Expert Report to the Infected Blood Inquiry: Bleeding Disorders and Blood Disorders

Infected Blood Inquiry

January 2020

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Letters of Instruction

Instructions to the clinical group: bleeding disorders and blood disorders

<u>Bleeding disorders</u>

15. As far as possible, your report should cover the following topics with regard to bleeding disorders insofar as they are within your areas of expertise and it is possible to address them on the evidence and data available to you.

15.1. A description of each of the following bleeding disorders and their symptoms and effects:

(a) haemophilia A;

(b) haemophilia B;

(c) haemophilia C;

(d) von Willebrand disease.

15.2. An explanation as to the mechanism by which each of these bleeding disorders occurs in a person, including how they may be passed on within family groups.

15.3. An explanation as to how, and by what criteria, each of these bleeding disorders is classified as mild, moderate or severe.

15.4. An explanation as to how each of these bleeding disorders is typically diagnosed and any significant changes in methods of diagnosis over the years.

15.5. A description of the typical impacts of each of these bleeding disorders (including the disorder's impact on susceptibility to infection). Please differentiate as appropriate between different severities of the same bleeding disorder and the different impacts at different ages.

15.6. A description of the treatments that were available for each of these bleeding disorders pre-1970, how they were delivered, how effective they were and their risks, side effects, impacts and/or consequences.

15.7. A description of the treatments that were available for each of these bleeding disorders from 1970 onwards (including cryoprecipitate, DDAVP, factor products, and recombinant products), how they were delivered, how effective they were and their risks, side effects, impacts and/or consequences.

15.8. A description of the treatments that are currently available for each of these bleeding disorders, how they are delivered, how effective they are and their risks, side effects, impacts and/or consequences.

15.9. The co-morbidities, prognosis and life expectancy of those with bleeding disorders and how that has changed over the years.

15.10. The particular difficulties of infection with HIV or hepatitis for people with a bleeding disorder.

Blood disorders

16. As far as possible, your report should cover the following topics with regard to blood disorders insofar as they are within your areas of expertise and it is possible to address them on the evidence and data available to you.

16.1. A description of each of the following, their symptoms and effects:

(a) thalassaemia (please describe each type of thalassaemia);

(b) sickle cell disease (please describe each type of sickle cell disease);

(c) other blood disorders that require regular treatment with blood or blood products;

(d) primary immunodeficiency disorder (please describe the particular disorders that may require regular treatment with blood or blood products).

16.2. An explanation as to the mechanism by which each of these disorders or types of disorder occurs in a person, including how they may be passed on within family groups.

16.3. An explanation as to how each of these disorders or types of disorder is typically diagnosed and any changes in methods of diagnosis over the years.

16.4. A description of the typical impacts of each of these disorders or types of disorder (including the disorder's impact on susceptibility to infection). Please differentiate as appropriate between different severities of the same disorder and the different impacts at different ages.

16.5. A description of the treatments that have been available for each of these disorders or types of disorder over the years, how they were delivered, how effective they were and their risks, side effects, impacts and/or consequences.

16.6. A description of the treatments that are currently available for each of these disorders or types of disorder, how they are delivered, how effective they are and their risks, side effects, impacts and/or consequences.

16.7. The co-morbidities, prognosis and life expectancy of those with these disorders or types of disorder and how that has changed over the years.

Supplemental questions

The following supplemental questions are extracted from the Supplemental Letter of Instruction and are addressed in this report.

5. When answering question 15.1 in the initial letter of instruction:

5.1. Please include a description of the different phenotypes of each bleeding disorder and how these impact on the symptoms and effects of the bleeding disorder.

5.2. Other than the fact that haemophilia in females is significantly rarer than in males, please indicate whether the gender of a person with a bleeding disorder has any bearing on how the condition is likely to affect them.

6. When answering question 15.2 please include an explanation of spontaneous genetic mutation.

7. In the part of your report which considers bleeding disorders, please add a section on inhibitors including the following:

7.1. a description of low level and high level inhibitors and an overview of the body's immune response;

7.2. an explanation as to what triggers inhibitors and how the occurrence rates differ between bleeding disorders;

7.3. a description of the standard treatments available for people with inhibitors and how this has developed over time;

7.4. an explanation as to the risks, effects and likelihood of the success of these treatments.

8. When answering questions 15.6 and 15.7 please include consideration of treatment with whole blood, fresh frozen plasma, avoiding activity and bed rest.

9. When answering question 15.7 please include tranexamic acid (a treatment often given concurrently with DDAVP).

10. When answering questions 15.6, 15.7 and 15.8, please explain whether an increase in the severity of a person's haemophilia means that there is likely to be a corresponding increase in the frequency of factor treatment, or that a higher dose of factor treatment is likely to be prescribed? If not, what factors dictate the frequency or dose of factor treatment?

11. When answering question 15.10, please include the following matters:

11.1. The particular impact of infection with hepatitis or HIV on a person's bleeding disorder and their treatment for their bleeding disorder.

11.2. The particular impact of co-infection with hepatitis and HIV on a person's bleeding disorder and their treatment for their bleeding disorder.

11.3. The particular impact of treatment for hepatitis and/or HIV on a person's bleeding disorder and their treatment for their bleeding disorder.

11.4. Whether people with bleeding disorders who are infected with HIV and/or hepatitis may experience difficulties receiving appropriate treatment for those infections.

11.5. Whether treatment for a bleeding disorder is affected by a person's viral load for hepatitis and/or HIV, and if so, why and how.

11.6. Whether the treatment for hepatitis has any impact on either a person's blood or bleeding disorder, including whether it may trigger an inhibitor, or on the treatment they receive for the blood or bleeding disorder.

11.7. Whether having hepatitis and/or HIV has an impact on the ability to clear an inhibitor.

11.8. Whether having an inhibitor may impact on a person's HIV/hepatitis infection and/or treatment for the HIV/hepatitis infection.

12. When answering question 15.1 in the initial letter of instruction please add a new subparagraph 15.1(e) 'rare factor deficiencies' (such as Factor VII deficiency, Factor X deficiency, Factor XIII deficiency and Glanzmann's disease). These can be covered in less detail than sub-paragraphs (a) – (d) but please take them into account where they are relevant to the questions in the initial letter of instruction. (**See Addendum**)

13.   When answering question 15.8 please explain what if any viruses could potentially be transmitted with modern day treatments. (**See Addendum**)

14.   When answering question 16.1 please:

14.1.   Include acquired haemophilia at paragraph 16.1(e). (**See Addendum**)

14.2.   Include haemolytic disease of the foetus and newborn at paragraph 16.1(f). (**See Addendum**)

14.3.   Include neonatal alloimmune thrombocytopenia at paragraph 16.1(g).

1. Haemophilia A – Current Understanding and Management

Haemophilia A is a bleeding disorder caused by a congenital (inherent) deficiency of Factor 8 (F8, sometimes written as Factor VIII or FVIII) which is a soluble clotting factor involved in amplification of the initial message to form a clot. People with haemophilia A show a markedly increased tendency to bleed into closed spaces in the body such as muscle and joints and also inside the brain or the gastrointestinal tract. People with haemophilia are also at high risk of bleeding with surgery including dental procedures. Without treatment, these bleeds are painful and debilitating and sometimes fatal. Unfortunately, blood is toxic to joint surfaces and repeated bleeding leads to increasing damage to joints (termed 'haemophilic arthropathy') and progressive disability. Without effective treatment, people with very low levels of F8 typically suffer severe disability and early death.

Inherited bleeding disorders – current understanding

The inherited bleeding disorders are a range of medical disorders caused by defects in the clotting (or coagulation) system. The clotting system acts to limit blood loss when blood vessels are injured. It is made up of two main components; platelets, small cells that circulate in the blood and respond to injury by binding to each other and to the injured wall of the blood vessel; and soluble clotting proteins which act in concert to cause a surge of the protein thrombin which converts fibrinogen to fibrin, forming a mesh of protein strands and ultimately a clot to stop bleeding.

Inheritance of haemophilia A

Haemophilia A is a genetic disorder caused by errors (called 'variants' or 'mutations') in the F8 gene. The F8 gene is located on the X chromosome which means that haemophilia A shows sex-linked inheritance and mostly affects boys and men. In brief, the normal human allocation of chromosomes is 46 – a pair each of chromosomes 1-22 and two sex chromosomes: two Xs in females and an X and a Y in males. As males only have one X chromosome, any change in a gene on that chromosome will clearly show itself, while, in females, changes in X chromosome genes are usually masked by a wild-type ('normal') gene on the other X chromosome. Thus, while haemophilia is quite rare in males, it is exceedingly rare in females. Women who have one affected F8 gene and one wild-type gene (termed 'carriers' of haemophilia A) typically have normal F8 levels though some can have reduced F8 levels. Interestingly, factor levels do not correlate well with bleeding amongst carriers and approximately 30% of them experience excessive bleeding (and are called 'affected or symptomatic carriers'). Rarely, there is an imbalance in which the X chromosome is active (termed 'extreme lyonisation') and this can lead to very low F8 levels and a more severe haemophilia picture.

Children of men with haemophilia are not normally at risk of haemophilia: any boys will have inherited the Y chromosome from their father rather than the affected X chromosome; any girls will have inherited the affected X chromosome together with the protective effects of a wild-type X chromosome from their mother.

In the UK, about 50% of children diagnosed with haemophilia are known to have haemophilia in the family and 50% are due to new ('de novo') variants. These variants have typically occurred a generation before but are only showing themselves with the birth of a boy – all cell division leads to errors (variants) but these are more common in sperm cell production than in egg cell production: most new variants in the F8 gene have occurred during sperm production in the maternal grandfather. This means that younger male siblings of new cases of haemophilia are also at risk of inheriting the condition.

Diagnosis of haemophilia

Haemophilia is diagnosed in two different scenarios: targeted testing in children born to mothers known to be carriers of haemophilia and new investigation of children presenting with bruising and bleeding without a family history of haemophilia.

Initial testing consists of a screening clotting test ('assay') – the Activated Partial Thromboplastin Time (APTT), part of the routine assessment of the clotting system. The APTT is abnormally prolonged in haemophilia (in other words it takes longer for the clot to form in the blood sample from a patient) and this finding, together with a consistent clinical presentation, would lead to a specific F8 or F9 assay most commonly a variant of the APTT carried out on the patient's plasma mixed with a series of dilutions in factor-deficient plasma (the liquid fraction of blood). Diagnosis should be confirmed with a repeat assay performed on a separate sample and then often by genetic analysis of the F8 gene.

APTTs and factor assays are prone to error if not carried out and interpreted with due caution: clotting times can be either factitiously shortened or prolonged and factor levels can be over- or under-estimated. For this reason, a cornerstone of practice is to avoid diagnosing any condition on a single assay. However, if samples are taken, processed and analysed carefully by experienced scientists and clinicians working in laboratories with good internal and external quality assurance programmes and any significant results are repeated to confirm the result, errors are rare.

Bleeding patterns in haemophilia A

The risk of bleeding in haemophilia A is closely related to the amount of F8 in the blood; this is termed 'the baseline factor level'. By convention, the average level of clotting factors in the blood is set at 100% (or 100 iu/dl) and the normal range in adults not affected by haemophilia is between 50% and 150% (iu/dl). Some people with haemophilia have close to zero (<1%) self-made (endogenous) F8 or 9 and this is termed 'severe haemophilia'. Levels of 1-5% are termed 'moderate haemophilia' and levels >5% are termed 'mild haemophilia'. People with untreated severe haemophilia suffer from spontaneous bleeds, episodes of joint, muscle or other bleeding not provoked by any physical injury (trauma) but occurring through normal day to day movements and activities. As levels of baseline factor rise, the risk of spontaneous and traumatic bleeds reduces: spontaneous and trauma associated bleeds occur regularly in moderate haemophilia, though less commonly than in severe haemophilia: they are uncommon in mild haemophilia.

Current treatment of haemophilia A

Treatment of haemophilia A is primarily aimed at increasing the levels of Factor 8 in the blood. It can be usefully split into 1) reactive (or 'on demand') treatment and 2) preventative treatment; either short term to cover things like surgery, or longer term to prevent bleeds (this is what we call prophylaxis).

Prophylaxis

The current standard of care for severe haemophilia is to start regular preventative F8 infusions (prophylaxis) around 1-2 years of age when a child is getting mobile and is at more risk of joint bleeds. Practice varies between centres as to whether an in-dwelling central venous catheter is inserted to facilitate these injections or efforts are made to proceed solely by peripheral venepuncture (inserting needles into veins in the arms or feet) but the aim is to achieve a position where the family is able to administer factor at home independently at a dosage and frequency that maintains factor levels above a trough of 1-3 iu/dl. For standard half-life recombinant F8 (see section below called 'Extended Half Life Recombinant F8'), this typically requires injections every 48 hours; for extended half-life (EHL) products, this is typically every 72 hours. Prophylaxis is expected to be lifelong. Prophylaxis is also given to some people with haemophilia with levels of 1-3% (iu/dl) and occasionally at higher levels. It is hoped and expected that children who start treatment around a year of age and receive recommended doses of prophylaxis will reach adulthood with normal joints and only bleed infrequently.

On demand treatment

Patients with non-severe haemophilia are more likely to be treated on demand; in other words, they do not receive regular preventive injections of F8 (prophylaxis) but are treated if they bleed or injure themselves. Some people with haemophilia may also give 'targeted prophylaxis' around high-risk activities such as sport. The duration and intensity of treatment after a bleed will depend on the severity of the bleed and the response to treatment. Often a single dose is enough; sometimes weeks of treatment are required.

Not treating or inadequately treating haemophilia

If a significant bleed such as a joint bleed were to be left untreated, particularly in more severe haemophilia, the bleed would likely progress, the joint would become grossly swollen and extremely painful, and it may take many weeks or months to improve. Haemophilic arthropathy (the progressive destruction of the joint linings due to damage from the blood) would progress and that joint would become more prone to bleeds in the future. This vicious cycle is what is known as a 'target joint', something that does occur today but is happily far less common with modern treatment in the UK. Other bleeding sites, for example inside the head or in the gastrointestinal tract, can be fatal if untreated.

F8 inhibitors

The most common complicating side effect of modern haemophilia treatment is the development of F8 inhibitors. These are antibodies produced by the immune system against therapeutic F8. These antibodies clear the F8 from the circulation and stop it working properly. Up to a third of previously untreated patients with severe haemophilia A will develop inhibitors to F8.

Inhibitors occur because the immune system does not recognise exogenous F8 as part of the host. The developing immune system goes through a process of self-tolerisation via a depletion of any self-reacting immune cells. In severe haemophilia, particularly severe haemophilia where no F8 is produced, the immune system has not tolerised to F8 so an immune response is likely. Exactly why an immune system produces inhibitors in some cases and not others is complicated and only partially understood but we know that certain factors are important: these include the underlying F8 genetic variant, the make-up of the immune system, the ethnicity of the patient, whether or not there is a family history of inhibitors, the severity of the haemophilia, and the situation and intensity of the first treatments with F8.

Management of inhibitors

Most inhibitors occur in severe haemophilia in the first 30 exposures to F8. As children with severe haemophilia are put on prophylaxis at the age of 1-2 with 3-4 F8 treatments a week, this is the age when inhibitors typically emerge.

Initial management of inhibitors is focused on tolerising the immune system to the F8. If the immune system is continuously exposed to high doses of F8 by daily or alternate day dosing, in most cases (75-80%) the antibody reaction will stop after some months (sometimes years) and the child is said to be 'tolerised'. This means that F8 can effectively be used for prophylaxis and treatment though in many cases, even when tolerised, children require larger doses and more frequent infusions of F8 than those with no history of an inhibitor.

Prior to successful tolerisation, and in the event that tolerisation is unsuccessful, F8 therapy is ineffective both for prophylaxis and treatment. Treatment options include the 'bypassing agents' FEIBA (the trade name for what is known as Activated Prothrombin Complex Concentrate, APCC see below) and Novoseven (recombinant activated F7). Bypassing agents are so-named as they swamp the clotting system with high levels of activated clotting factors, bypassing the need for F8. They are effective in people with haemophilia with inhibitors and are often life-saving but are not as effective as F8 either at treating bleeds or as a prophylactic agent. Patients with inhibitors are more likely to have lives limited by haemophilia with regular bleeds, target joints and disability. Happily, bleed prevention has become far more effective in patients with inhibitors over the past years with the introduction of emicizumab (trade name Hemlibra) into the UK market. See below.

Current treatments for haemophilia A in the UK

Desmopressin

Desmopressin (marketed in the UK as DDAVP) is a synthetic analogue of the naturally occurring hormone vasopressin. It is used in bleeding disorders to increase plasma levels of F8 and von Willebrand factor (VWF) and to enhance platelet function. A subcutaneous or intravenous dose of desmopressin typically results in an increase in plasma F8 and VWF levels of 2-4 times. This makes it a useful treatment in mild haemophilia and von Willebrand disease (VWD) but ineffective in severe haemophilia. Levels are maintained for 6-24 hours once raised but multiple doses show a diminished response and it is not generally used for long periods of time. Side effects of desmopressin include fluid retention and electrolyte disturbance and there is a significant risk of seizures if it is used in babies or without careful advice regarding fluid intake.

Recombinant F8

Recombinant F8 (rF8) has been the mainstay of treatment of haemophilia in the UK for the last 20 years. It is made in a laboratory using genetically engineered cell lines and thus is not at risk of carrying blood-borne infections (though some products do use human albumin in the extraction process). Calculated doses give predictable rises in F8 though there is some variation in how long it lasts in the system. It is very effective at treating bleeds and, with good doses, very effective at preventing them. Administration is a challenge though (it must be given intravenously) and the frequency of injections required for good levels is a very significant burden on people with haemophilia and their families. Apart from the very significant issue of inhibitors, the safety profile is excellent.

Plasma-derived F8

Plasma-derived F8 concentrates (pdF8) are factor concentrates made from the fractionation and purification of multiple blood donations. They remain the mainstay of treatment of more severe VWD but are now rarely used for haemophilia A in the UK. In 2018/19, according to the National Haemophilia Database Annual Report, 13.4 million units of pdF8 were used for haemophilia A out of a total UK F8 usage of 600 million units. As pdF8 comes from pooled blood donations, there remains concern about the possibility of transmission of infective agents and all products marketed in the UK go through multiple lines of initial screening and then multiple lines of virus deactivation procedures. There is some evidence that suggests pdF8 results in a lower incidence of inhibitor formation (though this is controversial) and there is also evidence that shows that pdF8 can be effective in immune tolerance induction where recombinant F8 has been ineffective, but it remains a rarity for children with haemophilia to receive pdF8 in the UK.

