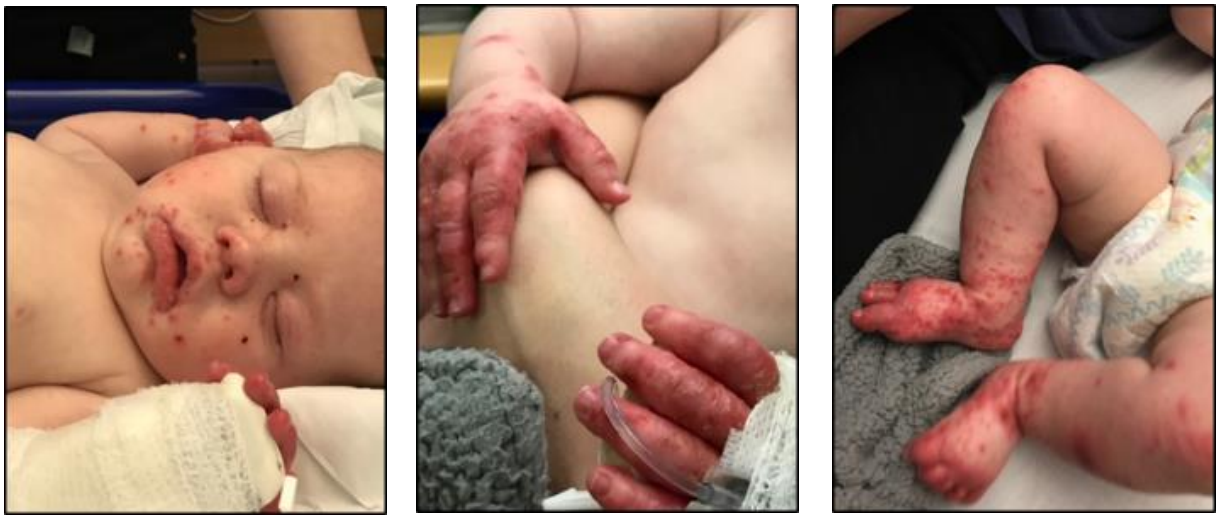
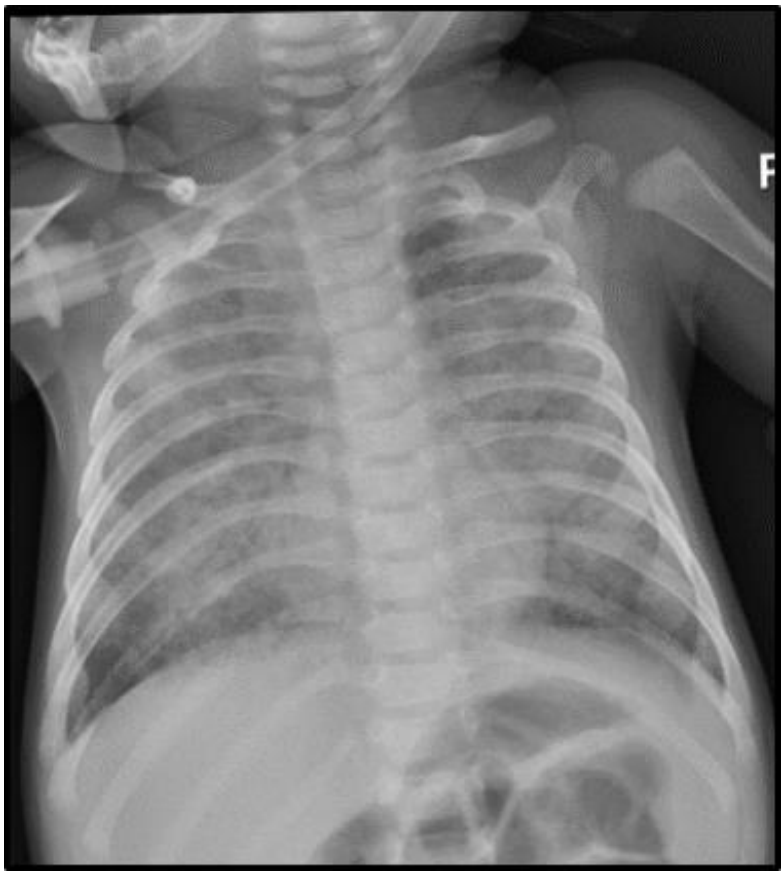
Fig 1. Classical presentation of WAS.



