GUIDELINES

Prescribing intravenous immunoglobulin: summary of Department of Health guidelines

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This is one of a series of *BMJ* summaries of new guidelines, which are based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists. Further information about the guidance is in the full version on bmj.com.

Why read this summary?

Therapeutic immunoglobulin, a preparation of normal human polyclonal immunoglobulin G derived from pooled human plasma, has become an important treatment option in a range of medical conditions beyond its use in immune deficiencies, particularly autoimmune and acute inflammatory diseases.[1] For some time, concern has been expressed over the availability of immunoglobulin. Severe global supply shortages began in the late 1990s, when demand exceeded supply by up to 30%,[2] and production problems specific to the United Kingdom have curtailed supply. This supply shortage has been compounded by increasing use in established indications[3] and widespread off-label prescribing.[4] To ensure that supply is maintained, even in times of acute shortage, for the patients considered to be the highest priority because of a risk to life without treatment, potential prescribers of immunoglobulin need help in identifying treatment indications for which its use is appropriate. This article summarises the most recent Department of Health guidelines on prescribing intravenous immunoglobulin, published in May 2008.[5]

Recommendations

Recommendations are based on systematic review of evidence based guidelines and Cochrane reviews, supplemented by expert opinion. The level of evidence for each indication is indicated as Ia, Ib, IIa, IIb, III, or IV; the grade of recommendation is given as A, B, C, or D. Our approach was adapted from the system used by the Agency for Healthcare Policy and Research (US Department of Health and Human Services).[6]

Recommendations are colour coded to reflect treatment prioritisation. Red indicates conditions for which treatment is considered the highest priority because of a risk to life without treatment, and blue indicates conditions for which, although the evidence base is reasonable, the priority is moderate because other treatments are available (see figure). Box 1 lists those conditions for which the evidence base is weak (these are known as grey conditions). For all blue and grey conditions, immunoglobulin treatment should be considered on a case by case basis, prioritised against other competing demands for immunoglobulin, especially in times of shortage. For definitions of short and long term treatment see box on bmj.com. Indications with evidence that immunoglobulin treatment may not be appropriate are listed in box 2.

Overcoming barriers

The biggest challenge is to change established prescribing patterns and encourage acceptance of the guideline recommendations. To engage prescribers in the guideline development process, the Department of Health launched a formal stakeholder review process involving royal colleges, medical societies, patient groups, and manufacturers of immunoglobulin. The review resulted in substantial changes to the guidelines and improvements in the terminology used in the recommendations.

The guidelines were formulated as part of a larger national demand management programme for immunoglobulin, sponsored by the Department of Health. This included a demand management plan for immunoglobulin use,[7] which recommends that trusts or strategic health authorities establish a local immunoglobulin assessment panel to approve and monitor the local prescribing of immunoglobulin, and also a national immunoglobulin database. The database will monitor immunoglobulin use to allow accurate forecasting, facilitate appropriate demand management, and provide a more accurate picture of prescribing by indication at national and local level.

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Summary of recommendations for treatment with intravenous immunoglobulin in diseases for which the treatment prioritisation is high (red) or moderate (blue). The appropriateness of immunoglobulin treatment is denoted as yes (appropriate in all cases if the physician wants to prescribe it), selected (appropriate in only selected cases and in these, only if the physician wants to prescribe it); and no (not appropriate).