Extended half-life recombinant F8

As one of the main difficulties in giving rF8 is the frequency of injections, extensive efforts have been made to extend the lifespan of rF8 in the body in the past decade and more. This has been done by linking the rF8 to different molecules including the Fc (fragment crystalisable) domain of immunoglobulin and polyethylene glycol (PEG). This has been partially successful, extending the half-life (the time it takes for the amount of the F8 in the body to halve) from an average of 12 hours to around 18 hours, meaning that the typical patient needs to infuse EHL rF8 every 3 days compared with every 2 days with a standard molecule.

Tranexamic acid

Tranexamic acid is an inhibitor of fibrinolysis – the normal physiological process whereby clots are broken down in the body. By inhibiting fibrinolysis, tranexamic acid can stabilise clots and reduce bleeding. This is effective in major trauma (injury) and it can be useful as an adjunct to factor concentrate in haemophilia or on its own in minor bleeding particularly mouth, nose or menstrual bleeding.

Factor Eight Inhibitor Bypassing Activity

FEIBA (Factor Eight Inhibitor Bypassing Activity) is the trade name for Activated Prothrombin Complex Concentrate (APCC), a plasma-derived concentrate consisting of the clotting factors 2, 7, 9 and 10, some of which are in their activated form. In much the same way as for Novoseven (below), FEIBA is able to drive the clotting mechanism and generate higher amounts of thrombin, without the F8-dependent amplification phase. It is moderately effective in both treating and preventing bleeding in people with haemophilia who have inhibitors. Unlike F8, it is not possible to measure its effects in the laboratory using conventional clotting assays.

Novoseven

Novoseven is recombinant activated F7 (F7a, FVIIa). Novoseven is mainly used as a bypassing agent in inhibitor patients in haemophilia where high levels of F7a can generate higher amounts of thrombin without the F8-dependent amplification phase. It is moderately effective in this context and further limited by its short half-life. It is also used in severe platelet function defects and F7 deficiency, and has been tried in life-threatening bleeding in various contexts (though with mixed success). It is not possible to measure its effects using conventional laboratory tests.

Emicizumab

Emicizumab (trade name Hemlibra) is a new F8 mimetic treatment in haemophilia. It is a specially engineered antibody that binds activated F9 and F10, essentially doing the job of F8 in the clotting 'cascade'. When given every one to two weeks as a subcutaneous injection, it gives relatively stable levels of activity and does not show the same peaks and troughs of activity that are seen with rF8. It is used for prevention rather than treatment of bleeds. As emicizumab is a completely different molecule from F8, antibodies (inhibitors) against F8 do not interfere and it is effective in inhibitor and non-inhibitor patients alike. It has been a transformative treatment for inhibitor patients. Emicizumab has shown some serious side effects when given in combination with high doses of FEIBA in inhibitor patients but these issues have not been seen, to date, in any other context. There are no high-quality studies comparing emicizumab with rF8 prophylaxis and long-term safety and efficacy is not yet known.

Gene therapy

There is a lot of interest in gene therapy in haemophilia A at present and in the past few years, studies have reported multiple patients with months and years of good levels of F8 without any need for factor concentrate. However, these studies remain in the experimental phase and long-term results are not yet known. It therefore remains to be seen whether gene therapy will become a safe, mass treatment option in haemophilia A.

2. Haemophilia B – Current Understanding and Management

Haemophilia B is a bleeding disorder caused by a congenital deficiency of F9 (or FIX), a soluble clotting factor involved, like F8, in the amplification of the initial clotting signal. The biological roles of Factors 8 and 9 are closely related (F8 is actually a cofactor for F9; it allows F9 to cleave and activate F10 by bringing them close together physically) and so the clinical picture that is caused by these deficiencies is near identical: like those with haemophilia A, people with haemophilia B show a markedly increased tendency to bleed into closed spaces in the body such as muscle and joints and also inside the brain or the gastrointestinal tract. Haemophilia B is less common than haemophilia A; the National Haemophilia Database has 1,836 reported cases of haemophilia B of whom 360 are severe, compared to 8,410 cases of haemophilia A of whom 2,060 are severe.

Inheritance of haemophilia B

The F9 gene is, like F8, located on the X chromosome and haemophilia B also shows sex-linked inheritance with an identical pattern to haemophilia B.

Bleeding patterns in haemophilia B

As with haemophilia A, the risk of bleeding in haemophilia B is closely related to the amount of F9 in the blood, the baseline factor level. People with haemophilia B with close to zero (<1%) self-made F9 are said to have severe haemophilia B; levels of 1-5% are termed moderate haemophilia and levels >5% are termed mild haemophilia. People with untreated severe haemophilia B suffer from spontaneous bleeds: episodes of joint, muscle or other bleeding not provoked by any physical injury (trauma). As levels of baseline factor rise, the risk of spontaneous and traumatic bleeds reduces: spontaneous and trauma-associated bleeds occur regularly in moderate haemophilia, though less commonly than in severe haemophilia; they are uncommon in mild haemophilia.

Diagnosis of haemophilia B

Haemophilia B is diagnosed either in children with a family history of haemophilia or those with new bleeding symptoms. Initial testing consists of the Activated Partial Thromboplastin Time (APTT) and, if the APTT is prolonged, a specific F9 assay, a variant of the APTT carried out on the patient's plasma mixed with a series of dilutions in F9-deficient plasma.

Diagnosis should be confirmed with a repeat assay performed on a separate sample and by genetic analysis of the F9 gene.

Current treatment of haemophilia B

Treatment of haemophilia B, as with haemophilia A, can be divided into on demand and prophylaxis. The standard of care is prophylaxis for all patients with severe haemophilia B, again starting at 12-18 months. As F9 lasts longer in the circulation, infusions are not as frequent as in haemophilia A: every 3 days for standard recombinant F9 (rF9), weekly for Extended Half-Live (EHL) rF9, see below. Infusions of F9 are again intravenous and often

require insertion of a central venous catheter such as a port-a-cath. Patients with mild or moderate haemophilia B are generally treated on demand unless they have a more severe bleeding frequency. Desmopressin does not raise F9 levels and is not an effective treatment for haemophilia B.

Inhibitors in haemophilia B

Inhibitors are much less common in haemophilia B than in haemophilia A (3% as compared to 30%) but are, in general, more problematic when they do occur. This is because many inhibitors are associated with anaphylaxis – a severe, life-threatening allergic reaction. Immune tolerance is less successful and protocols are less well established. Ongoing treatment with F9 can lead to a kidney condition, nephrotic syndrome. Treatment with bypassing agents is more limited as FEIBA contains significant amounts of F9 and is relatively contraindicated. Due to its mechanism of action, emicizumab is not an appropriate treatment. Therefore treatment options at present are largely confined to Novoseven though there are some promising agents in development.

Current treatments available for haemophilia B in the UK

Recombinant F9

rF9 is made in a laboratory using genetically engineered cell lines and thus is not at risk of carrying blood-borne infections. rF9 lasts considerably longer in the circulation than F8 with a half-life of 18-24 hours (though there is some variation between patients). It is very effective at treating and preventing bleeds if given in adequate doses. Administration is intravenous and therefore a challenge and, although the frequency of injections is less than in haemophilia A, this remains a very significant burden on people with haemophilia and their families. Apart from inhibitors, the safety profile is excellent.

Plasma-derived F9

Plasma-derived F9 concentrates (pdF9) are factor concentrates made from the fractionation and purification of multiple blood donations. In the UK, total pdF9 in 2018/19 was 4.5 million units out of a total F9 usage of 80 million units. As pdF9 comes from pooled blood donations, there remains concern about the possibility of transmission of infective agents, and all products marketed in the UK go through multiple lines of initial screening and multiple lines of virus deactivation procedures.

Extended half-life recombinant F9

As per rF8, extensive efforts have been made to extend the lifespan of rF9 in the body in the past decade. Happily this has been more successful in rF9 with half-lives extended to 96 hours and beyond, and good trough levels achieved with weekly or even fortnightly dosing. This has been done by linking the rF9 to different molecules including albumin, the Fc domain of immunoglobulin and polyethylene glycol (PEG).

Tranexamic acid

Tranexamic acid can be used in haemophilia B as in haemophilia A.

Factor Eight Inhibitor Bypassing Activity (FEIBA)

FEIBA contains significant amounts of F9 and is relatively contraindicated in patients with haemophilia B and inhibitors.

Novoseven

Novoseven can be used in haemophilia B with inhibitors in an identical fashion to haemophilia A.

3. Factor 11 Deficiency (Haemophilia C) – Current Understanding and Management

The congenital deficiency of F11 (sometimes Factor XI or FXI) is a rare bleeding disorder. There are 3,445 patients registered in the UK with F11 deficiency. It is generally thought of as an autosomal recessive condition: pathological (disease-causing) variants are present in both copies of the gene in affected individuals, though there are some dominant negative variants described and some carriers of typical variants have mildly reduced F11 levels and report bleeding. F11 deficiency is relatively common in populations with Ashkenazi Jewish family origins.

Bleeding patterns and severity

In contrast to haemophilia A, factor levels are not predictive of the bleeding picture (phenotype): some patients with undetectable F11 levels have only mild bleeding; a severe bleeding phenotype has been reported in patients with F11 levels up to 40% (iu/dl).

Spontaneous bleeding is very uncommon in F11 deficiency and many cases are asymptomatic. The most common symptoms are bleeding after surgery or trauma.

Treatment

As bleeding is uncommon, many individuals require no treatment. Treatment is most commonly given to cover surgery. There are/have been three main options for surgical cover: tranexamic acid, Fresh Frozen Plasma (FFP) and F11 concentrate.

F11 concentrate is produced by fractionation from pooled blood donations. It provides good haemostatic control (it prevents bleeding) but it has been associated with significant rates of thrombosis and for that reason is used with caution. Forty-five patients received F11 concentrate in the UK in 2018/19 – 1.3% of registered patients.

FFP is another source of F11 and can be used to cover surgery. In the UK in 2018/19, 14 patients received solvent-detergent FFP for F11 deficiency.

Tranexamic acid is remarkably effective in preventing bleeding in F11 deficiency.

4. Von Willebrand Disease – Current Understanding and Management

Von Willebrand Disease is a somewhat complicated group of disorders characterised by a deficiency of functional von Willebrand Factor (VWF). VWF is necessary to the clotting system in two ways: it is central to the process whereby platelets adhere (stick) to the exposed edges of blood vessels when breached and it binds to F8 in the circulation and protects it from degradation. Thus, patients lacking VWF show a defect in platelet-type clotting (termed 'primary haemostasis') with easy bruising and mucous membrane bleeding (mouth, nose, gastrointestinal tract, menstrual bleeding) and low F8 levels which at times give rise to haemophilia-type bleeding.

Classification and inheritance of von Willebrand disease

VWD is classified into Type 1 (reduced activity because of reduced VWF levels); Type 2 (reduced or abnormal VWF activity out of proportion to the levels); and Type 3 (no detectable VWF). Type 2 is further categorised into the subtypes 2A, 2B, 2M and 2N reflecting the defect in the VWF: for example, Type 2N does not bind to F8; Type 2B binds too strongly to platelets resulting in clearance of both platelets and VWF from the circulation. Even within the different subtypes of VWD, the clinical picture is very variable and thus VWD is far less uniform than the haemophilias.

Inheritance of VWD is also complicated though most cases of Type 1 and Types 2A, 2B and 2M are inherited in a dominant fashion: only one affected gene is necessary for inheritance, which means that an affected father or mother has a 50% chance of passing on the condition to a child. Type 3 VWD is recessive – two gene defects are necessary and the parents are not usually affected by VWD. VWD affects men and women equally.

Difficulties in diagnosis

Unless levels are very low, there is a lot of diagnostic uncertainty in VWD. Some people have a clear tendency to bleed and bruise more than others; some people have low VWF levels; some people have a tendency to bleed and have low VWF levels. However, some close relatives of people with bleeding and low VWF levels share the tendency to bleed but not the low VWF levels, and others share the low VWF levels but not the tendency to bleed: the two genes/gene markers do not always co-segregate. For this reason there is an increasing reluctance to diagnose VWD on moderately low VWF levels. Unfortunately genetic analysis often does not help as the genetic basis of type 1 VWD, the most common form of VWD, remains elusive.

Treatment of von Willebrand disease

Prophylaxis is rare in VWD though it is occasionally used in Type 3 (which is itself very rare). Most treatment is on demand. Treatment options include desmopressin, plasma-derived F8 concentrate (particular brands with measured VWF activity are marketed and used in VWD), and tranexamic acid, which is used both as an adjunct to other therapies and as a stand-alone treatment in minor bleeding. Desmopressin will increase levels of VWF and F8 an average of 3-4 fold so it is very useful in milder VWD and ineffective in Type 3. Patients will often have

a desmopressin test dose to quantify the size and duration of their response. A recombinant VWF product has just come to market but is not yet commissioned in the NHS. It does not contain F8. It is not licensed for use in children or as prophylaxis.

Inhibitors

Anti-VWF inhibitors are reported to occur in Type 3 VWD but never in Type 1 or Type 2. In Type 3 VWD they occur with a prevalence of 7.5% and complicate treatment by reducing response to infused VWF. Patients have been successfully treated with rF8 in these circumstances but, as this is a rare complication of a rare condition, there is little systematic data to guide clinical decision making.

Von Willebrand disease and menstruation

Unlike the haemophilias, VWD is at least as prevalent in women as in men. Both sexes suffer from mouth, nose and gastrointestinal bleeding but the clinical course for women tends to be more complicated as VWD often causes problematic menstrual bleeding. Treatment options for menorrhagia (heavy menstrual bleeding) in women with bleeding disorders would tend to progress as needed in a stepwise manner from tranexamic acid, to hormonal control (such as oral contraceptive pills or a local intrauterine device such as the Mirena coil), to desmopressin (either nasal or injected), to factor concentrate. Advice and review from a gynaecologist with an interest in bleeding disorders are often extremely helpful.

Von Willebrand disease and pregnancy

VWF levels naturally rise during pregnancy and many patients with milder forms will have good VWF levels at the time of delivery. However, some patients will suffer a severe drop-off in VWF levels after delivery, putting them at risk of bleeding (postpartum haemorrhage). Other more severely affected patients may require support for both birth and afterwards.

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5. Haemophilia Care Prior to 1970

General comments

Blood transfusion

The earliest report of the use of whole blood transfusion to treat a bleeding boy was in 1840 (Lane, 1840) but limitations in understanding and technology meant that this was not a viable treatment until the 20th century.

In 1901, the ABO blood group system – clinically the most crucial of the 24 blood group systems, was described and the first practical use of this was put to use in 1902.

During World War 1, anticoagulant technology was implemented to prevent donated blood from clotting in the bottle.

On the back of these developments, whole fresh blood transfusion became the mainstay of treatment and was life-saving for haemophilia throughout the 1930s. Life expectancy of a patient with haemophilia at this time was 20 years. The chief advantages of whole blood during that period were its ready availability in certain countries; the possibility to collect and transport the blood to the patient without the blood clotting in the bottle; and the possibility to identify ABO blood group matches between the blood donor and the patient, at least in countries where this technology could be implemented. The disadvantages were the large volume needed to treat severe bleeds (a unit of whole blood only contained small amounts of the factor required) and the lack of systematic availability of blood for civilians.

Blood banking started in the UK in 1921 but was systematised in 1938 based on experiences from blood banking during the Spanish civil war. This enabled systematic organisation of civilian blood donation and dispersal. Further development of blood transfusion services during World War 2 led to systematic availability of FFP.

Fresh Frozen Plasma

When the donated whole blood is centrifuged at specified speeds, it separates into two parts – the constituent cells (red and white blood cells and platelets) and the liquid portion (plasma). They comprise approximately 50% each of whole blood. When plasma is snap frozen at -70C, the function of its clotting proteins is retained. This product, FFP, can be thawed for use in bleeding disorders to replace clotting proteins lacking in the bleeding patient. By 1961, FFP was available in the UK from local blood services. Its main advantage was the ease of technology in production especially with the advent of plastic bags and ready availability from freezers. The blood group of FFP generally needs to match with the blood group of the recipient. The other advantage (although this was not relevant at this period) was that 1 unit of FFP comes from 1 donor. Thus a patient receiving 3 bags of FFP (a standard dose today in a non-haemophilia bleeding patient) is exposed to 3 donors. Chief disadvantages were the large volumes needed to achieve therapeutic levels, the risk of cardiac stress due to circulating fluid volume overload, and other side effects such as allergies and rashes.

From 1941, freeze-dried plasma was also available.

Other treatment during this time

Russell's viper venom (Stypven) at a dilution of 1 in a million was also used in the 1930s as topical treatment for acute bleeds. It was of limited use as it could not be used systemically (into a vein) because it was toxic.

Treatment of haemophilia A prior to 1970

Fractionated products – plasma-derived F8 concentrate

In the 1930s, there was improved understanding of clotting mechanisms in the blood. A number of different clotting factors were identified. This advanced the treatment of haemophilia as identification of clotting factors and the mechanism of bleeding were essential steps to move to specific therapies.

Further improvements in blood transfusion technology were discovered to separate plasma from whole blood donations and to use fractionation techniques to obtain different products from this separated plasma with distinct clinical uses. Most fractionation techniques used variations of that published by Cohn from the USA in 1940.

Anti-haemophilic globulin (AHG) was produced by fractionating donated (human) plasma in 1946 in the USA. A similar product using different techniques was produced in Oxford in 1952, called NHS F8.

The main advantage of F8 concentrates was that the products were more potent and easier to use compared to plasma. Therefore patients with severe disease could be treated more effectively.

There was an awareness of the potential for transmission of hepatitis before diagnostic tests for specific viruses became available. A significant proportion of transmission was due to what we now call hepatitis B, and testing became feasible following the identification of the infectious agent in 1964.

