Abstract

Approximately 500 cases of idiopathic systemic capillary leak syndrome (Clarkson syndrome) have been reported worldwide. This life-threatening condition is characterized by episodes of increase in vascular permeability with loss of fluid into the interstitium and presents with acute onset of edema, signs of tissue hypoperfusion, hemoconcentration and low blood protein level. It has been diagnosed mainly in middle-aged adults with a monoclonal gammopathy. We performed a review of the literature on Clarkson syndrome in subjects ≤18 years of age.

We identified 24 reports, published since 1989, providing data on 32 otherwise healthy subjects, who experienced 67 well documented episodes of Clarkson syndrome. The condition affected more frequently girls (21, 66%) than boys, presented throughout childhood and was preceded by a mostly viral illness in 75% of cases. A monoclonal gammopathy was never reported. Uncompensated circulatory shock, muscle compartment syndrome, acute kidney injury, pulmonary edema and either pleural or pericardial effusion were, in decreasing order of frequency, the most common complications. Four patients died.

In conclusion, Clarkson syndrome develops not only in adulthood but also in childhood. In this age group, this condition is not linked to a monoclonal gammopathy.

Abbreviations: None

What is known

• Clarkson syndrome is a rare condition that has been diagnosed mainly in middle-aged adults and is mostly linked to a monoclonal gammopathy.

What is new

• In subjects ≤18 years of age, Clarkson syndrome is not linked to a monoclonal gammopathy.

Introduction

Idiopathic systemic capillary leak syndrome, first reported in 1960 by Bayard Clarkson and colleagues [1], and often referred to as Clarkson syndrome, is an unexplained condition characterized by episodes of acute increase in vascular permeability resulting in loss of protein-rich fluid into the interstitial compartment [2]. Episodes of the syndrome are often preceded by an acute intercurrent illness, present with the extravasation phase (which includes a first oligosymptomatic stage and a second polysymptomatic stage), characterized by peripheral edema and hypovolemia, and end in the recovery phase, characterized by the normalization of vascular permeability [2].

Clarkson syndrome has been diagnosed mainly in middle-aged adults with a monoclonal gammopathy [2]. Stimulated by our experience with a girl affected by this condition [3], we conducted a systematic review of the pediatric literature. The main questions were to document the preceding triggers, the clinical features and the prognosis in children affected by Clarkson syndrome. The recently proposed treatment recommendations for these patients are also shortly discussed.

Methods

Between December 2017 and March 2018, we performed a search with no date limits of the Medical Subject Headings terms “idiopathic capillary leak” OR “Clarkson disease” OR “Clarkson syndrome” OR “primary capillary leak” OR “hyperpermeability capillary syndrome” in the US National Library of Medicine and Excerpta Medica databases. In an effort to detect all relevant secondary references, the literature of each included article as well as co-authors personal files were screened. The review was performed according to the Economic and Social Research Council guidance on the

conduct of narrative synthesis and on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [4].

We selected only articles reporting cases of Clarkson syndrome (with or without monoclonal gammopathy) initially presenting in subjects ≤18 years of age. Reports published in Dutch, English, French, German, Italian, Portuguese or Spanish were eligible, while articles in other languages were not considered. When more than one paper reported on the same patient, only the more comprehensive publication was retained. Patients affected by pre-existing conditions that have been associated with capillary leak such as adverse drug reactions, anaphylaxis, cancer, postoperative course, pregnancy, systemic inflammatory response syndrome, traumatic injuries or kidney diseases, were excluded [2].

The diagnosis of Clarkson syndrome was made in children with acute onset of i) peripheral edema, ii) signs of tissue hypoperfusion including tendency to cool extremities, delayed capillary refill time, high heart and respiratory rate, weak pulse or low blood pressure [5], iii) increase in the proportion of formed elements in the blood (hemoconcentration) and iv) low blood protein level (total hypoproteinemia, hypoalbuminemia or both) without any alternative explanation [2].

Episodes characterized by uncompensated shock (with or without acute kidney injury), muscle compartment syndrome, need for ventilatory support or death were defined as severe.