Condition	Treatment		Recommendation, evidence grade*
	Short term	Long term	
Immunology			
Impaired specific antibody production	No	Selected	C, III
Kawasaki disease	Yes	No	A, Ia
Primary immunodeficiencies	Selected	Yes	B, IIb
Haematology			
Acquired red cell aplasia caused by parvovirus B19	Selected	No	C, III
Adult HIV associated thrombocytopenia	Selected	No	A, Ib
Alloimmune thrombocytopenia — fetal therapy (treatment to the mother)	Yes	No	C, III
Alloimmune thrombocytopenia — neonatal therapy	Selected	No	C, III
Autoimmune (acquired) haemophilia	Selected	No	C, III
Autoimmune haemolytic anaemia	Selected	No	C, III
Autoimmune thrombocytopenia	Selected	No	A, Ia
Evans' syndrome	Selected	No	C, III
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	Selected	No	C, III
Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome	Selected	No	C, III
Idiopathic thrombocytopenic purpura — paediatric (<16 years)	Selected	No	A, Ib
Idiopathic thrombocytopenic purpura — adult	Selected	No	A, Ia
Post-transfusion purpura	Selected	No	C, III
Haemato-oncology			
Chronic lymphocytic leukaemia	No	Selected	A, Ib
Haemophagocytic lymphohistiocytosis/haemophagocytic syndrome	Selected	No	C, III
Low serum IgG levels after haematopoietic stem cell transplant for malignancy	Yes	Selected	B, IIb
Multiple myeloma	No	Selected	A, Ib
Neurology			
Chronic inflammatory demyelinating polyradiculoneuropathy	Selected	Selected	A, Ia
Dermatomyositis	Selected	Selected	B, IIa
Guillain-Barré syndrome	Selected	No	A, Ia
Lambert-Eaton myasthenic syndrome	Selected	Selected	A, Ib
Multifocal motor neuropathy	Selected	Selected	A, Ia
Myasthenia gravis	Selected	Selected	B, Ia
Paraprotein associated demyelinating neuropathy (IgG or IgA)	Selected	Selected	A, Ia
Paraprotein associated demyelinating neuropathy (IgM)	No	Selected	A, Ib
Rasmussen syndrome	No	Selected	B, IIb
Stiff person syndrome	No	Selected	A, Ib
Dermatology			
Dermatomyositis	Selected	Selected	B, IIa
Immunobullous diseases	Selected	Selected	C, III
Toxic epidermal necrolysis, Stevens-Johnson syndrome	Yes	Selected	B, IIa
Paediatrics			
Alloimmune thrombocytopenia — neonatal therapy	Selected	No	C, III
Fetal hydrops	Selected	No	D, IV
Haemolytic disease of the fetus and newborn (isoimmune haemolytic jaundice in neonates)	Selected	No	C, III
Idiopathic thrombocytopenic purpura (<16 years)	Selected	No	A, Ia
Toxin related infection in paediatric intensive care	Selected	No	C, III
Paediatric rheumatology			
Juvenile dermatomyositis	Selected	Selected	B, IIa
Kawasaki disease	Yes	No	A, Ia
Adult rheumatology			
Dermatomyositis	Selected	Selected	B, IIa
Infectious diseases			
Necrotising (associated with Panton Valentine leukocidin) staphylococcal sepsis	Selected	No	C, III
Severe invasive group A streptococcal disease	Selected	No	B, Ib
Severe or recurrent *Clostridium difficile* colitis	Selected	No	C, III
Staphylococcal toxic shock syndrome	Selected	No	C, III
Transplantation			
Pneumonitis induced by cytomegalovirus following transplantation	Yes	No	A, Ib

*Grade A: Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency evaluating the specific recommendation (evidence levels Ia, Ib). Grade B: Requires the availability of well conducted clinical studies but not randomised clinical trials on the topic of recommendation (evidence levels IIa, IIb). Grade C: Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities; indicates an absence of directly applicable clinical studies of good quality (evidence levels III, IV)

Box 1 Conditions for which the treatment priority is low because of weak evidence base

Rare diseases not listed below should be considered to be grey conditions, and immunoglobulin treatment should be considered on a case by case basis, prioritised against other competing demands.