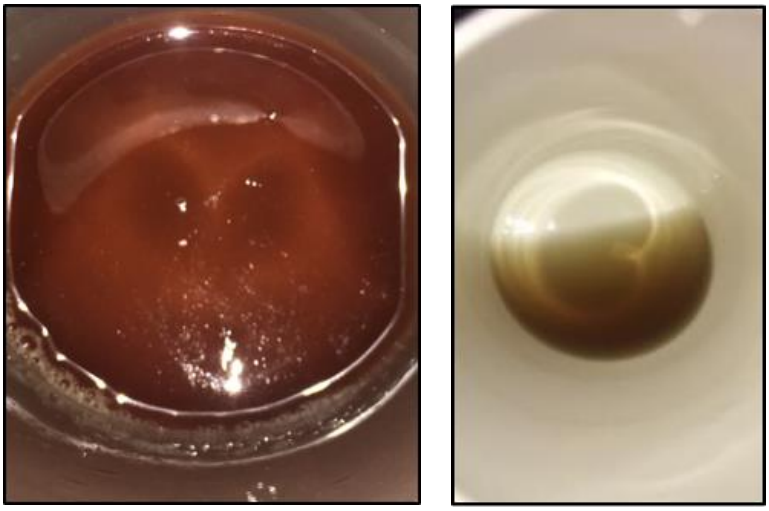
Case presentation: Severe hand-foot-and-mouth disease on a background of eczema since birth, cow's milk protein allergy and having a previous diagnosis of idiopathic thrombocytopaenia. Subsequently developed autoimmune haemolytic anaemia and thrombocytopenia.
Initial investigations: Low CD8+ T cells but otherwise normal lymphocyte numbers, with normal response to phytohaemagglutinin and vaccine response to tetanus. Platelet count was 27 x 10^9/L with normal mean platelet volume (automated). WAS protein expression was found to be absent and mutation in WAS gene [c.374G>A hemizygote, substitution of glycine for glutamic acid p.(Gly125Glu)] confirmed diagnosis.
Treatment: matched unrelated donor haematopoietic stem cell transplantation at 9 months old.

Fig 2. WAS and CMV infection.



Case presentation: Monochorionic diamniotic twins presented with cytomegalovirus (CMV) pneumonitis at 5 months old on a background of persistent thrombocytopenia, infected eczema, reflux and colitis in the context of cow's milk protein allergy. One twin subsequently developed pre-B infant acute lymphoblastic leukaemia.
Initial investigations: normal lymphocyte numbers and response to phytohaemagglutinin stimulation with normal vaccine responses to tetanus and pneumococcus (conjugate vaccine) but absent response to CD3 stimulation. Platelet counts were low, at 37 x 10^9/L, with low mean platelet volume of 6.9. WAS protein expression was absent by flow and immunoblot, with mutation in WAS gene (c777+1G>A splice site mutation) confirming diagnosis. CMV viral loads were 302 888 and 122 834 copies/ml at presentation.
Treatment: Haploidentical (T cell receptor/CD19 depleted) haematopoietic stem cell transplantation at 21 months old.

Fig 3. WAS and autoimmunity.



Case presentation: Thrombocytopenia was noted following an upper respiratory tract infection at 8 months old, with small amounts of blood in the stool, mild eczema and suspicion of cow's milk protein allergy. Subsequently developed molloscum contagiosum and warts but remained well until 8 years old with a phenotype otherwise consistent with attenuated Wiskott-Aldrich syndrome (WAS) (X-linked thrombocytopenia).
Initial investigations: Normal lymphocyte numbers, response to phytohaemagglutinin and vaccine responses to tetanus and pneumococcus (conjugate vaccine), but absent response to CD3 stimulation. Platelet count was low at 40 x 10^9/L. Raised IgA and IgG (not on replacement immunoglobulin therapy). Normal WAS protein expression by flow cytometry and mutation in WAS identified as c.1498T>C, (p.Trp500Arg).
Treatment: Splenectomy (age 3 years).
Progress: At 8 years old, remains well from infection and inflammation point of view but developed cola-coloured urine (left) with subsequent episodes of frank haematuria (right), associated with hypertension and mildly elevated creatinine (56 µmol/L) consistent with IgA nephropathy (confirmed on biopsy). Normalisation of platelet number and size occurred post-splenectomy, with no relapse of thrombocytopenia.

Table I. Typical characteristics of classical WAS and XLT patients.