A further disadvantage was the formation of antibodies against F8 in patients treated with factor concentrate: these were called inhibitors as they interfered with the effectiveness of the transfused F8.

The production was complex to organise and there were insufficient products and rationing of treatment. Oxford was the main centre offering this level of treatment and patients had to travel from afar to receive it.

Non-human F8 concentrates

The availability of plastics in the 1950s enabled the collection of large volumes (gallons) of porcine and bovine blood from slaughter houses. These were transported to the laboratory in Oxford where plasma was separated, fractionated into components and freeze dried. In 1954, these products were available for clinical use and the production of animal plasma was taken over by Maws and Sons (who also exported it).

The chief advantage of these bovine and porcine products was the availability of material to treat patients when human F8 was scarce.

The chief problems of porcine and bovine products were allergic-type reactions to the animal proteins. Some of these were very severe and resulted in patients dropping their blood pressure and oxygen levels rapidly. This form of reaction – called anaphylactic reactions –

could be fatal and was unpredictable in its occurrence. There were other disadvantages of early animal AHG (F8) including the risk of clumps of aggregated protein circulating in the body and blocking off circulation in small blood vessels. Some people were rendered transiently blind for example. Sometimes these aggregates trapped platelet cells resulting in a fall in the platelet count and a worsening of the bleeding, even while clotting factor levels were improved.

The reconstituted AHG or NHS F8 solution was a thick creamy substance that had to be infused fast. This caused an overload on the heart causing a high pulse rate and low oxygen levels. Fortunately most people who were treated were otherwise healthy young men who were able to withstand these reactions. Another important drawback of these concentrates was the time it took to produce solutions from the powder. For example, for a major operation, all office staff would sit shaking bottles during their break. The manner of mixing was important as the product could froth if shaken too vigorously rendering the product less effective. Despite these disadvantages, the experts at Oxford thought that these products had a role in treating haemophilia as there was insufficient human plasma to treat haemophilia patients in the UK. In 1954, it was estimated that every UK patient would need plasma from 1,000 donors per year to have adequate treatment.

In the mid 1950s, bovine and porcine F8 was only available in Oxford and people were referred there for treatment. Procurement of large volumes of plasma depended on proximity to the blood services, and dependable slaughterhouses: this was feasible at Oxford where there was also a large programme of research and manufacture of these products. At other centres, FFP was the main product in use.

Cryoprecipitate

In 1965, Pool in the USA described the production of cryoprecipitate. This was produced from controlled thawing of FFP at 1-8C which produced a precipitate rich in F8: thus a higher potency per volume of fluid was now available; at that time 1 unit of cryoprecipitate was obtained from 1 donor.

Cryoprecipitate was also rich in other clotting proteins: namely, fibrinogen and VWF. It was available for public use in the UK from around 1966-68. The availability was not uniform. For example, the London Red Cross panel had a ready supply of donors. Manchester did not have such a panel and therefore obtained cryoprecipitate from the blood service: indeed it continued with this arrangement for many years as it was not funded for use of F8 concentrate. Cryoprecipitate could be kept frozen in conditions manageable by domestic freezers (-20C) unlike FFP which required deeper freeze conditions (-70C). Even so, freezers were not easy to procure, install and monitor (to ensure that the temperature was stable 24 hours of the day) and therefore not all patients could have these products at home. The thaw time was long, especially in an acutely bleeding patient. However, the availability of cryoprecipitate enabled the start of home treatment since patients and their carers (mainly parents) could be taught to undertake injections using the bags of cryoprecipitate and thawing them. This was not possible with FFP because of limitations of domestic freezers and the unfeasibly large volumes required per dose.

Cryoprecipitate could be given as batched doses (1 bag = 1 donor) using multiple bags per dose depending on severity and body weight; or pooled with 1 bag from 4 to 5 donors, pooled for ease of administration. The bags required to be thawed at 37C in a water-bath for half an hour, each bag spiked with a tube which drained to pool all products into one bag. This was followed by washing each bag to drain the last of the cryoprecipitate to add to the pool. This bag was then infused through the vein over 30-40 minutes. This task would be carried out

variably by the transfusion service or haemophilia centre staff, or by junior doctors or nurses with little experience of pooling. A standard dose for a child may, for example, amount to 15 individual packs of cryoprecipitate.

From about 1967, cryoprecipitate from 10-15 plasma donations could be pooled. This could be freeze dried to produce a crystalline powder – labelled as factor concentrate. Frozen and thawed cryoprecipitate was processed chemically to provide a powder that was 10 times as potent as cryoprecipitate. This could be dissolved in sterile water and injected at home. The production of this level of potency required pooling from several donors to produce a vial of F8 concentrate.

Treatment patterns

Control of spontaneous bleeding and control of bleeding in the period around surgery were the main reasons for treatment. Treatment before 1968 was bed rest, usually in a hospital bed, and FFP. At some centres more effective products were available.

The main operations in the 1960s were surgical procedures for peptic ulcer. Standard of care for such patients would be 1st week porcine, 2nd week bovine and final 48 hours or so human F8. (Human F8 first became available in 1957.)

By 1958, it was possible to distinguish between F8 and F9 deficiency and to categorise patients as mild, moderate or severe based on the levels of the factor in their blood. Thus, the severity of the bleed could be correlated with factor levels in the blood; therefore treatment could be monitored rationally. It also became clear that spontaneous bleeds could be treated more easily than post-operative bleeding which required sustained levels of factors in the blood.

Interest in pre-emptive treatment started around 1964 when emphasis shifted from life-saving to life-enhancing: limit damage by early treatment and manage every bleed as an acute emergency. However, limited supplies in the early years resulted in suboptimal treatment leading to complications of further bleeding, infection, sepsis and their aftermath.

Patients requiring dental care were also managed with the use of animal and human products and were referred to Oxford for this purpose. Use of F8 concentrates improved outcomes in patients requiring dental extractions. It was estimated (Biggs et al., 1974) that each dental procedure required 2,330 F8 units, an equivalent of 35 donors. F8 concentrate was considered better than cryoprecipitate when high plasma concentrations of F8 were required, such as with surgery or dental extractions.

An important aspect of treatment at this stage was to define the product (what method of fractionation) and characterise its potency (how much F8 per ml of fluid). The former was relatively straightforward as each laboratory producing factor concentrates as described above used specified methods that were stable and mainly varied in detail from the method described by Cohn. The latter was more difficult and, although work started on this in 1960, it was only in 1970 that a certain preparation was accepted as the legally defining standard of F8 potency across the world. This standard was established by assaying a large number of samples from across the world and was available just around the time of licensing of commercial products in the UK in 1972.

From 1969, patients' data were collected regarding treatments and complications, and reports published in medical journals.

UK use of FFP rose until 1970 and then fell dramatically. Cryoprecipitate comprised 70% of total use for F8 replacement between 1969 and 1974, peaking in 1970. During this period, plasma-derived F8 concentrate comprised 26% of use, mainly commercially produced.

The growing demand for F8 posed three problems in the pre-1970s: low yield with existing technology; limited capacity to procure and process plasma in the UK; and inadequate standardisation of products. The first two led to the use of imported products from the USA. The third was resolved in 1970 as discussed above.

Patients with mild haemophilia

These patients did not require the intensity of treatment of severe haemophilia and were treated with more conservative methods or FFP/cryoprecipitate.

Treatment of haemophilia B prior to 1970

In 1952, it was possible to identify haemophilia B (or 'Christmas disease') as separate from haemophilia A by using a test called the thromboplastin generation test (TGT). Until then all bleeding patients were categorised under the generic diagnosis of haemophilia. This made it possible to consider specific treatments for the two conditions. The TGT also made it possible to have a crude measure of F8 and F9 activity in a product.

In 1961, F9 concentrate was given in Oxford to two patients with haemophilia B. This was manufactured from a fraction of plasma that was discarded after extraction of other factors. Therefore sufficiency was not as much a problem as with F8. The quality and potency of the product were high. Other adaptations of Cohn's fractionation also yielded F9 concentrates. Treatment of haemophilia B was with FFP or F9.

Treatment of von Willebrand disease before 1970

Treatment was mainly with FFP or cryoprecipitate during this period.

6. History of Haemophilia Treatment from 1970 Onwards

Haemophilia A treatment from 1970

In 1974, 1,634 patients were treated across 47 haemophilia centres in the UK. The use of cryoprecipitate accounted for 80% across the UK but no more than 40% in Oxford where fractionated products were preferred.

In 1972, the first large-pool commercial concentrates were introduced and comprised 13% of all F8 used in 1974. The average annual use of F8 per patient rose from 7,391u in 1970 to 12,575u in 1974.

Disadvantages of F8 concentrates

Disadvantages of F8 concentrates at this time included the higher likelihood of liver disease related to viral infections with hepatitis B and non-A, non-B hepatitis (NANBH, later hepatitis C) viruses. It was recognised through the early 1970s that F8 concentrates made from pooled plasma bore a risk of hepatitis B and NANBH. Jaundice remained relatively stable between 1969 and 1974 at around 2%. In 1974, there was a sharp spike related to one or two hepatitis B virus (HBV)-infected commercially imported batches: batch testing was done because jaundice rates seemed higher, using improved techniques for HBV. It was hard to incriminate a batch as patients were exposed to many products. In these 6 years, jaundice mainly occurred in people with severe haemophilia. Of the five patients who died of jaundice in this period, four had received only cryoprecipitate.

The distinction between transaminitis (abnormal liver enzyme tests) and hepatitis (a clinical problem with jaundice) was unclear till 1977 when chronic liver conditions such as chronic active hepatitis and chronic persistent hepatitis were identified. By the mid 1980s, the fact that a sixth of patients could have cirrhosis was published. It was also recognised that single donor or small-pool cryoprecipitate, or even FFP, could delay development of hepatitis but not reduce or abolish it (Mannucci, 2018). In 1989, hepatitis C was identified, enabling accurate diagnosis of NANBH. In 1992, it was recognised that even concentrates purified by the solvent detergent technology (technology then in use) could spread hepatitis A.

Higher likelihood of AIDS/HIV infection was a concern from 1982. In 1983, the first two British patients with AIDS were identified. Consequences to patients diagnosed with AIDS/HIV were severe (generalised illness, infections, cancers, death, stigma, suicide) and, until the introduction of anti-viral treatment, fatalities were common. Risk of spreading infection to sexual partners was significant. Clinically significant effectiveness of this treatment occurred with the introduction of combination therapy in the 1990s.

In 1983, parvovirus infection was identified as being caused by treatment with F8.

Variant CreutzfeldtJakob disease (vCJD) infections were recognised as rare but potentially fatal prion infection in the late 1980s, peaking in 1999/2000. It was also recognised that it could be transmitted via transfusion. One consequence of this was the introduction of a step to remove white blood cells from a donated unit of blood before releasing it for use. This step, known as 'leucodepletion', made transfusion overall safer as removal of white cells also reduced other side effects such as febrile reactions and other infections.

In relation to the shortage of products, despite increasing production of human F8 in 1972, it was still inadequate. In 1976, at a discussion about UK requirements for F8 in Sheffield, a conservative estimate of 40 million units for UK was proposed. This meeting also recorded discussions highlighting the different approaches of clinicians: some believed that they should encourage their patients to live within the limits of their disability and others felt the need to encourage normal sporting activities such as football. These decisions had an impact on patients' quality of life and management of bleeding.

Thromboembolism was reported with treatment with high-potency concentrates.

Advantages of F8 concentrates

F8 concentrates enabled home treatment including on demand treatment. The freeze-dried nature of the product made it easier, quicker and more convenient to use than cryoprecipitate which had to be stored frozen. Although costs to the NHS were not much different, the social impact of home treatment was significant: savings in time lost from school and work, greater sense of security, increased capacity for planning ahead. F8 and F9 were carried around on journeys and injected as required.

F8 concentrates were more potent, better defined and more purified compared to cryoprecipitate. They could be filtered to remove bacterial contaminants; there were fewer allergic reactions than with cryoprecipitate; they were amenable to large volume manufacture by processes compliant with 'good manufacturing practice'.

Commercial F8 concentrates

By 1972, freeze-dried F8 was generally the preferred product in England and Wales. Use of commercial products started in 1970 and on a named patient basis until 1973 when two were licensed. In comparison with the rest of the UK, Scotland produced a substantial proportion of their demand for F8. The use of F8 rose to 13% in 1974 (Biggs, 1977), 20% by 1975 and increased to 55% in 1976 (Jones, 1978). Commercial (foreign) products were available and licensed to be purchased under regional or hospital budgets.

The following commercial products were available in the 1970s and 1980s (Krever 1997 and Penrose 2015):

Early 1970s: Hemofil (Travenol/Baxter/Hyland), Kryobulin (Immuno)

Late 1970s: Hemofil, Koate (Cutter), Profilate (Alpha), Factorate (Armour)

1980s: Kryobulin, Hemofil, Profilate, Factorate, Humanate (Speywood), Koate

Mid 1980s: FEIBA (used in patients with inhibitors, plus a few other situations), porcine F8

Late 1980s: Profilate, Kryobulin, Monoclate, Haemate P.

Overall Armour's Factorate was the most used product until its withdrawal. The choice of product was usually based on purchasing arrangements between the suppliers and finance/procurement staff in hospitals or health authorities.

Recombinant F8

In 1983 recombinant F8 was made. This was a very high purity product. It was also safe from infection as it was not derived from blood.

The first UK patient to get recombinant F8 was in 1988; it was licensed in 1994. When it was licensed, one of the patients already on this product had to be switched back to plasma-derived product as the recombinant product was too expensive. UK 1997 guidelines recommended that patients should be treated with recombinant F8 as it was licensed and that they should be treated with recombinant F9 when it received a licence. Children were identified as a priority (by consensus of UKHCDO – the UK Haemophilia Centre Directors' Organisation). Of the approximately 600 children with severe haemophilia A, half were treated with a recombinant product: this was related to cost issues. Costs were borne mainly by the hospital and reimbursed by health authorities. A boy admitted to a hospital might receive a recombinant product but a boy in an adjacent bed might not because the health authority buying the services from the hospital would not pay for it.

Treatment patterns

By 1970, patterns of treatment were changing: there was an overall trend to increase on demand treatment. Treatment consisted of giving a calculated dose of AHG (F8) preparation as soon as symptoms of spontaneous bleeding arose or to cover operative procedures during and after surgery. More than 85% of treatment was for treating bleeding episodes (on demand treatment = when a patient feels a haemorrhage is occurring); 15% was used for surgery and dental extractions. Reconstructive surgery for damaged joints was conducted at specialist centres, commencing around 1970 in UK. During the 1980s in the UK, treatment was mainly organised via haemophilia centres.

Home therapy

Treatment of haemophilia was mainly reactive throughout the 1960s. That is, treatment would be initiated and maintained to treat a bleed to stability (days to weeks) or if there was a surgical procedure needed (days to weeks). Treatment was delivered in hospitals, usually on an in-patient basis in the early 1970s. The start of home therapy commenced in the UK in 1971 but peaked later in 1975. Home therapy was popular as it ensured early treatment, and studies in the USA showed less overall use of products per bleed through this strategy. The family would usually follow a protocol for dose of cryoprecipitate or factor concentrate and stocks would be replenished (in the UK) from the haemophilia centres every 1-2 months. When there were queries, the haemophilia services were contactable by telephone for advice or via Casualty for immediate attention.

Home care treatment could start as early as age 3 (when veins could be safely accessed for intravenous infusions). In children, injections were done by parents (usually the mother); in adolescence they were taught to self-inject. Clinical review would take place every 2-3 months. By 1976, 60% of haemophilia A patients were either receiving or being considered for home treatment. At this time, 55% of the products were imported.

Home therapy was usually offered to the most severely affected patients who therefore received more products. In 1975, Oxford had 54 (25% of all their patients) haemophilia A patients on home therapy and Newcastle had 38. Data collected between 1969 and 1974 show that a mean of 2.45% of haemophilia patients who received FFP and cryoprecipitate developed jaundice. During the same period, Oxford recorded a 3.80% of patients developing jaundice: they were exposed to more (UK, voluntary) donors as more F8 was in use. This, at that time, seemed reassuring in that NHS concentrates made from unpaid donors used for F8 production were safe as compared with commercial factors imported from the USA using very large pools of plasma from paid donors.

Prophylaxis

Prophylactic treatment started in the 1970s and became more popular in the 1980s. The aim was to increase the baseline levels of circulating F8 by giving F8 infusions every 36-48 hours. The rationale was that improving baseline levels would prevent new spontaneous bleeds from occurring. Due to short supplies, these programmes were usually short term. Although effective, there were concerns regarding inhibitor formation due to increased exposure to products and more exposure to donors. By the mid 1990s, recombinant products were available for this purpose.

Antibodies (Inhibitors)

Patients treated with blood products could develop antibodies to F8 protein. These antibodies or inhibitors posed significant clinical problems.

In the early 1970s, F8 inhibitors were present in 6.75% of patients, remaining more or less constant. These patients comprised 17.7% of deaths at an average age of 46 – which by then was the average age of death in all severe haemophilia patients.

The consequences of inhibitors were that elective surgery was avoided or, if required, surgical techniques were modified. Less invasive procedures were employed using radiation rather than surgery to remove abnormal tissue over damaged joints. In 1975, the Bethesda assay for inhibitors was introduced. This enabled a more rational method of F8 treatment in patients with inhibitors. High doses of F8 were used to overcome the inhibitor activity, and measurements of F8 and F8 inhibitor levels were used in dosing the patients. The risk of severe bleeding and deaths related to bleeding were noted to be higher than previously in the 1976 to 1980 report of haemophilia centres in the UK.

A product bypassing the inhibitor (FEIBA) was available from the 1970s. In 1983, F7a (FVIIa) was introduced to treat patients with inhibitors. This was derived from plasma. In 1988, recombinant F7a was introduced; this was a safer product because it was made from a genetic formula and not from plasma.

Alternatives

Desmopressin was introduced in Italy in 1975. In the UK, its use started around 1978-81 but was more frequently used in the period 1985 to 1991. The chief advantage of desmopressin was that it could be used in mild and even moderate haemophilia, and it was not a blood product. Its side effects could be unpleasant with palpitations, headache and changes in blood pressure.