Immunology
- Secondary antibody deficiencies

Haematology
- Acquired red cell aplasia not caused by parvovirus B19
- Acquired von Willebrand's disease
- Aplastic anaemia or pancytopenia
- Autoimmune neutropenia
- Haemolytic uraemic syndrome
- Post-exposure prophylaxis for viral infection if intramuscular injection is contraindicated or if hyperimmune immunoglobulins are not available
- Post-transfusion hyperhaemolysis (usually in patients with sickle cell disease)
- Systemic lupus erythematosus with secondary immunocytopenia

Haemato-oncology
- Graft versus host disease after allogeneic bone marrow transplant or haematopoietic stem cell transplant
- Infection after allogeneic bone marrow transplant or haematopoietic stem cell transplant
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS)

Neurology
- Acute disseminated encephalomyelitis
- Acute idiopathic dysautonomia
- Autoimmune diabetic proximal neuropathy
- Bickerstaff's brain stem encephalitis
- Central nervous system vasculitis
- Cerebral infarction with antiphospholipid antibodies
- Intractable childhood epilepsy
- Neuromyotonia
- Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)

Paraneoplastic disorders
- Polymyositis
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS)
- Potassium channel antibody associated, non-neoplastic limbic encephalitis
- Vasculitic neuropathy

Dermatology
- Atopic dermatitis or eczema
- Pyoderma gangrenosum
- Urticaria

Paediatrics
- Intractable childhood epilepsy
- Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)

Paediatric rheumatology
- Juvenile systemic lupus erythematosus
- Other systemic vasculitides
- Systemic juvenile idiopathic arthritis

Adult rheumatology
- Catastrophic antiphospholipid syndrome
- Polymyositis
- Systemic lupus erythematosus
- Systemic lupus erythematosus with secondary immunocytopenia
- Systemic vasculitides and antineutrophil cytoplasmic antibody disorders

Transplantation
- Acute antibody mediated rejection after solid organ transplantation

Box 2 Indications for which immunoglobulin is not recommended,* by specialty

Immunology

Immunodeficiency secondary to paediatric HIV infection

Haemato-oncology

Autologous bone marrow transplant

Neurology

Adrenoleukodystrophy, Alzheimer's disease, amyotrophic lateral sclerosis, autism, chronic fatigue syndrome, critical illness neuropathy, inclusion body myositis, multiple sclerosis

Rheumatology

Inclusion body myositis, rheumatoid arthritis

Infectious diseases

Neonatal sepsis (prevention or treatment), sepsis in the intensive care unit not related to specific toxins or *Clostridium difficile*

Other specialties

Asthma, autoimmune uveitis, Graves' ophthalmopathy, failure of in vitro fertilisation, recurrent spontaneous pregnancy loss

*Described as "black" indications in the *Demand Management Plan for Immunoglobulin Use*[7]

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Commentary: Controversies in the Department of Health's clinical guidelines for immunoglobulin use

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Variable supply, high product costs, and an increasing demand for both established and off-label indications have made the Department of Health's development of a management programme for intravenous immunoglobulin use in the United Kingdom essential. This programme includes three core elements: a demand management plan,[1] clinical guidelines,[2] and a national immunoglobulin database.

How effective is treatment?

Intravenous immunoglobulin is used in over 100 conditions by many different disciplines, and, although there is an adequate evidence base for some indications, this is not the case for many others, even where intravenous immunoglobulin is accepted as the most appropriate treatment. The need for improved clinical trial data is clear, but for rare conditions this is difficult. It is reassuring that feedback from neurologists indicates acceptance that the new national guidelines are similar in content to their existing specialty guidelines,[3] but in many areas (such as specific antibody deficiency in clinical immunology) best practice is still unclear. Cost benefit data are also lacking; globally, human plasma is an expensive commodity that requires specialised and lengthy processing. A further complicating factor in the supply in the UK is the risk of variant Creutzfeldt-Jakob disease, which precludes the use of local plasma and requires the purchase of plasma from the United States.

How well will the guidelines work?