From each reported case, following 10 data were sought: 1) gender, 2) age, 3) pre-existing conditions, 4) acute intercurrent illnesses preceding the extravasation phase by ≤7 days, 5) edema, 6) hemodynamic parameters (including shock), 7) laboratory data (including acute kidney injury and search for a monoclonal gammopathy), 8) rhabdomyolysis (with or without compartment syndrome), 9) management, and 10) number of episodes. In various instances, authors of published reports were also asked to provide additional missing data. The completeness of reporting was graded,

according to the number of the aforementioned 10 items that were clearly reported, as high (≥8 items), satisfactory (5 to 7 items) or low (<5 items). Acute kidney injury was categorized as stage I, II or III according to the KDIGO classification [6].

Literature search, report selection and data extraction were independently performed by two investigators (MAB, SAGL). Disagreements were resolved by consensus or adjudicated by a senior author (MGB). The Cohen's kappa index was utilized to assess the agreement between investigators in applying inclusion and exclusion criteria. Results are given either as frequency or as median and interquartile range, as appropriate. Proportions were compared with the Fisher exact test, continuous variables with the Mann-Whitney-Wilcoxon test. Statistical significance was assigned at $p<0.05$.

Results

Search results

The literature search process is summarized in figure 1. The chance-adjusted agreement between the two investigators on the application of the inclusion and exclusion criteria was 0.87. For the final analysis, we retained 24 scientific reports published since 1989 [3, 7-29]: 9 from Europe (France, N=3; Israel, N=2; Italy, N=2; Czeck Republic, N=1; Slovenia, N=1), 9 from North America (United States of America, N=6; Canada, N=3), 5 from Asia (Turkey, N=2; India, N=1; Lebanon, N=1; Japan, N=1) and 1 from Australia. Twenty-three reports were published in English [3, 8-29] and one in French [7]. Completeness of reporting was high in 12, satisfactory in 8 and low in 4 articles.

Findings

The aforementioned 24 reports provided data on 32 otherwise healthy children, who presented with edema (pitting and non-itching in all but one

case), signs of tissue hypoperfusion, hemoconcentration and low blood protein level (table 1). The condition affected more frequently girls than boys, initially presented throughout childhood and was preceded by an acute illness in 75% of the cases. A mononclonal gammopathy was never detected. Ten patients experienced a single episode of capillary leak. The remaining 22 patients developed two or more episodes.

Sixty-seven episodes were rather well documented (table 2). Uncompensated circulatory shock (with or without secondary cardiac arrhythmias), rhabdomyolysis (with or without compartment syndrome), acute kidney injury, pulmonary edema and either pleural or pericardial effusion were, in decreasing order of frequency, the most common complications. Out of the 14 episodes of pulmonary edema, only 3 also had suffered from acute kidney injury. Both newborn infants [14, 24], an 8-year-old girl [16] and a 12-year-old boy [28] died during the acute phases of the disease. Interestingly, Clarkson syndrome concurrently affected one of these two newborns and its mother [14]. Forty (60%) of the 67 episodes were severe. Severe and not-severe episodes did not significantly differ with respect to age and sex.

Following microorganisms were detected in 15 cases of Clarkson syndrome preceded by an acute intercurrent illness: Influenzavirus (type A, N=6; type B, N=1), Parainfluenzavirus (type 1, N=1; type 3, N=1), Enteroviruses (N=3), Respiratory syncytial virus (N=1), Rotavirus (N=1), and group A Streptococcus (N=1).

Intravenous hydration, with or without inotropics, and 0_2-therapy were provided in almost all episodes. The remaining treatment options that were used in the 67 mentioned episodes of Clarkson syndrome are depicted in table 3. Ventilatory support was provided in 19 (including extra corporeal membrane oxygenation in one case) and cardiorespiratory resuscitation in 5 episodes. Fifteen patients were prescribed various agents on a long-term basis in order to prevent recurrences.

Discussion

Approximately 500 cases of Clarkson syndrome have been reported worldwide, primarily in middle-aged adults with a monoclonal gammopathy [2, 29]. This comprehensive literature review documents 32 pediatric cases of Clarkson syndrome. Like in adults, childhood Clarkson syndrome is an acute non-familial condition that is life-threatening and tends to recur. Childhood Clarkson syndrome affects newborns, infants, toddlers, preschoolers and especially schoolers and is very often preceded by an acute mostly viral intercurrent illness and is not linked to a monoclonal gammopathy.