The procoagulant drug, Epsilon Aminocaproic Acid (EACA) was used in haemophilia A, B and VWD disease in the UK from the 1960s. It was used as an adjunct to factor concentrates. In the 1970s, its more potent analogue, tranexamic acid, was used in specific settings, notably in dental extractions and peri-operative settings. The use of these drugs reduced bleeding and use of factor replacement. Typically, tranexamic acid was commenced on the day of procedure and ceased about a week later when wound healing had started. The drugs could be used intravenously or orally; from 1986, tranexamic mouthwashes were used. Dressings for wounds, such as after dental extractions, included small amounts of pro-coagulant substances such as thrombin or EACA as topical agents to promote local clotting.

Haemophilia B

F9 use rose from 11,207u in 1970 to 20,523u in 1974. Availability of NHS F9 concentrate product was not a problem although some centres used commercial F9. In haemophilia B patients only 1% developed antibodies and in the UK there were fewer reports of HIV/AIDS. Patterns of hepatitis and deaths were similar to haemophilia A. Prothrombin complex concentrates were used especially in patients with inhibitors.

Von Willebrand disease

The main products used to treat VWD were cryoprecipitate and plasma-derived F8 (not high purity products). In the 1980s, DDAVP was commonly used in VWD. Surgical problems in VWD were more in the area of general surgical problems than orthopaedic. Since this disease affected women, management of pregnancy and labour were important considerations. The level of VWF increases during pregnancy and therefore it was through monitoring of levels in the blood that decisions could be made regarding treatment with cryoprecipitate or pdF8.

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7. The Particular Difficulties of Infection with HIV or Hepatitis for People with a Bleeding Disorder

Prior to 1990, infection with hepatitis C virus (HCV) was mainly transmitted via pooled plasma products as a treatment for hereditary bleeding disorders. Anti-HCV positivity in these patients was as high as >70% in some areas, while some of them were also co-infected with HIV. Since only about 20% of HCV-infected patients clear the infection naturally, chronic HCV infection caused a significant health problem in this group of patients. Mortality due to chronic HCV infection is estimated to be >10 times higher in patients with haemophilia than in the general population, and is mainly due to liver cirrhosis and hepatocellular carcinoma (Papadopoulos et al., 2018).

The antiviral treatment of HCV in patients with hereditary bleeding disorders is not different from that of any other infected patients. Nevertheless, many patients with hereditary bleeding disorders have previously declined (PEG)-interferon-based treatment because of side effects and the dominance of the unfavourable, reduced-interferon-responsive genotype 1. In recent years, multiple orally administered direct-acting antivirals (DAAs) have been approved for HCV treatment. The available data indicate that DAAs also have an excellent safety profile with a sustained virological response rate of >90% in patients with hereditary bleeding disorders.

In the setting of HIV co-infection, the likelihood of spontaneous clearance of HCV decreases substantially and is below 10-15%. In particular, with progressive immunodeficiency the risk of dying from HCV-associated liver disease increases significantly (Rockstroh et al., 1996). HIV co-infection has also been demonstrated to accelerate fibrosis progression, the precursor to cirrhosis. Although successful antiviral combination therapy for HIV and subsequent immune reconstitution can slow down the faster fibrosis progression, the risk of hepatic decompensation still remains higher in ART-treated HIV/HCV co-infected individuals versus HCV mono-infected subjects (Lo Re V 3rd, et al., 2014).

The particular impact of infection with hepatitis or HIV, or both, on a person's bleeding disorder and their treatment for their bleeding disorder

Cirrhosis as a complication of HCV infection may result in bleeding which would be worsened due to the presence of the inherited bleeding disorder. This may result in a higher use of clotting factors and also could be associated with worse outcomes of bleeding events such as oesophageal variceal bleeding (bleeding from swollen blood vessels around the stomach and oesophagus which occur as a result of liver disease) in the presence of cirrhosis-associated portal hypertension. In the setting of HIV and hepatitis co-infection, the risk of liver toxicity under HIV therapy is enhanced (Spengler et al., 2002).

HIV can cause thrombocytopenia which may also increase the bleeding risk of an individual with a known bleeding disorder. In the absence of advanced liver disease or HIV-associated low platelet counts, no impact of HIV or hepatitis would be expected on the course or treatment of the underlying respective bleeding disorders.

The particular impact of treatment for hepatitis and/or HIV on a person's bleeding disorder and their treatment for their bleeding disorder

There have been a few reports of increased bleeding episodes under commonly used HIV first-generation protease inhibitors which, however, were not observed in the Bonn HIV-infected haemophilia cohort with a preventive high-dose clotting factor substitution policy (Racoosin et al., 1999). Stopping the HIV protease inhibitors was associated with a decline or reversal in bleeding episodes. Increased bleeding events have not yet been reported for any other HIV drug class.

Whether people with bleeding disorders who are infected with HIV and/or hepatitis may experience difficulties receiving appropriate treatment for those infections

HIV care has been provided by many different physician groups including infectious disease specialists but also sexual health doctors and general practitioners. Improved survival is associated with physicians having greater experience of treating these infectious diseases (Kitahata, et al., 1999).

In the setting of hepatitis therapy, prior to the introduction of non-invasive measures, liver biopsy was recommended for fibrosis stage assessment. Liver biopsy was often not performed or very costly to undergo in patients with underlying inherited bleeding disorder. This may have had an impact on access to hepatitis therapy. Ever since non-invasive methods for fibrosis staging have become available, the need for liver biopsy has almost vanished.

In general, all patients with HIV and/or hepatitis were subject to stigma which could have made access to medical services or therapies challenging. This, however, was possibly even worse for persons with HIV and/or hepatitis due to transmission risk factors other than bleeding disorders.

Whether treatment for a bleeding disorder is affected by a person's viral load for hepatitis and/or HIV and, if so, why and how

In patients with haemophilia and late-stage HIV disease, viral load predicts disease progression independently of CD4 cell counts. Because viral load most strongly predicts progression immediately after load is measured, it seems to reflect the current level of immunosuppression. No data exist which suggest any impact of HIV viral load on treatment of a bleeding disorder. For HCV RNA, no impact on HCV disease progression nor treatment of bleeding disorder has been established. For hepatitis B, the level of HBV DNA is strongly associated with risk for liver disease progression and for development of hepatocellular carcinoma but not on treatment of underlying bleeding disorders.

Whether the treatment for hepatitis and/or HIV may trigger an inhibitor

There have been several case reports describing acquired F8 inhibitors in patients receiving interferon alpha for HCV treatment and in immune reconstitution inflammatory syndrome in patients being treated for HIV/AIDS (Zeichner et al., 2013). While the potential impact of HCV or HIV drugs on triggering an inhibitor cannot be ruled out, the fact that this was only reported in case reports suggests a low incidence of these events.

Whether having hepatitis and/or HIV has an impact on the ability to clear an inhibitor.

Due to a paucity of cases published, little information is available on the question whether hepatitis and/or HIV have an impact on clearing an inhibitor. Patients with such inhibitor development may be more challenging to treat due to HIV-associated immunosuppression and a prior AIDS diagnosis as there may be a risk for reactivation of some of these prior opportunistic infections (Malhotra et al., 2016).

Whether having an inhibitor may impact on a person's HIV/hepatitis infection and/or treatment for the HIV/ hepatitis infection

Again due to the small number of published cases, no informative literature can be found on this question. In general, inhibitors should not prevent HIV and/or hepatitis therapy.

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8. Blood Disorders

Red cell production and haemoglobinopathies

Haemoglobin (Hb) is the iron-containing protein contained within red blood cells. Its function is to bind and carry oxygen around the body. Haemoglobin consists of two types of globin chains (alpha and beta) enclosing the iron-containing protein haem. The predominant haemoglobin found in the body (after early infancy) is called 'Hb A'. Production of haemoglobin and red blood cells takes place within the bone marrow before being released into the circulation. Red blood cells have a lifespan of 120 days. They need to be deformable to travel through very small blood vessels. Abnormal or dying red blood cells are removed by the spleen. The iron released from dying red cells is recycled into new blood cells; any excess is stored as ferritin in the liver and bone marrow. Under normal circumstances, the amount of iron absorbed through the gut is equal to the amount lost.

Inherited disorders of haemoglobin (haemoglobinopathies) lead to a defect in the production or function of haemoglobin. Red cells are broken down more readily giving rise to a shortened life span, a process known as 'haemolysis'. The end result is anaemia and a variety of other clinical problems. These differ between the different disorders, as will be described below. Additional problems can arise as a result of treatment.

Haemoglobinopathies are common worldwide and predominantly found in people whose origins are from high prevalence areas such as Africa, the Middle East, South Asia and Southeast Asia. The prevalence in the UK relates to past and current patterns of immigration but it should be recognised that increasingly these disorders are found in all ethnic groups.

Universal antenatal and newborn screening programmes for sickle cell and other haemoglobinopathies are in place in the UK. The aim of the antenatal programme is to identify women who have the disorders (and who will need additional specialist care in pregnancy), and those who are healthy asymptomatic carriers but at risk of having a child with a major disorder if the baby's father also carries a significant gene. The aim is to offer prenatal diagnosis to identify if the foetus is affected, and to allow these couples to make an informed choice whether or not to continue with the pregnancy.

Newborn screening identifies babies with sickle cell disorder and most of those with significant thalassaemia, allowing early entry into specialist care. Screening programmes do not exist for other rare inherited anaemias.

Prevalence

The National Haemoglobinopathy Registry (NHR) has been in place for over 10 years and collects data for NHS commissioning on the numbers, geographical prevalence and treatments of different Hb disorders. As of September 2019, numbers on the NHR were as follows:

- Thalassaemia (clinically significant alpha thalassaemia, beta thalassaemia, Hb E/beta thalassaemia): 1,921
- Sickle cell disorders: 13,675
- Rare anaemias (these numbers are inaccurate and probably an under-estimate): 460

(Full report available on www.nhr.nhs.uk)

9. Thalassaemia Disorders

Thalassaemia is caused by genetic variations affecting production of one or more components of the globin chains of the haemoglobin molecule. Alpha thalassaemia and beta thalassaemia refer to impaired production of the alpha and beta globin chains respectively. These conditions result in an imbalance between the alpha and beta chains, and the excess chains damage the red blood cell; this then breaks down either within the bone marrow or in the circulation. The end result is anaemia with reduced haemoglobin in a small red cell.

Alpha thalassaemia is very common worldwide. Alpha chains are controlled by four genes (two from each parent), so clinical problems are only seen on individuals missing three out of four genes (Hb H disease) or all four genes (Hb Hydrops – incompatible with life). Hb H disease patients may need occasional blood transfusions, but most are able to manage with a mild to moderate degree of anaemia. Hb H tends to be seen in individuals from southern Europe, South Asia or Southeast Asia.

Beta thalassaemia disorders affect production of the beta chain or produce an unstable beta chain leading to its premature breakdown. There are hundreds of genetic abnormalities producing beta thalassaemias and thus a wide clinical spectrum of clinical phenotypes. Thalassaemia mutations are most commonly seen in individuals with origins in Southern Europe, the Middle East, South Asia and Southeast Asia. Patients carrying one mutation are carriers for the condition; although they may have a mild anaemia and red cell changes, they are healthy and do not require treatment. Persons inheriting two thalassaemia genes will suffer from more severe red cell changes, but the severity of clinical sequelae is very variable.

Beta thalassaemia may be classified clinically by the need for blood transfusions:

(a) Transfusion-dependent thalassaemia (TDT) – Patients normally need blood transfusions from early childhood to allow growth and normal development. Without transfusions, the child would typically die from the effect of anaemia in the first decade of life. Transfusions are typically required every 3-6 weeks. With adequate transfusion, the child or adult is able to grow and function effectively. The under-transfused patient will experience the clinical complications of thalassaemia, outlined below, due to anaemia and iron overload.

Approximately 900-1,000 individuals with beta thalassaemia in the UK are regularly transfused.

(b) Non-transfusion-dependent thalassaemia (NTDT) – The child or adult can survive without the need for regular transfusions but will be anaemic and at risk of iron overload and organ damage. The decision whether to give transfusions is made very carefully taking into consideration clinical symptoms and evidence of end organ damage such as poor growth, skeletal changes or significant organ enlargement.

Clinical complications of thalassaemia

(a) Related to anaemia and compensatory bone marrow expansion: fatigue, poor growth, skeletal deformity, enlargement of liver and spleen, excess iron accumulation.

(b) Related to haemolysis: gallstones and vascular abnormalities.

(c) Iron overload due to ineffective red cell production and increased recycling on the bone marrow: see below.

Clinical complications of transfusion for thalassaemia

Iron overload

Each unit of blood contains between 200 and 250mg of iron. The human body has no mechanism for removal of the iron and therefore patients who are regularly transfused will develop iron overload. Significant iron accumulations start to develop after about 20 transfusions (or 1-2 years of regular transfusion). However, they may be present in patients with very few transfusions or even in the complete absence of transfusion due to increased red cell breakdown, recycling in the bone marrow and increased iron absorption through the gut.

Excess iron exceeds normal storage capacity and is toxic to cells. Iron overload causes serious complications in the endocrine system, the liver and the heart. Endocrine complications begin at a young age with irreversible damage to the pituitary gland resulting in growth retardation and failure of pubertal development. In adolescents and adults, endocrine damage results in gonadal failure, insulin-dependent diabetes, hypopituitarism, hypothyroidism and hypoparathyroidism. Iron overload results in liver fibrosis, cirrhosis, liver cancer, cardiac failure, cardiac dysrhythmias and death. Heart disease is the most common cause of death due to iron overload.

Transfusion-transmitted infection such as hepatitis/HIV

Chronic hepatitis C has a high prevalence in transfusion-dependent patients who were transfused before the introduction of UK screening. However, chronic hepatitis C is seen still in patients arriving in the UK who have been infected in high-prevalence regions of the world. The risk of hepatocellular carcinoma due to chronic viral hepatitis is compounded by iron overload.

Red cell alloantibodies

These are caused by differences between blood groups of patient and donor and can result in transfusion reactions. The risks are reduced by selecting blood matched for blood groups.

Diagnosis of thalassaemia

Thalassaemia may be diagnosed at birth (by newborn screening) or suspected in an anaemic infant, child or adult when other causes such as iron deficiency have been excluded. Diagnosis is made by examining the blood count and blood film, and confirming the absence (or reduction) of normal haemoglobin (HbA) on electrophoresis. In some cases, another abnormal Hb may be present. Once diagnosed, DNA testing can confirm the genetic cause enabling genetic counselling for families and to predict the clinical course.

Treatment

All thalassaemia patients with significant disorders are regularly followed up in clinics with assessment of the effects of chronic anaemia and investigations to measure the amount of iron accumulation and any resulting organ damage. MRI scanning is now the standard for estimation of iron in the heart and liver.

Transfusion

The mainstay of treatment is blood transfusion and management of iron overload. A multidisciplinary approach is required, including specialist management of endocrine, bone liver and cardiac complications.

The decision to commence regular transfusions is usually taken by a specialist paediatric haematologist of paediatrician. Most TDT patients commence transfusions in early childhood but patients may also be placed on regular transfusion later in childhood or in adult life for symptoms and/or organ damage.

NTDT may require intermittent transfusions during childhood but a number of patients go on to need regular transfusions to control symptoms or prevent complications.

The UK TS publication on standards of clinical care (2016) recommends a target pre-transfusion range of 95-100g/L as this represents the best balance between complications due to anaemia (such as skeletal changes, liver and splenic enlargement) and iron overload. The amount of blood and frequency of transfusions is adjusted to achieve this target.

Splenectomy

This operation was often undertaken in the past as anaemia and under-transfusion caused splenic enlargement. This compounds anaemia and leads to increased blood requirements. This procedure is now infrequent in the UK as patients adequately transfused from early childhood should not develop splenomegaly. However, patients treated in other parts of the world and older adults have had splenectomy.

Many NTDT patients have a degree of splenomegaly and some require removal of the spleen.

Splenectomy carries with it an increased risk of certain bacterial infections and an increased thrombosis risk. Patients who have had a therapeutic splenectomy require to be immunised against certain bacterial infections and to take regular penicillin for life.

Iron chelation

Excess iron is removed with iron-chelating drugs. These bind iron and then excrete the bound complex in the urine or stools, or both. Desferrioxamine (DFO) was the first drug to become available in the late 1970s and has proven highly effective. However, it has to be given by continuous infusion, usually by the subcutaneous route, and patients self-administer it using pumps overnight, typically 5-7 nights a week for 8-12 hours. DFO can cause painful local skin reactions and adherence to the infusions can be very difficult for patients and carers. In the 1990s, pre-loaded balloon infusions became available which helped, but adherence remains an issue to date.

The oral iron chelators Deferiprone (DFP) and Deferasirox (DFX) became available in the 1990s and 2000s respectively. These avoided the problems with infusions and are generally much better tolerated although adherence remains an issue and these drugs require regular monitoring for side effects. The majority of UK patients now take one or more oral iron chelators, but some patients still require DFO for management of cardiac disease or intolerance of oral medications.

Poor adherence to iron chelator treatment puts patients at risk of serious iron overload leading to premature death. With good treatment lifelong, patients are expected to have a near normal lifespan though the condition carries a lifetime burden of treatment and quality of life is significantly impaired.

Due to the issues with adherence with iron chelation and the subsequent risk of iron-related complications, the threshold for regular transfusion in the past was higher but came at the cost of increased clinical problems related to anaemia, bone marrow expansion and iron-related organ damage.

Bone marrow transplant

Bone marrow transplant (BMT) (also termed 'stem cell transplant' [SCT]) from a compatible sibling or matched donor has been offered to children with transfusion-dependent thalassaemia since the 1980s. Successful treatment restores normal red cell development and avoids the need for transfusion and iron chelation. However, the procedure is associated with significant mortality (loss of life) and morbidity (side effects such as infertility), and compatible bone marrow donors are only available for <20% of patients in the UK. BMT is not currently offered to adult patients in the UK.

Future treatments

New treatments on the horizon for thalassaemia include drugs to prevent premature cell death within the bone marrow, drugs to prevent iron absorption and drugs to increase the levels of alternative haemoglobins. Trials of gene therapy have been successful in some genetic types of TDT and look promising for the future.