How well the guidelines will work is likely to vary from one healthcare trust to another and from one primary care trust to another. It is essential that potential prescribers understand the application process, which, in a rather odd decision, is published only in the demand management plan and not in the clinical guidelines.[2] For "red" indications (considered the highest priority because of risk to life without treatment, such as selected primary immunodeficiencies, Kawasaki disease, Guillain-Barré syndrome) clinicians may prescribe without prior approval, with retrospective completion of the immunoglobulin request form for sign-off by a designated person, and subsequent database registration. Linking the release of product funding to database entry should encourage healthcare trusts to ensure that this process is completed.

The process is more complex for other indications. For "blue" conditions (for which immunoglobulin is shown to be effective but alternatives exist) the local immunoglobulin assessment panel can approve use. For "grey" or unlisted indications (where there is insufficient evidence), approval from both the immunoglobulin assessment panel and the primary care trust is required. Emergency prescribing, sanctioned by at least two panel members, is possible for "blue" indications. The decision to use colour coding means that printing in black and white does not work well.

Other national guidelines

Management of intravenous immunoglobulin use is a global problem. Recent Australian guidelines are broadly similar, with four categories of use: established, emerging, and exceptional, and a "not funded" category equivalent to the UK "black" list (indications for which immunoglobulin is not recommended).[4] Inevitably, with the large number of diseases covered and poor evidence base, there are some differences in recommendations. The Australian guidelines, for example, list neonatal haemochromatosis as an established indication, but this rare condition is not listed in the UK guidelines. For other conditions the UK guidelines are more permissive. Immunologists from Asia and Pacific nations have also recently developed detailed regional guidelines, which provide an educational resource on immune deficiency diseases as well as information about the technicalities of intravenous immunoglobulin infusion and management of adverse reactions.[5]

If healthcare trusts are motivated, panels readily accessible, and primary care trusts' responses rapid, then these guidelines should be valuable and effective. However, serious delays in acquiring immunoglobulin are likely to result in resentment, complaint, and possible harm to patient care, as would lack of an appeal procedure. It is essential that feedback and responsive review of the guidelines continue and that the transition from commissioning by individual primary care trusts to commissioning by specialised commissioning groups, planned for April 2009, is smooth. Increased resources for clinical trials are needed to improve the quantity and quality of available data, especially for "grey" indications such as systemic lupus erythematosus and the systemic vasculitides. So far the score card reads "A for effort"—the score for efficacy is awaited.

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A PATIENT'S JOURNEY

Common variable immunodeficiency

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After 14 months of severe illness, this patient was diagnosed with common variable immunodeficiency

I am 36 years old and before I became ill in 2006, I was a self employed researcher and event organiser. I am married to Jonathan and we have one son and one adopted daughter. In June 2007, I received a diagnosis of common variable immunodeficiency, or hypogammaglobulinaemia. The diagnosis came after more than a year of constant diarrhoea, incontinence, vomiting, nausea, dizzy spells, extreme lethargy, sores in my mouth, burning sensation in my throat, stomach cramps, severe night sweats (changing the bed linen up to five times a night), and amenorrhoea. During this year I saw three NHS general practitioners, two NHS gastroenterologists, and a private allergy and immunology specialist. I had numerous blood and stool sample tests, a colonoscopy, and an endoscopy. By the time of my diagnosis, 14 months after first becoming ill, I had lost 12.7 kg (2 stone) and weighed just 40 kg.

Route to diagnosis

In March 2006, after three weeks in Australia, I returned home via Hong Kong. Within three days of my return, I developed severe diarrhoea (up to 20 times a day and night). Blood and stool tests showed nothing abnormal, but the diarrhoea and nausea continued and I steadily lost weight. In July 2006 my periods stopped.

In September that year my general practitioner referred me to a gastroenterologist for further tests. I saw the first gastroenterologist in December 2006, by which time my weight had fallen to 41 kg and everything I ate aggravated my stomach. An endoscopy in January 2007 showed an "increase in acute and chronic inflammatory cells thought to be non-specific duodenitis." The gastroenterologist said I probably had irritable bowel syndrome and did not offer further treatment. I requested a colonoscopy and a second opinion and was given an appointment in April 2007.