The initial oligosymptomatic extravasation stage [2, 29] is characterized by non-specific (such as fatigue, irritability, abdominal pain, vomiting, diarrhea, nausea and aches) and more specific symptoms and signs (such as polydipsia, and increase in body weight) during one to four days. It is followed by the polysymptomatic extravasation stage, which is characterized by peripheral edema, signs of tissue hypoperfusion such as cool extremities, delayed capillary refill time, high heart and respiratory rate, weak pulse and a tendency to low blood pressure and is often complicated by uncompensated circulatory shock, signs of end-organ ischemia including acute kidney injury, muscle compartment syndrome, pleural or pericardial effusion [2, 29]. Finally, during the recovery phase, which results from the normalization of vascular permeability, extravasated fluids are recruited back into the intravascular space with subsequent volume overload and risk of pulmonary edema [2, 29].

The mechanisms underlying Clarkson syndrome are still elusive. The vast majority of affected adults have a detectable monoclonal protein in blood, but this pediatric survey supports the assumption that the monoclonal protein does not play a pivotal pathogenic role. Multiple cytokines are

elevated in blood of these patients [2, 22, 29]. Furthermore, serum from affected patients induces hyperpermeability in human endothelial cells, suggesting that a soluble factor is pathogenically crucial [29]. The Clarkson case concurrently affecting both a newborn baby and its mother suggests that the factor may be transferred from the mother to the fetus [14]. Similar mechanisms underlie various neonatal diseases such as alloimmune hemolytic anemia or thrombocytopenia of the newborn, neonatal hyperthyroidism, neonatal myasthenia, neonatal systemic lupus erythematosus [30] and transient nephrotic syndrome [31]. The vascular dysfunction in Clarkson syndrome share similarities with that seen in Ebola and Marburg hemorrhagic fevers [2]. Interestingly, Ebolavirus, Marburgvirus and all the viruses documented in childhood Clarkson syndrome (influenzavirus, parainfluenzavirus, enteroviruses, respiratory syncytial virus and rotavirus) are RNA viruses [2].

The challenging diagnosis of Clarkson syndrome deserves consideration in previously otherwise healthy children with acute onset of pitting and non-itching peripheral edema associated with the "3 **H**s" triad of tissue **H**ypoperfusion, **H**emoconcentration and either total **H**ypoproteinemia or **H**ypoalbuminemia. In these patients, "allergic" findings such as hives, tongue or perioral swelling, wheezing, or stridor are not observed and urinalysis does not disclose a significant proteinuria [2, 29].

Like further cases of hypovolemic shock, acute episodes should be managed with intravenous crystalloids, inotropic agents and supplemental O_2. Intubation and mechanical ventilation may be required to relieve an increased work of breathing. In particular, clinicians should be watching for the development of an anterior tibial compartment syndrome, which may be exacerbated by fluid resuscitation.

The transition from the extravasation to the recovery phase should be appreciated thank to a decrease in the volume of intravenous fluids

required to maintain adequate perfusion. When this occurs, the treatment focus should shift to the prevention of intravascular volume overload and its complications. During this phase, many patients require diuretics to avoid volume overload with subsequent pulmonary edema.

There are no randomized trials to guide the prevention of this condition. Rather, recommendations rest on single-patient reports, observational studies and consensus statements. Long-term prophylaxis with a) an oral combination of the β_2-adrenergic agonist terbutaline and a methylxanthine and especially b) parenteral polyclonal immunoglobulins appears to be beneficial [22, 29, 32, 33]. Furthermore, affected subjects should be encouraged to seek medical care whenever they recognize initial symptoms because early administration of immunoglobulins might be helpful [22, 29, 32, 33].

Three main limitations of this work should be acknowledged. First, results must be viewed with an understanding of the inherent limitations of the analysis process, which incorporated data from case reports that were sometimes poorly documented. Second, the number of published cases is small. Third, available data do not allow to appraise the difference between pediatric and adult Clarkson's patients.

In conclusion, this survey points out that Clarkson syndrome develops not only in adulthood but also in childhood. In this age group, this condition is not linked to a monoclonal gammopathy.

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Compliance with ethical standards

The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

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Authors' Contributions

- Concept of the manuscript: G.P.M., M.G.B.
- Literature search and analysis: M.A.B., M.G.B., S.A.G.L.
- Statistical analysis: S.A.G.L.
- Drafting of the manuscript: M.A.B.
- Critical revision of the manuscript: G.P.M., E.F.F., S.A.G.L.
- Final manuscript: M.A.B, G.P.M., M.G.B., E.F.F., S.A.G.L.

