American Journal of Medicine 130(10): 1219e19-1219e27
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- Gousseff M, Arnaud L, Lambert M et al. (2011) The systemic capillary leak syndrome: a case series of 28 patients from a European registry. Ann Intern Med 154(7): 464-71

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