Before keeping that appointment, I visited a private allergy and immunology consultant, who palpated my spleen (which was painful) and said that I should have my immunoglobulin profile checked, believing I was fighting a parasite and that my levels would be raised. Aware that I was already in the process of seeing consultants in the NHS, she wrote to my general practitioner, recommending I have the blood test done locally. Before seeing my general practitioner, I visited the second gastroenterologist, who refused the recommended test, telling me it that it "did not comply with UK conventional medicine." He also told me that if my colonoscopy showed nothing abnormal my symptoms were probably psychosomatic. Very miserable, I returned to my general practitioner to inquire about the blood test again. He arranged for it to be done that day. My IgG, IgA, IgM, and IgE levels were checked and they were undetectable. At that point everything changed and I was quickly referred to a consultant immunologist at King's College Hospital in London and put through a battery of tests.

The diagnosis

The consultant discussed my symptoms, health, and medical history with me. He raised the possibility of common variable immunodeficiency, explaining what this meant and what the treatment would be. I had numerous blood tests and was immediately prescribed antibiotics to fight any infections I may have while transfusion treatment was arranged.

For the first time I felt that someone genuinely understood what was happening to my body. I was not particularly distraught about the diagnosis of a lifelong, incurable condition: seeing the strain on my family, having periods when I stumbled just walking across the room, being unable to drive owing to lack of concentration and falling asleep, feeling so very unwell all day every day for over a year—all these had left me numb. On bad days I felt I could not take any more and did not want to wake up the following morning. Being told I could receive treatment that should make me feel better could only be good news.

As a toddler, I had repeated coughs and colds. My health improved with the removal of my tonsils and adenoids when I was 4, and from then on I was a healthy

This is one of a series of occasional articles on patients' experiences of medical events that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

child and adolescent. However, for some time before 2006 I had experienced stomach cramps and intermittent diarrhoea in the morning. As a vegetarian, I put this down to too much fibre. Then when I was 24 I starting having frequent urine infections and from 2000 frequent chest, sinus, and ear infections. In 2001 I had various blood tests, all of which were normal—I joked with my general practitioner that I "didn't think I had an immune system." Every time I went on holiday I became ill, even on my honeymoon in Barbados, where I had emergency treatment for breathing difficulties and coughing flecks of blood. In 2004 I was admitted to hospital with pneumonia, pleurisy, and a collapsed lung. The diagnosis of common variable immunodeficiency explained this ill health; I was not a hypochondriac, after all.

Treatment

Since the diagnosis I have had frequent blood tests; ultrasound scans; chest scans; ear, nose, and throat scans; lung function tests; a barium meal; and bone density scans. I have been referred to a gastroenterologist; a chest physician; an ear, nose, and throat surgeon; and a gynaecologist.

Tests showed that I have mild bronchiectasis, splenomegaly, lack of absorption in my small bowel, bone thinning in my hips and spine, thickening of the tissue in my nasal passages; all these are caused by constant infections, lack of nutrients, and amenorrhoea. I had vitamin B-12 and iron deficiencies (hence the mouth sores and burning throat) and now receive regular vitamin B-12 injections. I provide regular phlegm samples from my chest and nose to check for any bacteria.

At the start of my treatment, I was given a 30 g immunoglobulin transfusion every other week to raise my levels to normal. Once my levels were in the normal range, I had transfusions every three weeks. Immunoglobulin transfusions can have side effects lasting up to four days—flu-like symptoms including muscle and joint aches, migraines, and raised temperature. However, I feel I have been lucky as I did not experience the extreme reactions that some people do. Generally, I developed headaches and muscle and joint pain, feeling I was about to "come down with something." As time went on and my transfusion routine became established, I did experience withdrawal symptoms when a transfusion was due. They could start as early as five days beforehand, making me very tired and irritable. Having to attend so many hospital appointments (an hour away from my home) and transfusions every two to three weeks, along with side effects, made it hard to resume normal life.