References

1. Clarkson B, Thompson D, Horwith M, Luckey EH (1960) Cyclical edema and shock due to increased capillary permeability. Am J Med 29(2):193-216. https://doi.org/10.1016/0002-9343(60)90018-8

2. Siddall E, Khatri M, Radhakrishnan J (2017) Capillary leak syndrome: etiologies, pathophysiology, and management. Kidney Int 92(1):37-46. https://doi.org/10.1016/j.kint.2016.11.029

3. Milani GP, Dellepiane RM, Castellazzi ML, Mazzoni MB, Bianchetti MG, Fossali EF (2013) Episodic idiopathic systemic capillary leak syndrome in a girl. Pediatr Int. 55(4):e81-e82. https://doi.org/10.1111/ped.12068

4. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(4):264-269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135

5. Corneli HM (1993) Evaluation, treatment, and transport of pediatric patients with shock. Pediatr Clin North Am 40(2):303-319. https://doi.org/10.1016/S0031-3955(16)38512-1.

6. Lameire N, Van Biesen W, Vanholder R (2017) Epidemiology of acute kidney injury in children worldwide, including developing countries. Pediatr Nephrol 32(8):1301-1314. https://doi: 10.1007/s00467-016-3433-2.

7. Luquel L, Glaser E, Canuel C, Vayvet C, Offenstadt G (1989) Hyperperméabilité capillaire - cause exceptionnelle de choc hypovolémique. Rev Med Interne 10(4):359-360. https://doi.org/10.1016/S0248-8663(89)80037-2.

8. Dolberg-Stolik OC, Putterman C, Rubinow A, Rivkind AI, Sprung CL (1993) Idiopathic capillary leak syndrome complicated by massive rhabdomyolysis. Chest 104(1):123-126. https://doi.org/10.1378/chest.104.1.123

9. Foeldvari I, Waida E, Junker AK (1995) Systemic capillary leak syndrome in a child. J Pediatr 127(5):739-741. https://doi.org/10.1016/S0022-3476(95)70163-X

10. Karatzios C, Gauvin F, Egerszegi EP, Tapiero B, Buteau C, Rivard GE, Ovetchkine P (2006) Systemic capillary leak syndrome presenting as recurrent shock. Pediatr Crit Care Med 7(4):377-379. https://doi.org/10.1097/01.PCC.0000227120.61949.FB

11. Onal H, Aktuglu-Zeybek C, Altun G, Ozyilmaz I, Alhaj S, Aydin A (2007) Capillary leak syndrome in a 5-month-old infant associated with intractable diarrhoea. Ann Trop Paediatr 27(1):81-86.https://doi.org/10.1179/146532807X170556

12. Dowden AM, Rullo OJ, Aziz N, Fasano MB, Chatila T, Ballas ZK (2009) Idiopathic systemic capillary leak syndrome: novel therapy for acute attacks. J Allergy Clin Immunol 124(5):1111-1113. https://doi.org/10.1016/j.jaci.2009.06.043.

13. Ebbeson RL, De Kock MJ, Penny N, Kollman TR (2009) Rhabdomyolysis, acute renal failure, and compartment syndrome in a child with parainfluenza type 1 infection. Pediatr Infect Dis J 28(9):850-852. https://doi.org/10.1097/INF.0b013e3181a33522

14. Kapoor P, Greipp PT, Schaefer EW, Mandrekar SJ, Kamal AH, Gonzales-Paz NC, Kumar S, Greipp PR (2010) Idiopathic systemic capillary leak syndrome (Clarkson's disease): the Mayo clinic experience. Mayo Clin Proc 85(10):905-912. https://doi.org/10.4065/mcp.2010.0159

15. Sion-Sarid R, Lerman-Sagie T, Blumkin L, Ben-Ami D, Cohen I, Houri S (2010) Neurologic involvement in a child with systemic capillary leak syndrome. Pediatrics 125(3):e687-e692. https://doi.org/10.1542/peds.2009-1691

16. Gousseff M, Arnaud L, Lambert M, Hot A, Hamidou M, Duhaut P, Papo T, Soubrier M, Ruivard M, Malizia G, Tieulié N, Rivière S, Ninet J, Hatron PY, Amoura Z; Capillary Leak Syndrome Registry (2011) The systemic capillary leak syndrome: a case series of 28 patients from a European registry. Ann Intern Med 154(7):464-471. https://doi.org/10.7326/0003-4819-154-7-201104050-00004

17. Piastra M, Pietrini D, Conti G, De Rosa G, Rigante D (2012) Sudden shock from capillary leak. Lancet 379(9819):976. https://doi.org/10.1016/S0140-6736(11)61819-9

18. Aldemir-Kocabaş B, Karbuz A, Ciftçi E, Demir M, Ince E (2013) An unusual cause of secondary capillary leak syndrome in a child: rotavirus diarrhea. Turk J Pediatr 55(1):90-93.