	Classical WAS	**XLT**
Clinical features		
Thrombocytopenia	Yes	Yes
Eczema	Moderate/ severe	None/ mild
Infections	Yes	None/ mild
Autoimmunity	Yes	No*
Malignancy	Yes	No
Typical WASp expression	Absent/ low levels	Low/ normal levels
Typical *WAS* mutation	Deletions/ insertions/ early stop codon/ splice site	Missense/splice site

A clinical scoring system is often used to aid classification of WAS patients with one point being assigned for each of the clinical features (Ochs*, et al* 2009, Zhu*, et al* 1995). A score of $\geq$ 3 suggestive of a more severe phenotype typically correlates with a diagnosis of classical WAS.

*Some centres will consider a diagnosis of XLT with autoimmunity where this develops at a later stage, in the context of a mutation known to be associated with XLT and without other clinical features of classical WAS such as severe/ recurrent infections.

Prophylactic antibiotics		
1st line	Trimethoprim/ sulfamethoxazole	children < 1 year: 30mg/kg once daily; children > 1 year: 450mg/m^2, rounded to nearest dose band; adults: 960 mg orally once daily (based on trimethoprim component)
2nd line	Azithromycin	children and adults: 10 mg/kg orally once daily for 3 consecutive days every 14 days, or 3 days per week (maximum 500 mg/day)
Immunoglobulin replacement therapy		
1st line	Subcutaneous immunoglobulin	Typically weekly to achieve total dose of 300-500 mg/kg over 3 weeks
2nd line	Intravenous immunoglobulin	300-500 mg/kg intravenously once every 3 weeks
Eczema		
1st line	Topical emollient	apply at least twice daily
2nd line	Topical 1% hydrocortisone	apply sparingly to the affected area(s) twice daily
or	Topical betamethasone valerate (0.1%)	apply sparingly to the affected area(s) twice daily
or	Topical fluocinolone (0.025%)	apply sparingly to the affected area(s) twice daily (>3 months of age)
or	Topical clobetasol (0.05%)	apply sparingly to the affected area(s) twice daily (>12 years of age)
3rd line	Oral prednisolone	1 mg/kg/day orally given in 2 divided doses for 2-3 weeks, then taper gradually, maximum 60mg od
or	Topical tacrolimus (0.03%)	apply sparingly to the affected area(s) once or twice daily (children >2 years; for children >15 years 0.1% can be used)
Active bleeding		
1st line	Platelet transfusion	children up to 10kg: 10-15mls/kg; children > 15kg and adults: 1 pool, repeated according to clinical response
+/-	Aminocaproic acid	children: 100-200 mg/kg orally as a loading dose, followed by 100 mg/kg every 4-6 hours; adults: 4-5 g orally as a loading dose, followed by 1 g/hour for 8 hours (maximum 30 g/day)
Minor nose bleeding	Tranexamic acid	IV preparation used topically
ITP		
1st line	Oral prednisolone	children and adults: 2 mg/kg/day orally for 1-2 weeks then taper gradually, maximum 60 mg/day
or	Methylprednisolone	children and adults: 4 mg/kg/day intravenously for 4 days then taper gradually, maximum 60 mg/day
1st/ 2nd line*	Intravenous immunoglobulin	children and adults: 1 g/kg intravenously as a single dose; consult specialist for guidance on subcutaneous dose *IVIg and steroids given together as first line in children
3rd line	Rituximab	375 mg/m^2 weekly for 4 weeks

Table II. Supportive therapy in classical WAS and XLT. ITP, idiopathic thrombocytopenia; WAS, Wiskott-Aldrich syndrome; XLT, X-linked thrombocytopenia.

Table III. Frequency of significant infections pre-transplant in our cohort of children with classical WAS (adapted from Elfeky et al, 2018).

	Organism	No.	%
Viral	CMV	6	17.65
	RSV	2	5.88
	Unspecified respiratory viruses	2	5.88
	EBV	1	2.94
	Varicella	1	2.94
	HPV	1	2.94
	Molloscum	1	2.94
	Coxsackie	1	2.94
	Adenovirus	0	0.00
	Parainfluenza	0	0.00
Fungal	Fungal pneumonia	3	8.82
	Candida	3	8.82
Bacterial	Chronic otitis media	1	2.94
	Recurrent perianal abscesses	1	2.94
	Recurrent cellulitis	1	2.94
	Atypical mycobacteria	0	0.00
Parasitic	Cryptosporidium	1	2.94

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HPV, human papilloma virus; RSV, respiratory syncytial virus; WAS, Wiskott-Aldrich syndrome.