I recently opted to learn to treat myself at home. I am currently five weeks into the "one day a week for eight weeks" training programme and things are going very well. I receive my immunoglobulin via a subcutaneous catheter, in smaller amounts, once a week. The side effects have reduced dramatically as I no longer get the highs and lows of large doses of immunoglobulin. Once I have completed the training, I shall be able to choose the time and day to receive my treatment.

A DOCTOR'S PERSPECTIVE

Common variable immunodeficiency is an umbrella diagnosis that encompasses a group of genetic disorders that result primarily in hypogammaglobulinaemia or failure of antibody production. In most patients, specific genetic defects have yet to be identified, unlike with some of the other immunodeficiency disorders. Patients typically present with recurrent infections, particularly of the respiratory tract, although gastrointestinal disease, autoimmune and inflammatory features, and lymphoma are more frequent.

Onset of symptoms can occur at any age, although there are peaks in the first and third decades of life. In about 10-20% of patients, other family members are affected. The disease is more common than generally perceived and is thought to have a prevalence of 1:10 000 to 1:50 000. It is still under-recognised and underdiagnosed by general physicians, with an average diagnostic delay of four to seven years from onset of symptoms. These delays in diagnosis often result in long term sequelae, most commonly bronchiectasis and chronic sinusitis. This permanent damage is responsible for most of the chronic ill health and mortality associated with common variable immunodeficiency.

When we first saw Abigail in our department, she had already lost a substantial amount of weight owing to chronic illness and had seen many healthcare professionals in primary and secondary care. Her symptoms had not been accorded sufficient weight, and the appropriate test had been done only after much effort on her part. Unfortunately, this scenario is not uncommon in patients presenting with common variable immunodeficiency or other immunodeficiency disorders.

In addition to the difficulties faced by patients in getting their illness diagnosed, treatment of the condition brings its own difficulties. Specialist care is often restricted to teaching hospitals, and patients often require input from several disciplines, resulting in considerable time spent attending to healthcare needs. Immunoglobulin therapy, the mainstay of treatment in common variable immunodeficiency, is a product with limited availability as it is sourced from human donors. Supply problems with this important product have resulted in anxiety for patients.

This case has clearly reminded us that greater awareness of the primary immunodeficiency disorders among generalists is still needed to avert late diagnosis and subsequent chronic ill health in patients. To this end, various organisations with a stake in this have tried to improve awareness of primary immunodeficiency, and hopefully this will help future patients.

Resources

- European Society for Immunodeficiencies (www.esid.org)—Enables exchange of ideas and information among doctors, nurses, biomedical investigators, and patients and their families; promotes research on these disorders; maintains a Europe-wide disease registry.
- Immunodeficiency Foundation (www.primaryimmune.org)—US based national patient organisation that seeks to improve the diagnosis and treatment of primary immunodeficiency diseases, promotes and funds research, and provides support for affected individuals.
- International Patient Organisation for Primary Immunodeficiencies (www.ipopi.org)—Umbrella organisation for national patient groups that seeks to improve access to early diagnosis and optimal treatment and care, and promotes the establishment of national member organisations. The website provides links to national patient support groups globally.
- Jeffrey Modell Foundation (www.jmfworld.com)—US based foundation dedicated to early and precise diagnosis, meaningful treatments, and ultimately cures of the primary immunodeficiency diseases. It raises funds for research, is a national and international source for the dissemination of information and education, and advocates on behalf of patients and families.
- Primary Immunodeficiency Association (www.pia.org.uk)—UK based patient group that helps patients with primary immunodeficiencies; raises funds for research; campaigns for the rights of patients, and liaises with clinicians and immunologists.

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Life with common variable immunodeficiency

I have been regaining weight. When my weight reached 48 kg my periods resumed, and my weight now seems to have stabilised at 51 kg. Over time my stomach has settled, but I still have flare-ups. I have supplies of antibiotics for such flare-ups and for infections elsewhere.