10. Other Rare Inherited Anaemias

There are a number of genetic conditions associated with anaemia, a tendency to iron overload and a requirement for intermittent and regular transfusions. These conditions may be associated with other inherited abnormalities (e.g. Diamond Blackfan Anaemia, red cell enzymopathies) and the diagnosis will be made on clinical assessment and genetic testing. The numbers of children and adults with these conditions is unknown in the UK but likely to be in the order of 500-1,000. The conditions are now included with thalassaemia in NHS specialist commissioning as the management follows similar principles to that of thalassaemia, with transfusions and iron chelation as needed.

11. Sickle Cell Disorders

Sickle haemoglobin (HbS) is a haemoglobin which is structurally different from normal adult haemoglobin (HbA). HbS is a result of a genetic mutation in the beta globin chain of haemoglobin. It is unstable in conditions of low oxygen and precipitates within the red blood cell causing distortion of the cell (which becomes sickle cell shaped) and premature destruction of the cell: a 'haemolytic' anaemia. Obstruction of blood vessels by the abnormal sickle cells causes tissue damage and inflammation.

Individuals who carry two copies of the gene (Hb SS) have sickle cell disease (SCD). There are other genes that can interact in the compound heterozygous state with HbS to produce clinical features of sickle cell. These conditions include Hb SC disease, Hb S/beta thalassaemia and Hb SD disease. All sickle cell disorders have a tendency for red cell sickling and clinical complications although some types are less severe than others. Haemoglobin SS disease is the most severe form of the disease with the highest incidence of sickle crises and other complications, though the frequency in which these occur varies considerably between individuals.

Individuals who carry a single copy of the gene are said to be sickle cell carriers as they can pass the gene onto their children. They produce both HbA and HbS within the red cell. This is sometimes called 'sickle cell trait'. Sickle cell carriers rarely develop clinical symptoms and complications and the vast majority remain asymptomatic throughout life; there is no evidence that sickle cell carriage interferes with normal life expectancy.

Sickle cell carriage is found in approximately 1 in 9 people of African or Caribbean origin. The sickle gene is also found in Southern Europe, the Middle East and India.

The number of patients with SCD in the UK is estimated to be around 15,000. About two thirds have Hb SS with most of the remaining having Hb SC disease. Around 85-90% are of African or African-Caribbean origin. Although the majority of patients live in London, increasing numbers are seen in other urban communities reflecting migration and relocation.

Diagnosis of sickle cell disorders

Newborn infants or those arriving in the UK under 1 year of age are offered bloodspot screening. This will detect significant sickle cell disorders. All women are tested for SCD in pregnancy. Testing is also indicated if patients present with symptoms and signs. The majority of patients will have a history of symptoms and be aware of their diagnosis from childhood, but those with less severe symptoms may be picked up for the first time in adulthood or on routine screening.

Diagnosis is made by electrophoresis of blood demonstrating the presence of Hb S. In SCD there will be absent, or very little normal, Hb A.

Clinical complications of sickle cell disorders

These arise as a result of increased breakdown of red cells (haemolysis) leading to anaemia and vascular complications or occlusion of vessels. SCD is a multisystem disease and any organ may be affected. The pattern of disease varies between individuals, even with the same genotype, and also, in any one individual over time. For instance, infections and splenic sequestration are more common in children while chronic organ damage and osteonecrosis is seen more in adults.

The spleen is affected early in SCD as cells sickle within the spleen causing death of tissue and loss of function. This occurs from a very early age and increases the risk of serious bacterial infection (and also malaria).

A full description of clinical complications is beyond the scope of this report but the salient complications of SCD are listed below. These are split into acute (short-term, rapid onset) and chronic (long-term, slow onset).

Acute complications of sickle cell disease

Painful episodes (sickle cell crisis)

These are experienced by most individuals and some have very frequent attacks. Pain may be very severe and be widespread or localised. It is unpredictable in nature and may be precipitated by infection, stress, pregnancy and hormones, and exposure to cold and dehydration. The severity of pain often warrants treatment with opiates and hospital admission. Hydroxycarbamide (HC, see below) is offered to those with frequent crises. If ineffective or not tolerated, some patients with very severe frequent crises requiring multiple hospitalisations will be offered regular transfusion.

Anaemia

Increased anaemia beyond baseline may occur during crisis and may be due to concurrent infection (including viral). This may require transfusion.

Acute chest syndrome

Acute chest syndrome (ACS) is a serious acute pulmonary (lung) complication of SCD giving rise to low oxygen levels (hypoxia) and respiratory failure. It can be fatal. Management is with antibiotics, oxygen and judicious intervention with blood transfusion.

Infections

Infections are a serious risk in SCD. These occur in part due to poor splenic function. Treatment is with early and regular immunisation and regular penicillin (mandatory in all children up to the age of 16). Infections include pneumonia, osteomyelitis and septicaemia.

Stroke

Strokes occur due to vascular damage in the cerebral vessels and are far more common in SCD than in the general population. Approximately 10% of children will have a major overt stroke and a further 20% experience changes to the white matter of the brain which affects cognitive development and function. The incidence of stroke reaches a peak in the first decade of life in children with Hb SS. Regular red cell transfusion has been shown to prevent secondary stroke in those who have had a stroke.

Transcranial doppler (TCD) screening is offered to all Hb SS children from the ages of 2-16 in the UK and predicts those at increased risk of stroke. For those children with abnormal TCDs, regular transfusion has been shown to prevent stroke. Some children are able to discontinue transfusions after a time (see below). In the UK, primary or secondary prevention of stroke is the most common reason for SCD patients to be on regular transfusion (Trompeter S, Bolton-Maggs P, Ryan K, et al. 2019)).

Splenic sequestration

Splenic sequestration is usually seen in young children and is characterised by rapid pooling of large volumes of blood in the spleen. Emergency blood transfusion is usually needed.

Priapism

This is painful and sustained penile erection, and can cause erectile dysfunction if left untreated.

Complications of gallstones

In common with other anaemias with high rates of red cell breakdown (haemolysis), patients with SCD are at high risk of gallstones. These can, in turn, cause complications such as obstructive jaundice, biliary colic and pancreatitis.

Chronic complications of sickle cell disease

Chronic organ damage occurs increasingly with age and is a major cause of morbidity and mortality for adult patients. Conditions include:

• Proteinuria and chronic kidney disease. Increasingly seen with age and the incidence of end stage renal failure is predicted to rise as the population ages.

• Cardiorespiratory disease. This is emerging as a major cause of death as patients reach the sixth decade of life.

• Osteonecrosis of joints – hips and shoulders. Can occur in young adults but increasing frequency with age. Causes severe painful arthritic changes and often requires surgical intervention with joint replacement.

• Chronic liver disease. Incidence rising with age. Caused by combination of chronic infection, repeated sickling, iron overload (from transfusion), chronic viral infection (HBV, HCV) and long-term analgesic medication.

• Chronic eye disease, leading to visual loss.

• Painful leg ulcers.

Treatment of sickle cell disease

Supportive

This is the mainstay of treatment and includes patient education, analgesia, fluids, and treatment of infections and complications. Many patients manage their crises at home but come to hospital if pain is very severe and/or there are features to suggest complications. Transfusion may be needed for some acute complications (see below).

Hydroxycarbamide

This drug has been used since the mid 1990s and has been demonstrated to be effective in children and adults at preventing crises and reducing the incidence of acute chest syndrome. Its efficacy for other chronic complications remains unclear at present. UK guidelines recommend that HC is offered to all children with Hb SS from the age of nine months and to adults with frequent crises or recurrent chest syndromes. Some children who are regularly transfused for stroke risk are able to convert to HC after a period of time on transfusions. HC requires daily dosing and regular monitoring. It is generally well tolerated.

Blood transfusion

This is used to correct anaemia or to reduce the proportion of circulating sickle cells thereby reversing the clinical and pathological process of SCD. Transfusion efficacy is measured by the reduction in Hb S% levels. There are two approaches to transfusion – namely, top-up transfusion and exchange blood transfusion

- Top-up, where one or more units of blood are given by simple infusion. The amount of blood that can be given by top-up is limited as taking the Hb level too high can result in hyperviscosity.
- Exchange blood transfusion is a procedure whereby a quantity of blood is removed and replaced with transfused blood. Since equal volumes of red cells are exchanged, it is possible to get the proportion of Hb S% down to effective levels without allowing the Hb to rise too high.

Both approaches to transfusion are effective in lowering Hb S% but the reduction in Hb S% that can be achieved following top-up transfusion will depend on the pre-transfusion Hb levels.

Transfusion is not routine for painful sickle cell crisis but is needed for the following specific indications (Davis, Allard et al. 2016):

- Acute anaemia – in practice, many patients have intermittent top-up transfusions for this indication at some point either in UK or abroad.
- Acute chest syndrome
- Primary or secondary prevention of stroke – this is the most common indication for transfusion in the UK.
- Recurrent painful episodes of Acute chest syndrome not responding to hydroxycarbamide.
- Acute multi-organ failure.
- Surgery. Transfusion has been shown to reduce the perioperative risk of surgery in SCD and is now the standard of care for Hb SS patients undergoing surgery. Other SCD patients may also be offered transfusion after individual assessment.
- High-risk pregnancy. Blood transfusion is currently not indicated for standard sickle pregnancy (although pregnancy in all women with SCD carries increased risks for mother and baby). This is the subject of an ongoing national trial.
- Chronic cardiorespiratory disease.

Many patients, even if not on regular transfusion, will have received one or more blood transfusions in their lifetimes for acute indications or for surgery.

In a 2014 UK audit of 1,290 SCD patients having transfusion over a 6-month period, 85% were for elective indications with stroke prevention being the single most common indication; 50% of adults and <10% of children were having exchange blood transfusion. Those on regular top-up will accumulate iron and need iron chelation. It is predicted that numbers of transfusions will continue to increase.

Iron chelation

Patients with significant iron overload are offered treatment with iron chelators as outlined above for thalassaemia and rare anaemias. Patients on EBT are much less likely to accumulate iron and may not need chelation.

Stem cell transplant from a matched sibling

This is offered to children with stroke or other specific indications. It is not currently commissioned for adult patients in the UK. This is currently under review by NHS England.

New treatments

A number of new drugs are in trial which target the pathophysiological process of SCD and will therefore prevent or treat crisis and other acute complications. Gene therapy is also under trial and may offer a curative option in the future.

Life expectancy in sickle cell disease

SCD is associated with a reduced life expectancy. Hb SS patients on average live 20 years less than non-sickle individuals. Life expectancy has increased over the years due to better management, which includes improved supportive care and medical treatment. Some recent studies have shown that, although the average age of reported deaths remains in the mid to late 40s, estimated survival is increasing for the population as a whole. Survival of an adult cohort of patients managed at King's College Hospital, London, over a 9-year period was published in 2016 (Gardner et al. 2016). In this series, 43 (33 deaths in 450 Hb SS) patients died at a mean age of 42 years. Kaplan Meier analysis estimated a median survival of 67 years for haemoglobin SS patients. This estimate came from extrapolation of observational data but needs to be confirmed by true observational data since most Hb SS patients in the UK are currently under 50 years and rates of new complications after this age are unknown. There appeared to be no difference between male and female patients. Patients with other forms of SCD such as Hb SC disease lived longer than Hb SS but less than non-SCD individuals.

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12. Other Transfusion-Dependent Diseases

Blood transfusion is required to replace blood when there is significant acute loss or destruction of blood cells, or to compensate for lack of production. Examples are major haemorrhage (rapid and massive loss of blood), autoimmune haemolytic anaemia (destruction of cells) and acute leukaemia (lack of production of normal cells). Requirements are usually of short duration, or intermediate if the underlying cause of lack of blood persists uncorrected. Anaemia or low platelet counts due to problems with production in the bone marrow (bone marrow failure, bone marrow cancers) also need transfusion support and usually tend to be for longer periods.

These transfusions are provided in the UK using blood components such as red cells or platelets rather than whole blood. FFP and cryoprecipitate are required to replace clotting factors in bleeding situations such as haemorrhage in labour or trauma, where the cause of bleeding is not inherited as in haemophilia but rather an acquired problem due to processes leading to excess use of the clotting proteins in blood or reduced production of clotting proteins by the liver.

The threshold for transfusion used to be an Hb level of 10g/dl or 100g/L to transfuse red blood cells and 20-30x10^9/l to transfuse platelets. Abnormalities of >1.5 times normal in timed clotting tests were usually indications for transfusing plasma. The use of cryoprecipitate in preference to plasma was/is employed when patients require/d swift correction of fibrinogen, an important protein in the clotting mechanism. In certain types of haemorrhage, fibrinogen is depleted rapidly and this worsens the bleeding unless it is specifically corrected. An example of this is bleeding in pregnant women at the time of delivery. Historically, replacement of products was based sometimes on the basis of repeat blood tests to guide replacement on an ongoing basis, and at other times to a formulaic replacement with a fixed ratio of products to simulate whole blood replacement. Evidence on use of safe targets to replace blood products was evaluated and guidelines published by the National Institute for Health and Care Excellence (NICE) in 2015: these have set the transfusion thresholds at lower levels than were used historically. The 2004-08 specifications for procuring imported (USA) FFP or platelets obtained by apheresis were withdrawn in 2019 because the risk of vCJD had been recognised as small. Prior to 2004, products available to treat acquired bleeding/clotting disorders comprised methylene blue treated FFP or cryoprecipitate, Octaplas and pheresed platelets; these were for patients born after 1 January 1996. In addition, prothrombin complex concentrates and fibrinogen concentrates were available.

The common situations for long-term transfusion support of acquired conditions are in bone marrow failures due to cancer (such as acute leukaemia), failure (aplastic anaemia) or dysfunction (myelodysplasia). Usually red cells and platelets are required until the bone marrow is able to recover capacity to produce blood such as with successful chemotherapy treatment.

In acute myeloid leukaemia, an analysis from Australia (see the journal, Haematologica, 2009) shows that for the standard three courses of treatment a total of 150 donations are required. Two analyses from Italy and the USA (1988 Blood, 1988 Haematologica) in patients with acute leukaemia transfused before 1985 show no seroconversion in 91 Italian patients (exposed to 7,000 donors) and 18/211 cases of seroconversion in the USA where a mean of 100 donors were used per patient.

Other situations where top-up transfusions were used for weeks to months to treat anaemia were kidney disease and anaemia of prematurity.

In renal dialysis patients, red cell transfusions were used to maintain stable levels of haemoglobin. This was replaced with erythropoietin hormone treatment (since the late 1980s) and transfusion is now exceptional. Patients also received cryoprecipitate and platelet transfusions to control bleeding. In these patients the chemicals accumulated in the body due to kidney failure adversely affected the function of platelets; therefore bleeding was a significant problem. Of patients on dialysis in Miami between 1986 and 87, 23% were found to be positive for HIV-related antibodies: the primary cause was IV drug abuse, the second cause was blood transfusion. In a study from 1990 on renal transplant patients transfused prior to 1985, 2.7% of 220 patients were infected.

Neonatal units use red cell transfusion in preterm babies. In Japan, 2.3% of neonates transfused between 1975 and 85 were found to have seroconverted. The treatment of anaemia of prematurity is now mainly erythropoietin.

13. Primary Immunodeficiency Disorders

Introduction

Primary immunodeficiencies are diseases which result from a specific defect in one or more components of the immune system and classically result in increased susceptibility to infection. There are now more than 300 primary immunodeficiencies described.[1] Nonetheless, primary immunodeficiencies are rare, and while it is difficult to give precise estimates of the prevalence of these conditions, due to the paucity of data, as well as variations between different ethnic groups, these diseases are estimated to occur in 1 in 13,000 live births in the UK.

The first primary immunodeficiency was described in 1952 when a young boy was characterised as having absent immunoglobulin by Colonel Ogden Bruton, and this condition was subsequently termed 'Bruton's agammaglobulinaemia' (it is now known as 'X-linked agammaglobulinaemia', XLA).[2] Knowledge of primary immunodeficiency diseases has increased very rapidly over the subsequent 60+ years, and these are increasingly recognised. It is likely that the vast majority of these conditions are genetically determined, although in many cases the exact genetic cause is unknown. Most patients with primary immunodeficiencies will experience severe, persistent, unusual or recurrent infections. Other symptoms that may affect an individual with a primary immunodeficiency include failure to thrive (grow and develop normally) in infancy or childhood; autoimmune disease, where the immune system turns on the individual and attacks itself; and cancer. Because these diseases are determined by genetic mutations, some will run in families, but this is not always the case.

Secondary immunodeficiencies are much more common than primary immunodeficiencies. Secondary immunodeficiencies are caused by conditions which impair the normal function of the immune system as a downstream event, and include severe kidney or liver failure, nutritional deficiency, ageing, viral infections such as HIV, cancer, and a variety of different drugs and toxins.

The focus of this review is primary immunodeficiencies, because long-term treatment with blood products has been a cornerstone of treatment of some types of primary immunodeficiencies since the 1960s. While long-term treatment with immunoglobulin is part of the routine treatment of an increasing number of different types of secondary immunodeficiencies, this affected a very small proportion of patients receiving immunoglobulin replacement therapy in the 1980s and 1990s.

Primary immunodeficiency disorders that may require regular treatment with blood or blood products

The latest report of the International Union of Immunological Societies classifies primary immunodeficiencies into nine different categories.[3] Each of these categories of immunodeficiency is characterised by a different pattern of infection and associated features.

Categories of Primary Immunodeficiencies
1. **Immunodeficiencies affecting cellular and humoral immunity**
2. **Combined immunodeficiencies with associated or syndromic features**
3. **Predominantly antibody deficiencies**
4. Diseases of immune dysregulation
5. Congenital defects of phagocyte function, number, or both
6. Defects in intrinsic and innate immunity
7. Autoinflammatory disorders
8. Complement deficiencies
9. Phenocopies of primary immunodeficiencies

A variety of treatments are available for individuals with primary immunodeficiencies. The main group of conditions that require regular treatment with blood or blood products are those which are associated with antibody deficiency, either alone, or in combination with other immune deficiencies (Groups 1-3, marked in bold in the table above). These will therefore be discussed in more detail below.

Why do patients with primary immunodeficiency fail to produce immunoglobulin, and why does this matter?