19. Iwasa T, Ohashi H, Kihira K, Koike Y, Otake K, Inoue M, Sawada H, Toyoda H, Komada Y (2014) 10-year-old girl with life-threatening idiopathic systemic capillary leak syndrome: a case report. BMC Pediatr. 2014;14:137. https://doi.org/10.1186/1471-2431-14-137

20. Perme T, Pokorn M, Markelj G, Avčin T, Battelino T, Uršič T, Vidmar I, Grosek Š (2014) Two episodes of systemic capillary leak syndrome in an 8-year-old boy, following influenza A virus infection. Pediatr Infect Dis J 33(2):222-224. https://doi.org/10.1097/INF.0000000000000029

21. Xie Z, Chan E, Yin Y, Wisch L, Nelson C, Young M, Parikh SM, Druey KM (2014) Inflammatory markers of the systemic capillary leak syndrome (Clarkson Disease). J Clin Cell Immunol 5:1000213. https://doi.org/10.4172/2155-9899.1000213

22. Hsu P, Xie Z, Frith K, Wong M, Kakakios A, Stone KD, Druey KM (2015) Idiopathic systemic capillary leak syndrome in children. Pediatrics 135(3):e730-e735. https://doi.org/10.4172/2155-9899.1000213

23. Kerketta J, Lodh M, Mandal K (2015) Clarkson disease - systemic capillary leak syndrome in a 6-year-old girl: case report. Paediatr Int Child Health 35(2):160-163. https://doi.org/10.1179/2046905514Y.0000000161

24. Kulihova K, Prochazkova M, Semberova J, Janota J (2016) Fatal primary capillary leak syndrome in a late preterm newborn. Indian J Pediatr 83(10):1197-1199. https://doi.org/10.1007/s12098-016-2134-y

25. Moreira DC, Ng CJ, Quinones R, Liang X, Chung DW, Di Paola J (2016) Microangiopathic hemolytic anemia due to ADAMTS-13 loss in idiopathic systemic capillary leak syndrome. J Thromb Haemost 14(12):2353-2355. https://doi.org/10.1111/jth.13506

26. Sacy R, Sokhn M, Bechara E, Hamzeh R (2016) Idiopathic systemic capillary leak syndrome. A case report of an eleven years old girl with review of literature. J Pediatr Neonatal Care 4(1):00128. https://doi 10.15406/jpnc.2016.04.00128.

27. Simonin M, Corbeau P, Durand P, Rosenzwajg M, Filleron A, Tran TA (2016) A possible role for IL-17 in Clarkson's disease. Eur J Paediatr Neurol 20(6):953-956. https://doi.org/10.1016/j.ejpn.2016.08.003

28. Pierce RW, Merola J, Lavik JP, Kluger MS, Huttner A, Khokha MK, Pober JS (2017) A p190BRhoGAP mutation and prolonged RhoB activation in fatal systemic capillary leak syndrome. J Exp Med 214(12):3497-3505. https://doi.org/10.1084/jem.20162143

29. Asmundsson ASE, Bjorklund AR, Fisher GA (2018) Diagnosis of systemic capillary leak syndrome in a young child treated with intravenous immunoglobulin in the acute phase. J Pediatr Intensive Care 7(2):94–96. https://doi.org/10.1055/s-0037-1607342

30. Druey KM, Parikh SM (2017) Idiopathic systemic capillary leak syndrome (Clarkson disease). J Allergy Clin Immunol 140(3):663-670. https://doi: 10.1016/j.jaci.2016.10.042.

31. Vanoni F, Lava SA, Fossali EM, Cavalli R, Simonetti GD, Bianchetti MG, Bozzini MA, Agostoni C, Milani GP (2017). Neonatal systemic lupus erythematosus syndrome. Clin Rev Allergy Immunol 53(3):469-476. https://doi 10.1007/s12016-017-8653-0.