My condition has affected the entire family. Not only has my husband had to become the sole breadwinner, but everyone else has to deal with my stomach problems and adjust to never having privacy in the bathroom—I am liable to rush in without warning. I still get tired and find that if I rush about subjecting myself to the normal stresses and strains of daily life I can become run down and begin to feel nauseous and dizzy, and my stomach will often flare up the next day.

As common variable immunodeficiency is a genetic condition, there was concern over my son. Tests showed his immune system to be healthy, but whether he could develop the condition later in life is not known. Specialists believe that common variable immunodeficiency can also skip generations, so the condition is not only a consideration for my son but also for his children, my sister, and her children. My mother was advised to have her immune system checked and it is "low"—she is now seeing the same immunologist at King's College Hospital for further tests.

My general practitioner has had to learn about the condition along with me and has been very understanding. The immunology consultants and nurses and the other specialist consultants at King's College Hospital have been fantastic. I have been listened to, understood, and referred to other specialist consultants to cover all health concerns. The specialist nurse in particular has had to endure my constant questioning since my transfusions began in July 2007 and is probably looking forward to me doing my home treatment so she can get some peace. I was placed on the same cycle of transfusions as three other people with the condition, which has enabled me to learn about how they have dealt with their conditions and ask yet more questions.

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DRUG POINT

Acute psychosis caused by co-amoxiclav

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Co-amoxiclav is a fixed dose combination of amoxicillin and clavulanate that offers antibacterial activity against some strains that produce β lactamase. Recognised adverse effects include exfoliative dermatitis, deranged liver biochemistry, and anaphylaxis.[1] We report the occurrence of acute psychosis after giving co-amoxiclav, with a strong temporal relationship and recurrence after drug rechallenge.

Case report

A 55 year old woman was prescribed oral co-amoxiclav for suspected pneumonia. Within two hours of receiving 375 mg she became disorientated and confused and seemed unable to hear her husband. On arrival in the emergency department the symptoms had resolved, and physical examination was normal. Later the same day she received a further dose of 750 mg co-amoxiclav, and about 90 minutes later her behaviour became increasingly agitated and bizarre, and she experienced visual hallucinations, persecutory delusions, and disordered speech. Chest radiograph, cranial computed tomography, serum electrolytes, and cerebrospinal fluid microscopy were normal. Urinary toxicological screening was negative, and there was no laboratory evidence of infection or inflammatory response. She was treated initially with oral haloperidol and intravenous midazolam, and her symptoms resolved promptly and did not recur in the next 24 hours. Psychiatric assessment found no underlying disorder, and a diagnosis of drug induced psychosis was made. Hospital case notes showed that she had previously had hallucinations after a single intravenous dose of co-amoxiclav for surgical prophylaxis.

Co-amoxiclav has been reported to cause behavioural disturbance in children.[2] The yellow card scheme has received 3935 reports of adverse reactions to co-amoxiclav (to 30 September 2007), including psychiatric effects in 102 (2.6%).[3] A broadly similar proportion of psychiatric adverse effects has been reported after amoxicillin, indicating that this component might be responsible. Symptoms coincided with the expected peak circulating drug concentrations at about one hour.[1] We are reminded to consider the possibility of drug induced acute psychosis, even in the absence of pre-existing psychiatric illness or other predisposing factors.

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1 Sweetman SC, ed. *Martindale: the complete drug reference*. 35th ed. London: Pharmaceutical Press, 2007.
2 Macknin ML. Behavioral changes after amoxicillin-clavulanate. *Pediatr Infect Dis J* 1987;6:873-4.
3 Medicines and Healthcare Products Regulatory Agency. Drug analysis prints: data on suspected adverse drug reactions. www.mhra.gov.uk/Onlineservices/Medicines/Druganalysisprints/index.htm.