In some patients with primary immunodeficiency, antibody deficiency occurs as a result of failure to produce normal functioning proteins known as 'immunoglobulins' (also referred to as 'antibodies'). Immunoglobulins play a key role in defence against bacteria and, while there are multiple points of overlap and redundancy in the immune system, it is clear that failure to produce effective immunoglobulin results in susceptibility to bacterial infection.

Immunoglobulins are soluble proteins that are made up of two 'heavy' chains and two 'light' chains. There are five different families of heavy chain – IgG, IgA, IgM, IgE or IgD – and these determine the precise function of the immunoglobulin molecule. The light chains determine the exact target of the immunoglobulin molecule, and there are an infinite number of different light chains that can be produced. The heavy and light chain component of a single immunoglobulin molecule act together to recognise the infectious target; once recognised, the fate of the infectious target is determined by the heavy chains of the immunoglobulin molecule.

A particular feature of the antibody-producing component of the immune system is that it becomes efficient if it has seen the infection before. What does this mean? Well, the first time the immune system sees a particular infection, it may take 5-10 days for specific antibodies to be detected in the blood, and the response will generally be a bit 'clunky'. (This period is characterised by IgM antibodies.) Only after 1-2 weeks are the high efficiency, high specificity antibody families produced (these are mainly IgG antibodies, but may also include IgA and IgE), which are more effective at clearing the infection. If months or years later the individual is re-exposed to that infection, the immune system 'remembers' the previous encounter, and immediately produces high specificity, highly efficient antibody families. As these antibodies may be necessary to clear the infection, a second infection is often far less severe than a first-time infection.

As hinted at previously, the most important immunoglobulin family for defence against infection is IgG. IgG antibodies are important in mobilising the activity arms of the immune system, such as the 'killer cells' (natural killer cells), the 'eating cells' (phagocytes), and a part of the immune system call complement which can punch holes in circulating bacteria. In addition, IgG may directly neutralise toxins and targets. We know that IgG is crucial to survival because the isolated failure to produce IgG is associated with a high risk of serious and overwhelming infection, and sometimes death. These infections are generally caused by bacteria, reflecting the importance of immunoglobulin in defence against bacterial infection.

Treatment of antibody deficiency: immunoglobulin replacement therapy

Whatever the underlying cause of disease, if an individual is unable to make effective IgG antibodies, then the only therapeutic option is to try and replace these (i.e. there is no way of 'kickstarting' a patient with primary immunodeficiency to make their own antibodies).

If the patient has a severe immunodeficiency affecting multiple components of the immune system (in addition to the antibody-producing component), then the only long-term treatment option is to completely replace the patient's own immune system with an immune system from a healthy individual. This is known as stem cell transplantation (previously called bone marrow transplantation). Although this can be very successful, it is a high-risk procedure which carries a significant risk of life-threatening complications and even death. Survival figures for stem cell transplantation since 1973 for primary immunodeficiency disorder (PID) in the UK is 83%.[4] For this reason, it is only used in highly selected individuals with severe complex immunodeficiencies.

The vast majority of patients with antibody deficiencies do not require stem cell transplantation. For them, the mainstay of treatment is regular transfusions of antibodies that other, healthy individuals have made. This is called 'immunoglobulin replacement therapy'.

History of immunoglobulin replacement therapy

Immunoglobulin replacement therapy is a human blood product. It consists of IgG extracted from donated plasma, which has been separated from units of blood from thousands of blood donors. It contains IgG antibodies that reflect the infection history of each of the thousands of blood donors who have contributed to the plasma, and thus covers a wide variety of common organisms. Because each batch of immunoglobulin replacement therapy depends on the donors who contributed to it, there is considerable variation in antibody composition from batch to batch, and product to product.

Donated purified immunoglobulin (immunoglobulin replacement therapy) was first used in the treatment of patients with primary antibody deficiency in 1952, and was introduced in the UK in 1956.

Mode of adminstration of immunoglobulin replacement therapy

There are two major forms of immunoglobulin replacement therapy currently available in the UK:

- **Intravenous immunoglobulin (IVIG)** involves giving immunoglobulin straight into the blood via a cannula in a vein. This is generally administered every 3-4 weeks, and treatment needs to be given for life.

- An alternative to IVIG is **subcutaneous immunoglobulin (SCIG)**. This has been available since 1980 and was widely adopted in the UK in the mid to late 1990s, once it was shown that it could be safely delivered at home.[5] SCIG is delivered via a needle into the fatty tissue under the skin over 45-60 minutes, from where it enters the blood slowly over a few days. There is not much room under the skin, so the dose of immunoglobulin that can be given is smaller than with IVIG. For this reason, SCIG is usually given every week. A particular advantage of SCIG is that most people can learn how to do this at home, avoiding the need for repeated hospital visits. As with IVIG, this also needs to be given for life.

IVIG and SCIG are essentially equivalent in terms of safety and efficacy; thus, patient preference can be used to guide these choices. While all licensed immunoglobulin products have similar efficacy, safety and tolerability, they are not interchangeable. Therefore product selection depends on availability and choice. Once patients are stabilised on one preparation, this should not be changed except for sound medical reasons.

Prior to the introduction of IVIG and SCIG, immunoglobulin replacement therapy was delivered intramuscularly. **Intramuscular immunoglobulin** (IMIG) caused significant pain and discomfort during administration and, because only limited volumes could be administered, it took a long time to reach peak serum levels. IMIG gradually ceased to be used in the late 1980s, as alternative approaches became available.

Dosing of immunoglobulin replacement therapy

The goal of treatment with immunoglobulin replacement therapy is to reduce the frequency and severity of breakthrough infections, rather than to achieve a particular level of IgG in the blood. To achieve this, treatment needs to be individualised for each patient by altering the dose or frequency of administration.

Typical starting doses are 400 to 600mg/kg every 3-4 weeks for IVIG, and 100 to 300mg/kg once weekly for SCIG. Adequacy of replacement therapy is determined by a combination of clinical criteria (freedom from infections and prevention of their complications; and general energy and wellbeing). For most patients, this requires pre-infusion (trough) IgG levels to be kept middle of the normal range for IgG (approximately 8 g/litre).

The half-life of IgG immunoglobulin was originally calculated to be 21 days, but current intravenous immunoglobulin preparations have half-lives closer to 30 days, probably because of protein modification during the different manufacturing processes. The half-life of immunoglobulin may also vary considerably between individuals, for reasons that are not clear. Thus, changing the frequency of administration as well as the dosage may be needed in order to optimise a patient's treatment regimen.

Manufacture of immunoglobulin replacement therapy

Immunoglobulin replacement products are regarded as pharmaceutical products derived from plasma. All products currently licensed in the UK are manufactured by commercial pharmaceutical companies from non-UK sourced plasma. This has been the case since the use of UK sourced plasma was discontinued in 1998, in light of the new variant CreutzfeldJakob disease outbreak (see below). Starting in 1983, the Scottish National Blood Transfusion Service (SNBTS) produced immunoglobulin products from Scottish donors, and these were widely used both in Scotland and in Northern Ireland in particular. The SNBTS protein fractionation centre closed in 2008.

It has always been recognised that there is a risk of the transmission of plasma-borne infectious agents from immunoglobulin replacement therapy. In a review article published in 1957, Pennell suggested that 'no fraction prepared from pooled plasma by any technique (could) be presumed to be free from the virus of homologous serum hepatitis unless shown to be so by volunteer studies or by application of an effective sterilising technique'.[6] Thus, anti-viral safety is regarded as a key requirement of the manufacturing process of immunoglobulin products. This is currently addressed through a combination of different steps which may differ between companies: donor-targeted safety steps include using well-screened pools of well-characterised blood donors, and quarantining of plasma for at least three months after donation so that donors may be rechecked to reveal any previously unrecognised infection. Manufacturing steps that are used to minimise risks of infection transmission include cold-ethanol fractionation, pasteurisation, solvent detergent treatment, the use of caprylic acid treatment and nanofiltration. These are thought to kill all known classes of virus.

Prior to the steps being implemented, there were a number of outbreaks of hepatitis C infection related to immunoglobulin usage in the UK. The first was in 1983, when a British-produced plasma product was implicated.[7] A second outbreak occurred in relation to Scottish product in Scottish patients.[8] In 1994, there was a third outbreak centred on Oxford, related to product made by Baxter pharmaceutical. In that outbreak, 36 UK patients with primary antibody deficiencies were exposed to the infected batch and 29 of these were found to be HCV-positive on two or more occasions.[9]

It is noteworthy that, in the 25 years since the outbreak in 1994, there have been no further recognised episodes of hepatitis C or other viral infection associated with immunoglobulin replacement therapy in the UK. This is widely credited to the improved stringent screening processes for donors and antiviral production steps in production of every immunoglobulin product. Confidence in immunoglobulin products is now so high within the immunology community that previous practices, including regular storage of serum samples and annual testing for hepatitis viral transmission, are no longer widely practised.

Risk of prion transmission

There is a theoretical risk of transmission of prions through IVIG, although this has not been documented to date as prion infection cannot be detected in blood. The epidemic of bovine spongiform encephalopathy (BSE) in the 1990s and the link between BSE and a novel form of Creutzfeld-Jakob disease (new variant CJD) led to major concerns about the safety of plasma donated from individuals resident in those countries affected by BSE, in particular the UK. As a result of these concerns, a ban was put in place on the use of UK-derived plasma for the manufacture of immunoglobulin. This remains in place and is likely to do so for the foreseeable future.

Manufacturers' own assessments indicate that significant removal of prion particles occurs during the fractionation process, filtration steps and precipitation procedures, suggesting that the risk of prion transmission is extremely low. However, a theoretical risk remains and it is an essential standard of care to ensure that patients and their carers are fully aware of the potential long-term risk from immunoglobulin replacement therapy.

Non-infectious adverse effects of immunoglobulin replacement therapy

Infusion-related reactions

About 10% of patients experience mild infusion-related reactions during or immediately after IVIG therapy. These include headaches, malaise, backache, nausea and myalgia. This can usually be overcome by a combination of reducing the infusion rate, and/or giving antihistamines, and antipyretics such as paracetamol. Infusion reactions can be more severe if a patient has a current infection: infusions should be avoided, or given at a very slow rate, until infections have resolved on antibiotic therapy. Premedication with paracetamol, antihistamines, and/or hydrocortisone, or changing the immunoglobulin product, often helps in patients who develop repeated adverse reactions.

Adverse reactions are rare with SCIG therapy, apart from local pain and swelling at the site of administration. Switching to SCIG may be an option for patients who fail to tolerate IVIG.

Outcome of antibody deficiency

Prospective studies have shown that optimal immunoglobulin replacement therapy reduces the incidence of sepsis, especially by encapsulated bacteria. If this is instituted before structural lung damage is established, recipients are likely to have greatly decreased morbidity and mortality. However, the occurrence of non-infectious complications of primary immune deficiency nonetheless results in increased overall mortality due to higher risk of cancer, particularly non-Hodgkin's lymphoma and gastric carcinoma.

Making the decision to start immunoglobulin replacement therapy

In the UK, there are clear guidelines for the administration of immunoglobulin replacement in patients with primary immunodeficiencies.[10] The decision to start treatment is made by a multidisciplinary team of specialist doctors and nurses (immunoglobulin assessment panels), in conjunction with the patient and their carers, and informed by these commissioning guidelines. In addition, decisions are informed by the national demand management plan,[11] which was first put in place in 2008 to prioritise the allocation of immunoglobulin within the NHS because of a global supply shortage. To complement the Clinical Guidelines and Demand Management Plan, support long-term planning and provide data on the use of immunoglobulin in rare disorders, the National Immunoglobulin Database has been developed. This provides a record of all individuals in England who have received immunoglobulin replacement therapy (with a similar database in the devolved nations). This database, in combination with the UKPID registry (see below) allows immunoglobulin usage in different treatment centres to be compared across the UK.[12]

It is standard for patients to sign a consent form, which includes being advised about the risks of inadvertent infection with known and unknown infectious agents. It is important to note that the decision to start immunoglobulin replacement in an individual patient results from a holistic assessment of their immunological function, rather than simply relying on a low level of serum immunoglobulin.[13]

Supplementary management of antibody deficiency

In addition, even with optimal immunoglobulin replacement therapy, breakthrough infections can occur in these patients. Health care teams should have a low threshold for treating infections with antibiotics. Recurrent infections, especially when associated with structural lung damage, may require long-term prophylactic antibiotic prophylaxis. Postural drainage of lung secretions may be helpful.

Patients with serious lung disease, gastrointestinal disease or impaired liver function should be managed with multidisciplinary input from relevant organ-based specialists. Patients should be encouraged to join support groups for education and counselling as well as practical help with social problems. Referral for genetic counselling should be considered in patients with a familial disorder or a known gene defect. It is also important to note that clinicians involved in care of patients with PID adopt a partnership approach with patient representative groups in establishing principles of care.[14]

Which primary immunodeficiencies are associated with failure to produce antibodies?

Antibody deficiency is a common pathway for many different immunodeficiencies

Antibody deficiency diseases are characterised by a decrease in the levels of serum immunoglobulins below the fifth centile for age. The reduction may be in all classes of immunoglobulins or a single immunoglobulin family.

Although there are many – as many as 100 – causes of antibody deficiency in individuals with primary immunodeficiency, the central effect is the same: the absence of functioning antibody results in recurrent bacterial infections. The individuals are particularly susceptible to infections caused by bacteria which are coated with a waxy capsule – *Streptococcus pneumoniae and Haemophilus influenzae*. This is because antibody is a critical line of defence against these organisms, and there is no component of the immune response that can effectively substitute if an individual's antibodies are not working effectively. If untreated, an individual with antibody deficiency will experience repeated infections of the respiratory tract, eventually resulting in structural lung damage. Some patients will also experience arthritis, and diarrhoea and malabsorption may also occur due to chronic infection with intestinal pathogens or bacterial overgrowth in the small intestine. The more severe forms of these disorders may present in infancy, but others can present in adulthood.

Here we list a handful of the more common conditions associated with antibody deficiency. However, it should be emphasised that these are only a selection.

Diseases where antibody deficiency occurs in combination with other major immunological defects

Severe combined immunodeficiency

This rare syndrome is characterised by severe failure of multiple components of the immune response. Affected individuals usually develop problems in the first weeks of life, with failure to thrive and recurrent, severe, potentially life-threatening bacterial, viral or fungal infections. These infections are often caused by opportunistic infections, infections that do not usually cause problems unless the immune system is weakened. The hallmark of SCID is low numbers

of circulating T lymphocytes, with or without B lymphocytes, compared to age-related normal controls, as well as markedly reduced antibody levels. SCID should be considered a medical emergency, as patients can rapidly succumb to life-threatening infections. Untreated, SCID is invariably fatal, with most dying in the first year of life and the balance succumbing within the second year.

The definitive treatment for SCID is bone marrow transplantation, which if given early in life before the onset of chronic infection results in excellent long-term survival.

Diseases where antibody deficiency is the major immunological feature

Common variable immune deficiency

Common variable immune deficiency (CVID) is a clinically defined syndrome characterised by susceptibility to infection, accompanied by a reduction of serum IgG below the fifth centile for age, and with evidence of impaired specific antibody production in response to natural microbial infection or vaccination.

CVID is a highly heterogenous disease, the diagnosis being based on the exclusion of other known causes of antibody deficiency. The estimated incidence of CVID is 1 in 10,000 to 1 in 50,000. It affects both sexes equally, and can present at any age, although the most usual time of presentation is in the second or third decade of life.

Most patients with CVID experience recurrent infections caused by encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*), as described above. Less common pathogens include *Staphylococcus aureus* and gram-negative bacteria such as *Pseudomonas spp*. Infections by fungi, intracellular bacteria (e.g. mycobacteria), or parasites are not usually a problem in these patients. Overwhelming viral infection is also unusual. Sites involved are the upper and lower respiratory tract, middle ear, meninges, bones and joints. The large majority of patients with antibody deficiency suffer from repeated bacterial respiratory tract infections which eventually result in structural damage if untreated; structural lung damage (bronchiectasis, pulmonary fibrosis) is the most important cause of morbidity and mortality in these patients.

In addition to recurrent infections, patients with CVID may experience other problems:

- A form of aseptic arthritis may occur, resembling seronegative rheumatoid arthritis;
- Diarrhoea and malabsorption may occur due to chronic infection with intestinal pathogens such as giardia, campylobacter, salmonella or cryptosporidium, or as a consequence of bacterial overgrowth in the small intestine.
- For reasons which remain unknown, some patients with CVID develop paradoxical antibodies against their own tissues, resulting in antibody-mediated autoimmune diseases such as idiopathic thrombocytopenic purpura and autoimmune haemolytic anaemia.
- CVID is associated with an increased risk of cancer, particularly lymphoma.
- An unusual form of granulomatous disease may also occur.

The predominant diagnostic feature of CVID is low serum IgG levels and failure to make antibody responses to natural infection or vaccination. The underlying molecular defect in most CVID patients is unknown, although with the availability of genome sequencing in the past few years, molecular defects resulting in impaired B cell maturation and development have been described in 10-15% of patients. Most cases are sporadic, although familial recessive and dominant modes of inheritance have been described.

The treatment for CVID is immunoglobulin replacement therapy and antibiotics as required. If treatment is instigated early in the disease, the outlook is good.

X-linked agammaglobulinaemia

X-linked agammaglobulinaemia (XLA) is caused by a defect in a molecule called 'Bruton's tyrosine kinase'. This causes the cells that make immunoglobulin, known as 'B cells', to fail to develop, and so affected patients make no immunoglobulin at all. This condition is genetically determined and, as the affected gene lies on the X chromosome, it only affects boys, who typically develop recurrent bacterial infections from around 6 months of age. For reasons that are incompletely understood, affected individuals may also experience specific viral infections (especially enteroviral encephalitis) and a protozoal infection known as 'giardiasis'.

A hallmark of XLA is the absence of circulating B cells. Although the molecular basis of this condition has been firmly established, the clinical presentation may vary even within the same family, and some affected males may present late in life.

Immunoglobulin replacement therapy is the mainstay of treatment, together with early antibiotics for established infections and supportive management of structural lung disease.