32. Lagrue G, Branellec A, Niaudet P, Heslan JM, Guillot F, Lang P. Transmission d'un syndrome néphrotique à deux nouveau-nés – Régression spontanée. Presse Méd 1991;20(6):255-257.

33. Pineton de Chambrun M, Gousseff M, Mauhin W, Lega JC, Lambert M, Rivière S, Dossier A, Ruivard M, Lhote F, Blaison G, Alric L, Agard C, Saadoun D, Graveleau J, Soubrier M, Lucchini-Lecomte MJ, Christides C, Bosseray A, Levesque H, Viallard JF, Tieulie N, Lovey PY, Le Moal S, Bibes B, Malizia G, Abgueguen P, Lifermann F, Ninet J, Hatron PY, Amoura Z; EurêClark Study Group (2017) Intravenous immunoglobulins improve survival in monoclonal gammopathy-associated systemic capillary-leak syndrome. Am J Med 130(10):1219.e19-1219.e27. https://doi 10.1016/j.amjmed.2017.05.023.

34. Eo TS, Chun KJ, Hong SJ, Kim JY, Lee IR, Lee KH, Eisenhut M, Kronbichler A, Shin JI (2018) Clinical presentation, management, and prognostic factors of idiopathic systemic capillary leak syndrome: A systematic review. J Allergy Clin Immunol Pract 6(2):609-618. https://doi 10.1016/j.jaip.2017.07.021.

Figure 1 - Legend

Idiopathic systemic capillary leak syndrome (Clarkson syndrome) in childhood. Flowchart of the literature search process. The case of a patient reported on two occasions was counted only once.

Tables

Table 1 Characteristics of 32 pediatric patients with Clarkson syndrome reported in the literature. Results are given either as median and interquartile range or as absolute number and percentage.

N	**31**
Females : males*, N (%)	21 (66) : 11 (34)
Age at first episode, years	4.5 [1.8-7.4]
≤28 days, N (%)	2 (6.3)
1-23 months, N (%)	5 (16)
2-3 years, N (%)	5 (16)
4-5 years, N (%)	6 (19)
6-18 years, N (%)	14 (44)
Preceding acute illness, N (%)	24 (75)
Monoclonal gammopathy‡, N (%)	0 (0.0)
Number of attacks	
1, N (%)	10 (31)
≥2, N (%)	22 (69)
2, N	5
3, N	6
4, N	2
5, N	2
6, N	1
unknown but ≥2, N	6

‡ this test was not performed in 11 cases.

Table 2. Complications of 67 rather well documented episodes in pediatric patients affected by Clarkson syndrome.

	N	%
Extravasation phase		
Uncompensated circulatory shock	38	57
Rhabdomyolysis	18	27
Without compartment syndrome	9	13
With compartment syndrome‡	9	13
Acute kidney injury	14	21
Stage 1	6	
Stage 2	1	
Stage 3	3	
Stage not reported	4	
Effusion*	8	12
Brain edema	3	4.5
Disseminated intravascular coagulation	3Δ	4.5
Ischemic or hemorrhagic stroke	2	2.9
Generalized tonic-clonic seizures	1	1.5
Autonomic dysfunction	1	1.5
Recovery phase		
Pulmonary edema	14	20

‡anterior tibial compartment syndrome in all cases; *either pleural (N=4) or pericardial (N=4); Δcomplicated by microangiopathic hemolytic anemia in one case.

Table 3. Treatment options other than intravenous hydration or inotropics and prophylactic management in pediatric subjects with Clarkson syndrome. Information on treatment options was available for 67 episodes. Information on prophylactic management was available for 15 subjects. More than one treatment strategy or prophylactic management were applied in some cases.

Treatment Option	**N**	**%**
Blood products*	19	28
Antimicrobials	21	31
Corticosteroids	18	27
Polyclonal immunoglobulins	11	17
Diuretics	9	13
Methylxanthines	6	8.9
Tumor necrosis factor inhibitor	1	1.4

Prophylactic Management	**N**	**%**
Polyclonal immunoglobulins	8	53
Methylxanthines	6	40
Terbutaline	4	27
Leukotriene receptor antagonists	2	13
Ginkgo biloba	2	13
Calcium channel blocker	1	6.8

* Albumin (N=12), fresh frozen plasma (N=5), platelets (N=1), red blood cells (N=1).