Specific antibody deficiency with normal immunoglobulins

Specific antibody deficiency with normal immunoglobulins, also called 'specific antibody deficiency' or 'functional IgG antibody deficiency', is a poorly characterised condition which causes defective antibody responses to polysaccharide antigens. Some patients are deficient in the antibody subclasses IgG2 and IgG4, and this condition was previously called 'IgG subclass deficiency'. Some patients may progress to a more global antibody deficiency over time.

Individuals with specific antibody deficiency experience recurrent respiratory tract infections and, on diagnostic testing, they fail to respond to specific microbial antigens despite having normal immunoglobulin levels in the blood. The typical defect is an inability to respond to bacterial capsular sugars, while responses to bacterial proteins are maintained.

The diagnosis is established by demonstrating normal IgG levels, accompanied by a failure to respond to immunisation with bacterial sugars (the Pneumovax vaccine is used for this). Interpretation of the results is difficult because of the lack of age-specific normal ranges and the considerable variation in results in healthy individuals. This is an area of much debate for example, while a consensus group in the USA published provisional criteria for interpreting post-immunisation responses to pneumococcal polysaccharide vaccines,[15] the evidence base upon which these criteria were based were very limited and professional debate in this area continues.[16]

Most patients with specific antibody deficiency benefit from the additional protection of vaccination and early treatment with antibiotics, whilst others may require immunoglobulin replacement therapy.[17]

Other conditions where immunoglobulin replacement therapy may be an important part of treatment

Other conditions where immunoglobulin replacement therapy may be an important part of treatment include:

- WiskottAldrich syndrome, an X-linked syndrome characterised by eczema and pinpoint bleeding (purpura), and with small, defective platelets. Antibody production to bacterial capsular polysaccharides is often defective, and patients may also develop recurrent viral and fungal infections because of T cell deficiencies. This is caused by a mutation in the WASP gene, which regulates the structural proteins of platelets and white cells. Immunoglobulin replacement therapy is often used as supportive treatment while awaiting stem cell transplantation.

- Antibody deficiency associated with thymoma. Patients with a thymoma (thymic tumour) may develop antibody deficiency along with features of autoimmunity and T cell immunodeficiency. As the tumour can be locally invasive, thymectomy is recommended, although the immunodeficiency is not reversed by this procedure and patients are likely to require lifelong immunoglobulin replacement therapy.

- Transient hypogammaglobulinaemia of infancy. In some infants there is a delay in the maturation of the immune response, which causes delay in the production of immunoglobulin. These children have decreased IgG levels, which recover spontaneously by 3 years of age. Occasionally antibiotic prophylaxis is needed, but only rarely is immunoglobulin replacement therapy required.

United Kingdom primary immune deficiency registry

As the recognition and description of primary immunodeficiency disorders increased, it became increasingly obvious that there was a need for national and international registries of patients to identify how common were these conditions and also to best characterise their clinical features and prognosis.

In 1990, the UK established a paper-based primary immunodeficiency registry. At that time, there was recognition of probably fewer than 20 primary immunodeficiency disorders and the prevalence of the most common of these causing recurrent infections – i.e. common variable immunodeficiency (CVID) was put at 0.9/100,000. Subsequently, in 2004, a Europe-wide online registry was established in Freiburg and this registry platform was subsequently adopted by the United Kingdom Primary Immunodeficiency Network (UKPIN) as the United Kingdom Primary Immune Deficiency (UKPID) registry.

There is widespread engagement of the primary immunodeficiency community with this registry with over 90% of centres looking after primary immunodeficiency patients in the UK submitting data. As all patients requiring immunoglobulin replacement therapy for primary immunodeficiency are managed by specialists, this indicates that the vast majority of patients will be logged into this registry (which is voluntary and dependent upon patient consent).

The registry reported its first 4 years of data in 2012[18] and more recently, in 2018, a further report was published, summarising findings.[4] Currently there are over 5,000 patients identified in the UKPID registry. The prevalence of PID was estimated at 5.9/100,000 population in 2017. The annual incidence of PID from 1980 to 2000 was 7.6 cases/100,000 live births [1:13157 births]. The most common condition on the registry is CVID and this is the most common form of primary antibody deficiency in a group of patients whose treatment is primarily with immunoglobulin replacement therapy.

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Addendum: Further Supplemental Answers

This addendum answers the supplemental questions as indicated on pages 2–4

Factor 7 deficiency

Deficiency of the clotting factor 7 (F7, sometimes FVII) is a rare inherited bleeding disorder affecting about 1 in every 500,000 people worldwide. F7 deficiency is caused by variants (mutations) in the F7 gene. It is an autosomal recessive condition where usually both copies of the F7 gene need to be affected for there to be a clinically significant deficiency. People with one affected copy typically have F7 levels of 40-60iu/dl (%) or even lower, and this can show itself in an abnormal clotting screen (the Prothrombin Time or PT is prolonged) which often leads to further investigation. However, it is believed that F7 levels of as low as 10iu/dl are normally adequate to control bleeding. There are 1,620 patients in the UK registered as having low F7; 138 of these have levels <5iu/dl and 80 received treatment in 2018/19.

The diagnosis of F7 deficiency is made by doing a specific F7 activity assay (based on the PT) and confirming with genetic analysis.

People with F7 deficiency may report no problems at all, or may report bleeding from the nose, mouth or gut, heavy menstrual bleeding, joint bleeding or, in rare cases, bleeding inside or around the brain. Severe bleeding is more common when F7 levels are <1iu/dl.

Treatment

F7D can be treated with prothrombin complex concentrate (PCC) and plasma-derived F7 concentrate, though these have largely been replaced by low dose Novoseven (recombinant activated F7, see main report). Milder bleeding can be treated with tranexamic acid. Treatment with low dose Novoseven is most commonly given to treat significant bleeding or to cover surgery, though regular preventative treatment with Novoseven (prophylaxis) is sometimes given in patients with severe deficiency (<1iu/dl) and those who have had serious bleeding events in their past or in a family member.

Factor 10 deficiency

Deficiency of the clotting factor 10 (F10, sometimes FX) is a rare inherited bleeding disorder believed to affect about 1 in every million people worldwide. F10 deficiency is caused by variants in the F10 gene. F10 deficiency causes prolongation of both the PT and the APTT in the routine clotting tests, and is diagnosed by demonstration of low F10 activity in the specific, PT-based F10 assay. Diagnosis is then confirmed by genetic testing.

Bleeding patterns are dependent on F10 activity – in cases reported in international registries, those with F10 levels >10iu/dl have tended to have only surgical bleeding, or mild mouth or nasal bleeding; those with levels <10iu/dl were more likely to show severe bleeding; the most severe bleeding patterns, including bleeding in or around the brain, have been seen in those with F10 levels of <2iu/dl. Children may present in infancy with bleeding in or around the brain.

In the UK, there are 282 patients registered as having low F10, 43 of whom have levels <10iu/dl. 37 were treated in 2018/19.

Treatment

Treatment of F10 deficiency is with prothrombin complex concentrate (PCC) or with plasma-derived factor concentrate. Prophylaxis (regular preventative treatment) is given to some patients, particularly children, with very low levels of F10 and a history of severe bleeding.

Factor 13 deficiency

Factor 13 (F13, sometimes FXIII) is a clotting factor fundamental to establishing clot strength and appropriate wound healing. The F13 in the circulation is made up of two A subunits and two B subunits. F13 deficiency is usually caused by a quantitative or qualitative defect in the A subunit due to variants in the F13A gene. More rarely, F13 deficiency can be caused by changes in the F13B gene causing a quantitative defect of the B subunit. Inheritance is autosomal recessive – both copies of either the F13A gene or the F13B gene need to be affected to give clinical deficiency. Those with one affected gene (carriers) show F13 levels of between 20 and 70iu/dl, and though some mild bleeding is reported, it is not certain that this due to the F13 deficiency.

F13 deficiency can present with prolonged bleeding from the umbilical stump in infancy. Bleeding in or around the brain is also relatively common (in around a third of cases). Other bleeding seen includes joint and muscular bleeds, as well as bleeding from the mouth, bladder and kidney, and the gut. Severe bleeding is mostly seen in those with levels of <10iu/dl.

Treatment

Patients with F13 deficiency and levels <10iu/dl or a history of bleeding are usually given regular prophylactic injections of F13 concentrate, given the risk of bleeding in or around the brain. In the UK this is with a plasma-derived concentrate. A recombinant F13 concentrate is available internationally.

Glanzmann's Thrombasthenia

Glanzmann's Thrombasthenia (GT, also known as Glanzmann's disease) is a severe platelet function disorder caused by abnormal or absent Glycoprotein IIb/IIIa on the surface of platelets. Glycoprotein IIb/IIIa (also known as integrin αIIbβ3) is a receptor essential for platelet aggregation (the clumping together of platelets that is an essential part of a healthy blood clot).

Children with GT will normally come to medical attention early in childhood with unexplained bruising and bleeding, particularly from "mucosal" surfaces (mouth, nose, gastrointestinal tract), often accompanied by widespread petechiae (pin-prick rash). Platelet function testing is less straightforward than the testing of plasma clotting factors, especially in young children. Screening tests, such as a PFA100, are often used and are grossly abnormal in GT, as is formal platelet aggregometry. Definitive diagnosis is made by flow cytometric assessment of platelet glycoproteins and genetic testing. The inheritance is autosomal recessive and is caused by variants in both copies of either the gene coding for the GPIIb subunit, ITGA2B, or for the GPIIIa subunit, ITGB3.

Treatment

Treatment options in GT include tranexamic acid, high dose Novoseven and platelet transfusion. Platelet transfusion is the most effective, but can be complicated by the development of antibodies against the transfused platelets, either against other proteins on the platelet surface (HLA or HPA molecules) or against the GPIIb/IIIa itself. When this happens treatment is complicated as platelet transfusion can be ineffective.

A stem cell (bone marrow) transplant is sometimes used to treat GT, as replacement of the bone marrow can deliver a long-term "cure". However, as this procedure carries a significant risk of death, it is only recommended in rare selected cases.

Acquired haemophilia

Acquired haemophilia A is a rare bleeding disorder, which occurs as a result of a sporadic antibody (inhibitor) forming against clotting F8. As such, it is classified as an autoimmune disease and is not associated with genetic variants in the F8 gene; the inhibitor is an auto-antibody directed at the F8 produced by the patient in their body, rather than an allo-antibody as seen when inhibitory antibodies develop against infused F8 in congenital haemophilia A. It can affect both men and women. Typical age of onset is around 65 years. The condition tends to present with dramatic excessive bruising, also known as "sheet haemorrhage", rather than bleeding into joints which is typically seen in congenital haemophilia A, although bleeding may occur anywhere. In many cases the reason for developing this autoimmune condition is unknown, but it may relate to development of cancers, certain medications, underlying autoimmune disease or hormonal changes (e.g. after giving birth).

Treatment

The aim of treatment is twofold: firstly to control any active bleeding and secondly to treat the underlying immune disorder to eradicate the coagulation inhibitor. Medications that may help to control bleeding include tranexamic acid, DDAVP (desmopressin), F8 concentrate, FEIBA, high dose Novoseven or recombinant porcine factor 8 concentrate (Obizur). Often, DDAVP and F8 concentrates are inadequate to overcome the inhibitory effects and one of the by-passing agents is required. Examples of medications to treat the underlying immune disorder include corticosteroids, cyclophosphamide, rituximab and mycophenolate mofetil.

Haemolytic disease of the foetus and newborn (rhesus disease)

Haemolytic disease of the foetus and newborn (HDFN) is a condition that occurs when maternal antibodies cross the placenta and cause haemolysis (destruction of red blood cells) in the foetus. This haemolysis will usually continue after birth in the newborn baby.

HDFN-causing antibodies occur when there is a mismatch between proteins on the surface of red cells in the mother and foetus – caused by the foetus inheriting protein subtypes from the father that do not occur in the mother. If there is a leak in the placenta between the maternal and the foetal blood, the maternal immune system will often recognise these proteins as foreign and mount an antibody response. The first time this occurs, the antibody will be at a low level and harmless, but if there is exposure of the protein to the maternal immune system in a subsequent pregnancy, the immune system will show an "anamnestic response" and produce large amounts of the antibody. This antibody then crosses the placenta and, if it is at a high enough concentration, causes destruction of the foetal red cells – haemolysis.

There is a long list of red cell proteins (called antigens as they can provoke an antibody response) that can cause HDFN. However, the most common protein implicated is known as RhD, previously known as the Rhesus antigen. HDFN due to anti-RhD antibodies can also occur if women who are RhD negative (rhesus negative, about 15% of the population) have previously received a transfusion of RhD positive blood. Thus, this is avoided in good transfusion practice.

Haemolysis is a problem for two reasons: first, the red cells can break down so quickly that the red cell production cannot keep up and there is a worsening anaemia; and second, the breakdown of red cells cause the release of a large amount of waste haemoglobin, which is broken down to bilirubin causing jaundice. The main problem in the foetus is anaemia, as it may go unnoticed and cause foetal death. Jaundice is less of a problem as the excess bilirubin is cleared via the placenta and dealt with by the maternal liver. Anaemia can be a problem in the newborn, but the severe jaundice in HDFN can be life-threatening, as the newborn liver is unable to cope with the load of bilirubin. High levels of jaundice can cause brain damage and death.

Treatment

Management of HDFN takes three strands: prevention, monitoring and treatment.

Prevention of HDFN involves minimising the risk of RhD negative mothers being sensitised (exposed) to RhD. This is done by giving doses of anti-RhD immunoglobulin (concentrated antibody taken from blood donations, called anti-D for short) to RhD negative mothers at times when there is likely to be a sensitisation event (a leak of blood). The anti-D quickly mops up any foetal blood in the maternal circulation and stops it from activating the immune system. Anti-D is given to cover any invasive procedures to the womb, such as amniocentesis, routinely in the last third of pregnancy, and to all RhD mothers who have RhD positive babies. Larger doses are given if there is evidence of a big leak (foeto-maternal haemorrhage).

Monitoring for HDFN involves the screening of all pregnant women for evidence of known HDFN-causing antibodies. In cases where antibodies are detected, blood levels of the antibodies are watched closely with serial blood tests. Where there is a risk of foetal haemolysis, the pregnancy is watched closely with detailed ultrasound scans, and where there is evidence of anaemia, an intra-uterine red cell transfusion may be given. Often, repeated intra-uterine transfusions are given to bring a foetus to safe delivery.

The clinical picture of HDFN in a newborn is one of severe early jaundice with or without anaemia. Laboratory assays show that the baby's red cells are coated with antibodies (positive Coombs test or DAT) and the blood film shows typical microscopic features. Treatment of jaundice is with phototherapy which helps reduce bilirubin levels. If phototherapy is ineffective, intravenous immunoglobulin may be given to reduce the rate of haemolysis. This can sometimes avoid the need for the other treatment for HDFN: exchange transfusion.

Exchange transfusion is a procedure where blood is continuously taken from the baby and replaced with transfused red cells, so that the baby's circulating volume remains constant. This continues until 1-2 times the circulating volume of the baby has been exchanged. The benefit of an exchange transfusion is that most (75-85%) of the antigen-positive red cells are removed, together with about half of the bilirubin. While it can be very effective, it is a risky procedure, and it is now less common in the UK due to the success of anti-D prophylaxis and HDFN monitoring.

Neonatal alloimmune thrombocytopenia

Neonatal alloimmune thrombocytopenia (NAIT) or foeto-neonatal alloimmune thrombocytopenia (FNAIT) is the platelet equivalent of HDFN: maternal antibodies cross the placenta and attack foetal platelets resulting in a low platelet count (thrombocytopenia) in the foetus and newborn (neonate). Like HDFN, it is caused by a mismatch of protein subtypes, though in the case of FNAIT, these are on the surface of the platelets rather than the red cells.

FNAIT will often go undiagnosed if the child suffers no significant bleeding and no blood count is checked. When it does show itself, it may show with bruising, a typical "petechial" (pin prick) rash, or more significant bleeding. Some babies will present with signs of bleeding in or around the brain (intracranial haemorrhage or ICH).

Treatment

Treatment of FNAIT in the newborn is with transfusion of specially selected platelets that lack the most common platelet antigens associated with FNAIT, HPA 1a and 5b (responsible for 95% of cases). Blood tests from the parents and the baby can confirm the diagnosis. Intravenous immunoglobulin will raise platelet counts in cases of FNAIT, but this takes 1-2 days to see a response. In the absence of compatible platelets, unselected platelets are sometimes given.

Intrauterine platelet transfusions are sometimes given for FNAIT, but modern treatment of affected pregnancies is usually with intravenous immunoglobulin as this is less invasive and risky.

FNAIT has a very high rate of recurrence in subsequent pregnancies. Estimates of incidence of FNAIT vary, but screening studies show that approximately 2% of pregnancies are mismatched for the protein most commonly responsible for FNAIT – HPA 1a. 10% of those pregnancies that came to birth show evidence of a maternal antibody response. 30% of babies resulting from those pregnancies have platelet counts <50 x 10^9/l: severe thrombocytopenia. This together gives a projected incidence of severe FNAIT of 60 per 100,000 live births. In collected screening series, 2 of 71 affected foetuses were stillborn, and a further 5 suffered an ICH, though this figure may be an underestimate, as affected pregnancies were treated in screening studies.

Risk of viral transmission with current treatments for haemophilia

As previously highlighted, this group is not expert in either viral transmission or the preparation and processing of blood products, and thus may not be best placed to answer supplemental question 13. It would be possible to give a non-specialist answer, but I am not sure what help that would be to the Inquiry.

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Verifying Statements

Each contributing group member confirms that he or she understands his or her duty to provide independent evidence and has complied with that duty.

All contributing group members confirm that in respect of those parts of the report to which they have contributed:

(i) They have made clear which facts and matters referred to in this report are within their knowledge and which are not.

(ii) Those that are within their knowledge they confirm to be true.

(iii) The opinions they have expressed represent their true and complete professional opinions on the matters to which they refer.

Authors

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Professor David Edgar is Consultant Immunologist at St James's Hospital and Clinical Associate Professor at Trinity College Dublin. Previously (until June 2019) he led the Northern Ireland Regional Immunology Service for 23 years, providing secondary and tertiary clinical services in allergy and immunology to adults and children. Prof Edgar actively contributes to several research groups within the fields of immune function and immunodeficiency and is particularly focussed on studies on diagnosis and treatment of primary immunodeficiency. He is the co-chair of the World Allergy Organisation (WAO) Special Committee on Immunodeficiency, and previously chaired the UK Primary Immunodeficiency Network (UKPIN). He was very actively involved in the establishment of the UKPID patient registry and was a board member of the European Society for Immune Deficiency (ESID) patient registry.

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Dr Richard Gooding is a consultant haematologist with a specialist interest in haemostasis and thrombosis. Having started work as a consultant haematologist in 2012, he moved to the sub-specialty of haemostasis and thrombosis before becoming the director of the Leicester Haemophilia Centre in 2018. In this role, he works with other members of the UK Haemophilia Centre Doctors Organisation (UKHCDO) to promote and provide high quality haemophilia care. He is also part of the UKHCDO Prophylaxis Working Party. He is co-chair of the UHL Anticoagulation Committee, and has an interest in various aspects of complex venous thrombosis, including cancer related VTE and antiphospholipid syndrome.

Dr Sara Marshall

Dr Sara Marshall is head of Clinical and Physiological Sciences at the Wellcome Trust, a position which she has held since 2016. Prior to that, she was a professor of Clinical Immunology at the University of Dundee and clinical lead for Immunology at NHS Tayside. Dr Marshall obtained her medical degree from the National University of Ireland and worked as a junior doctor in Dublin before going to Stanford University, California as a fellow in Lung Transplantation. She holds a PhD in Immune Tolerance from the University of Cambridge, and held an MRC Clinician Scientist award from the University of Oxford while she was senior lecturer in Clinical Immunology at Imperial College London. She was Director of the Dundee Clinical Academic Track and Deputy Head of Research & Development for NHS Tayside. Her research mainly focuses on the immunogenetics of inflammatory diseases, and she is passionate about maximising research opportunities for clinical trainees and medical students as a means of improving patient care in the medium and long term.

Professor Jürgen Rockstroh

Jürgen Rockstroh is professor of Medicine and head of the HIV Outpatient Clinic at the University of Bonn, Germany, which treats the world's largest cohort of HIV-infected haemophiliacs. In addition to his clinical practice, Dr Rockstroh is involved in HIV research on; antiviral therapy, including new drug classes; the course of HIV disease in haemophiliacs; and HIV and hepatitis co-infection. He has been an investigator in multiple clinical trials of

antiretroviral agents and treatments for HIV and hepatitis co-infection. He was the president of the German AIDS Society from 2007 to 2011, has been an executive committee member of the European AIDS Clinical Society (EACS) since 2009 and in 2019 was elected as president of EACS. Dr Rockstroh has been a member of the governing council of the International AIDS Society since 2011, and currently chairs the hepatitis research activities in NEAT (European AIDS treatment Network) and EuroSIDA. Between 2011 and 2017 he chaired the National German AIDS Advisory Panel, and the EACS co-infection guidelines. Dr Rockstroh has authored and co-authored over 500 publications in peer-reviewed journals, and over 70 book chapters. The German Society for Infectious Diseases awarded Dr Rockstroh the national AIDS research prize in 2005.

Dr Kate Ryan

Dr Kate Ryan is a consultant haematologist at Manchester Royal Infirmary. She has 25 years of experience as a consultant haematologist with a broad base of clinical and laboratory experience. She has a special interest in haemoglobin disorders; sickle cell disease; thalassaemia and other rare inherited anaemias. She was chair of the NHS England Clinical Reference Group for Haemoglobinopathies Specialist Commissioning from 2015 to 2019. She has written national guidelines and standards of care for these conditions, and led the Adult Sickle Cell and Thalassaemia peer review programme from 2012 to 2013. She has chaired the National External Quality Assessment Service (NEQAS) General Haematology Steering Group, and also the General Haematology Task Force of the British Committee for Standards in Haematology from 2006 to 2012. She has also sat on advisory groups for national commissioning in haemoglobinopathies (DOH), the National Haemoglobinopathy Registry and NICE guidelines. Dr Ryan lectures widely on haemoglobinopathies to all levels of staff and has developed a regional service for post-transplant lymphoproliferative disorders with renal transplant teams.

Dr Mallika Sekhar

Dr Mallika Sekhar is a consultant haematologist and honorary senior lecturer at UCL. She specialises in myeloproliferative diseases and blood transfusion, across the University College London Hospital and Royal Free Hospitals, with a special interest in patients with vascular thrombosis and myeloproliferative diseases. She has been involved with writing Management Process Description (MPD) guidelines for the British Committee for the Standards in Haematology (BCSH). Dr Sekhar has been the lead investigator in studies on abdominal vein thrombosis in myeloproliferative diseases and transfusion in haematological malignancies, and a member of the National Cancer Research Institute (NCRI) MPD and supportive care clinical studies group. She was a member of the clinical expert panel on the Pathology Modernisation initiative for London, and is the lead for undergraduate education in haematology at the Royal Free campus. Previously, she was chair of the London Regional Council of the Royal College of Pathologists and has been a member of the National Blood Transfusion Committee Group on Education since 2012.

Dr Michelle Sholzberg

Dr Michelle Sholzberg is a clinical haematologist who received her MDCM and residency training in Internal Medicine at McGill University. She completed additional postgraduate training in Haematology at the University of Toronto, following which she completed a research haemostasis fellowship in Toronto. She holds a Master of Science degree from the University of Toronto in Clinical Epidemiology and Health Care Research. Her work as a clinical haematologist focuses on bleeding, and she is the medical director of the

Coagulation Laboratory at St. Michael's Hospital. Dr Sholzberg is also the co-director of the Blood Immunology Trauma Translational Research Theme. Her research interests include disorders of haemostasis and common anaemias. Currently, she is involved in the study of prediction tools for perioperative bleeding; new treatments for immune thrombocytopenia; von Willebrand disease and haemophilia, as well as innovative tools for the management of iron deficiency anaemia.

Dr Oliver Tunstall

Dr Oliver Tunstall is a consultant paediatric haematologist at the Bristol Royal Hospital for Children. He is network lead at the Southwest Paediatric Haemophilia Clinical Network, clinical lead at Bristol Paediatric Haemophilia Service, and a member of the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) Paediatric Working Party. He is currently a member of the UKHCDO Prophylaxis Guideline Writing Group. His areas of special interest include paediatric haemophilia; paediatric anticoagulation and thrombosis; and leukaemia in patients with Down Syndrome. Dr Tunstall holds a PhD in Leukaemogenesis in Down Syndrome from Imperial College London, and chaired the writing group for the 2018 BSH Guideline on Transient Leukaemia of Down Syndrome. He is a member of the Royal College of Paediatrics and Child Health, Royal College of Pathologists, British Society of Haematologists and International Society of Thrombosis and Haemostasis.

Annex

The experts were asked to describe the treatments available for haemophilia (A, B and C) and von Willebrand's disease from 1970 onwards, their risks, side effects and/or consequences. In order to do so, it has been necessary for them to provide some factual background to place their opinions in context. This broad background material has been placed into this annex to emphasise that the expert group is not seeking to express its own conclusions or views about what happened and when, historically – these are matters of fact on which the Inquiry will draw its own conclusions of fact. The Inquiry is investigating and will continue to investigate these for itself, with the help of core participants and drawing on all the available evidence.

Some useful statistics at the start of the 1970s

Preparation	F8 units/ml of product as made up for administration	Yield during preparation (%)	Recovery of activity in the patient u/u/kg/dose
Whole blood	0.3 u/ml		
Plasma	0.6 u/ml	80	2.0
Cryoprecipitate	2-10	10-40	1.6-1.8
NHS freeze-dried concentrate (from 200-750 blood donations)	5-6	30-35	1.6-2.0
Commercial concentrate (1,000-4,000 litres plasma collected by plasmapheresis approx. 2,500 donors)	20-30	15-20	1.8-2.2

F8 activities of various therapeutic materials (adapted from Biggs, 1974; Biggs, 1977).

A report (Biggs 1974) describes how to define and measure F8 and thus calculate the dose required: the amount of F8 used to treat patients was initially expressed as the number of donor units (= number of blood donations) required to supply the therapeutic material. 'Donor units' was thought to be a useful concept because it could show the amount of blood required to supply the F8 product and whether the occurrence of jaundice correlated with the number of donors. In the event, no correlation was found at that time. With the onset of commercial factors and better detection of hepatitis B virus, the source of the donor (paid/voluntary) rather than the number of donors seemed important. Therefore, after this period (1972), the amount of F8 activity per unit of product was expressed rather than the number of donor units.

The concentration of F8 varies in a product of cryoprecipitate depending on variation between donors and care taken in preparation of batches. Percentage yield is determined by the amount and activity of F8 from a specified volume of starting plasma. To obtain a measurement of response, the dose is expressed as units/kg of the patient's body weight.

The recovery of F8 activity in the patient's plasma after treatment is expressed as percentage rise of plasma F8 level per unit of dose activity per kg of patient's weight. At a dose of 1 u/kg body weight, the maximum rise in plasma F8 level is expected to be around 0.024 u/ml or 0.024 u/u/kg/dose (2.4% when expressed as a percentage). The observed rise in plasma F8 for various preparations varies depending on time of measurement and preparation used. Using this concept, it was possible to calculate the dose required in a particular patient to achieve a desired rise in plasma F8.

Between 1969 and 1971 (Biggs, 1974), the F8 concentrate had a variable level of quality across the UK. This mainly related to how soluble the freeze-dried powder was in water. In a batch devoid of solubility problems, recovery levels were reliably adequate.

Large-scale fractionation

Large-scale fractionation to produce F8 concentrate required pooling of plasma from at least 1,000 fresh blood donors or from as many as 60,000 donors when recovered or frozen-thawed plasma was used. This degree of donor exposure was a significant clinical problem because a unit of treatment entailed exposure to many thousands of donors with the attendant risk of infections. The national production of fractionated blood products was organised at BPL, Elstree, which produced gamma globulin, albumin and F8 on a large scale (the first two were more in quantity due to wartime requirements). From around 1954, Elstree also supplied some F8 to clinicians in need but it was only from 1972 to 1973 with use of improved technology that it could provide larger quantities – however, this was insufficient to match national needs. Factor supply from Elstree was pro rata: if a region put in large amounts of plasma for fractionation, it received large amounts of F8 for its haemophilia centres.

F8 concentrates

Plasma-derived F8 concentrates are made from pooling thousands of units of donor plasma. The entire pool could be contaminated by a single donor infected with HIV. In the early years, there was a belief that protective antibodies could also be transmitted via large pools. The four methods to reduce infection were donor exclusion, product testing, product modification and change in practice. The last two are considered here.

Using the fractionation methods of Newman and Johnson, intermediate and high purity F8 were made in 1972. Purity refers to the amount of F8 relative to other substances in a product. Producing a high purity product entails removing other substances from it: it does not address infection-related safety but contaminants (for example, other blood proteins which may alter immune function/result in reactions). Intermediate purity products were made after standard fractionation. High purity products were made with a more exacting technique: namely, 'ion exchange chromatography', and were available in the early 1990s.

Intermediate purity products had 4-8 iu/ml of F8 and were supplied as 100ml volume which was freeze dried. It was reconstituted by adding sterile distilled water (water for injection). This was then injected intravenously using a syringe or by infusion depending on the volume to be injected. The volume depended on the amount of F8 required to treat the bleed. Each bottle when dissolved gave 400-800u F8 with a potency of 8-16 u/ml. In comparison, a dose of 6 units of cryoprecipitate gave a total of 250u; the commercial product Hemofil gave 20 u/ml. In 1970, continuous infusion of F8 was reported in severe haemophilia.

In Scotland, after 1974, Cohn's fractionated anti-haemophilic globulin product was replaced with this intermediate purity product. Prothrombin complex concentrates (such as FEIBA, an activated prothrombin complex concentrate) were also available during this period, used especially in patients with inhibitors.

The choice of which product to use at this time was based on:

(a) Quality of the product: yield of F8 from given volumes of plasma (thus, a superior method may enable higher yield from lower volumes of plasma) and recovery of the factor in the patient after infusion (the same superior method may give a lower circulating level in the patient compared to another method).

(b) Convenience of the material for preparation: cryoprecipitate was easier to manage if small volumes were required. For large-scale use, it was easier to handle freeze-dried F8 produced through large fractionation.

(c) Reliability of material from batch to batch: cryoprecipitate had variation in yield and recovery between centres, its dosing was variable and therefore consistent assays of dose activity were not possible. The freeze-dried material was made in large batches (which were uniform) and could be assayed reliably for dose activity.

(d) Complications associated with each, which were different.

Heat-treated concentrates

Heat-treated plasma-derived products were introduced as they were considered virologically safer than non-heat-treated plasma concentrates. The method of heat treatment (temperature, duration, timing) was not uniform across products. First-generation heat treatment to prevent NANBH in 1983/84 failed and this dashed the hopes of many clinicians who were not convinced that similar heat treatment processes would work for the LAV/HIV/AIDS-causing virus.

In February 1985, it was established that this method worked for prevention of seroconversion for AIDS. Second-generation heat-treatment strategies (temperature of 80C rather than 60C) were found to be successful to prevent NANBH between 1986 and 1988.

Disadvantages of heat-treated concentrates:

Throughout this period there were concerns about the possibility of increasing inhibitor formation due to changing the antigenic nature of the F8 protein and the possibility of making the product less effective due to denaturation of F8, a heat labile protein.

Impacts and consequences:

Heat-treated products were no different from previous products in terms of their usage. There was variation in heat-treatment methods as stated above and new products had to be tested in clinical trials. When HIV was identified in 1984 and HCV in 1989, these could be tested for clinical purposes and in trials monitoring effectiveness of specific protocols to purify the product.

Pattern of deaths

In 1973, of 62 deaths recorded in the UK, the top 2 causes were bleeding in 16 and jaundice in 5 (Biggs, 1977).

Annual death rate in severe haemophilia remained at 8 per 1,000 between 1977 and 1984. Of 89 recorded deaths between 1976 and 1980 (Rizza 1983), 43% were due to bleeding. Patients with inhibitors were more at risk of dying due to haemorrhage.

Between 1985 and 1992, annual death rates remained at 8 per 1,000 in HIV seronegative patients but rose steeply to 81 per 1,000 in seropositive patients in 1991 and 1992 (Darby et al., 1995).

The pattern was similar in patients with mild and moderate haemophilia with initial death rates rising from 4 per 10,000 to 85 during these periods; 85% of deaths in seropositive patients were attributed to AIDS or AIDS-related conditions. From 1989, PCP prophylaxis and Zidovudine became available, despite which mortality rose in 1992. For patients seronegative for HIV, between 1985 and 1992, deaths related to bleeding, liver disease, injury and suicide rose.

F8 concentrate usage

Between 1971 and 1975, 33,400 units F8/per patient on home therapy/year was used. In comparison in 1974, an average of 12,575 units/patient/per year was reported across 47 haemophilia centres in the UK.

UK dosing was low, compared with other countries such as Norway – possibly due to variations in products or timing of treatment. The UK practice was 1 vial with 250 IU of F8 activity injected intravenously as early as possible after onset of bleed. Average UK dose was estimated at 4 iu/Kg, maximum 10 IU/Kg (1-2 vials based on severity of bleed and weight). Recommended F8 levels were 20% for minor and 40% for major bleeds. Treatment was monitored variably by using clinical response and/or laboratory response (Jones, 1978); 87% of bleeds treated with this dose ceased without further treatment. These data were in keeping with other publications.

In 1975, it was acknowledged in a letter from Dr Biggs that 90% of patients in the UK received less (and in some cases much less) than optimum treatment for their disease. The therapeutic goal at the start of the 1970s was to enable patients to lead clinically independent lives. Under-treatment led to avoidable, painful and destructive bleeds into joints and muscles, loss of education time, and inability to hold onto continuous employment.

A survey of haemophilia A and B patients (Biggs and Spooner, 1978) describes the situation in 1975: of 3,068 haemophilia A patients in the UK (excluding Scotland), 55% were severe; of 526 haemophilia B patients, 39% were severe. Only 58% of haemophilia A and 55% of haemophilia B patients received treatment in 1975: this was considered suboptimal. At 97 hospitals which were not recognised as haemophilia treatment centres, cryoprecipitate was used most frequently. NHS and commercial F8 and F9 were used occasionally.

By the early 1980s, 80% of blood products used in haemophilia were imported in England, N Ireland and Wales; by the end of the 1980s, this reduced to 20% as national capacity increased.

Choice of products

Heat-treated products to reduce the risk of HIV/AIDS were expected from domestic sources in the UK by April 1985, but by June 1985 many centres were still using non-heat-treated domestic products. By summer 1985, this had improved and only heat-treated domestic products were available. In July 1985, the Armour Factorate product was found to have caused seroconversion for AIDS despite heat treatment. The company withdrew its operations in the UK in October and its product was not used thereafter.

At this time (1985), the choice of products was left to the discretion of treating clinicians (haemophilia centre directors of 110 centres across the UK) but guidelines on the hierarchy of safety as of January 1985 were:

(1)   Heat-treated domestic Factor Concentrate

(2)   Single donor cryoprecipitate

(3)   Heat-treated imported concentrate

(4)   Non-heat-treated domestic concentrate

(5)   Non-heat-treated imported concentrate.

The recommendations were as follows:

- Mild haemophilia A, VWD: DDAVP
- Children and unexposed haemophilia A: cryoprecipitate or heat-treated NHS concentrate
- Severe/moderate haemophilia A previously exposed to F8: heat-treated NHS F8 or heat-treated commercial concentrate
- Mild haemophilia B: fresh frozen plasma (FFP) or NHS F9
- Haemophilia B never exposed to Factor Concentrate: FFP or NHS F9
- Severe/moderate haemophilia B previously exposed to F9: NHS F9.

(N.B. heat-treated F9 was not available then)

Although decisions were left to clinicians and there was a preference for domestic products, the guidance emphasised in January/February 1985 that heat-treated concentrates were probably better. In June 1985, this was stated unequivocally.

The purchase of commercial products was negotiated by the budget holder at the district health authority level with the supplier. In some institutions, patients were treated with FC products from the same batch until that was exhausted. This diminished the potential for infective risk from multiple batches (assuming that the batch used by a patient is devoid of infection and another batch may be more risky). The timelines of full conversion to heat-treated imported products and individual institutions' choice and use of products are not known.

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