Key Issues Dialogue: HAE and PID
Featuring Dr. Hilary Longhurst, Dr. Richard Herriot, Chris Hughan and Eddie Owens
From left to right, Chris Hughan, Dr. Richard Herriot and Dr. Hilary Longhurst
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In February, three well-known members of the U.K. primary immunodeficiency community met with Eddie Owens of CSL Behring to discuss challenges and advances in diagnosis and treatment.

This dialogue is part of a series, sponsored by CSL Behring, for patients, caregivers and members of the worldwide primary immunodeficiency community.

Diagnosis: The Challenge

EDDIE OWENS: A question in two parts for all of you. Is it common for both Hereditary Angioedema (HAE) and primary immunodeficiency disorders of the immune system (PID) patients to go for years without diagnosis, or with misdiagnosis and what changes have been put in place or could be put in place to encourage earlier diagnosis for these conditions?

CHRIS HUGHAN: We are covering a range of PID here as well as HAE so you cannot be too general about things. The primary immunodeficiencies are a group of genetically determined incurable conditions that affect the body’s immune system. A person who has one of these conditions has little or no natural defense against infections. He or she can experience a variety of problems, ranging from recurrent colds and other respiratory ailments to heart problems, pneumonia, skin disorders and arthritis.

The comparative rarity of these conditions means that some people remain undiagnosed for many years, resulting in organ damage and even disability.

Some more severe PID mean that children have a limited lifeline unless they get treatment, while Common Variable Immunodeficiency (CVID), will go on for years without being diagnosed. Obviously these delays can result in serious long-term damage so the earlier you can get to those patients the better.

The advent of the specialist clinical immunologist based in centres of excellence means that people can now be diagnosed; at one stage we did not even have that. The challenge in the U.K. and Europe is two-fold. First, it is the ability of primary care practitioners to recognize PID, especially as they see very few cases in their lifetime and second, it is the level of priority that health systems attach to PID. With over 80 different PID conditions, these are the challenges we face and have to resolve.
We know the most common problem that patients with PID have is antibody deficiency. So why is there not a system that says, “Recurrent infections!” and the alarm is triggered with three infections a year...

**EDDIE:** So what can be done to improve awareness and education amongst clinicians?

**CHRIS:** One of the things that we are looking at seriously is how infections, particularly recurrent infections, can act as a stimulus for the primary care practitioner to consider PID. They do audit their patients, so we are looking at the possibility of developing some software that will sit on the patient database, which will red flag recurrent infections and so on. This will give them the opportunity to look at PID as a possible diagnosis.

**RICHARD HERRIOT:** I agree. We are competing for the attention of general practitioners in the context of a vast range of other clinical and service pressures. Awareness is crucial along with availability of information in an accessible and easy-to-understand format. We know the most common problem that patients with PID have is antibody deficiency. So why is there not a system that says, “Recurrent infections!” and the alarm is triggered with three infections a year, perhaps a pneumonia, an ear infection and a skin infection and the action is to measure serum immunoglobulins.

**CHRIS:** It could work better if this went hand in hand with an advocacy program, which brings attention to government and health authorities.

**RICHARD:** I absolutely agree some sort of advocacy program combined with a fiscal payment for relevant activity would be a way forward. There is also the issue around the impact of guidelines. The 1995 guidelines were supposed to go to all primary care practitioners, but there is still a huge lack of awareness. This is not helped by the simple fact that the average primary care practitioner in the U.K. may see a PID about every 12–14 years. We must maximize the impact of the new 2007 edition of the guidelines—this will be an important opportunity.

**HILARY LONGHURST:** A message I would like to get across here is that there is not just the clinical value in treating these conditions but also a big economic value. It becomes cost-effective to diagnose early and initiate treatment.

**RICHARD:** There is some work at Birmingham University, which shows the cost-effectiveness of early diagnosis and institution of immunoglobulin therapy in PID patients.

Another important development would be the annual registration of PID patients. We certainly need accurate numbers of the number of patients being looked after by immunologists both pediatric and adult across all categories of PID and HAE as well.
Across Europe there is also the development of the ESID database, which will assist in this.

CHRIS: We also are producing health managers’ guidelines, which are aimed at raising awareness amongst this group.

RICHARD: Ideally, we should go for a three-pronged strategy; guidelines and emergency treatment protocols, advocacy and a patients’ register.

EDDIE: *What is the difference in levels of understanding between HAE and PID?*

HILARY: They are very different diseases. They are both immune deficiencies, but basically with HAE you can swell up and with PID you get infections. I would say probably there is more public understanding of PID through the ‘Jeans for Genes’ campaign and the visual examples of the baby in a bubble.

In HAE another challenge is to ensure greater knowledge amongst the medical profession. One important difference from PID is that people with HAE may not have frequent attacks and they are completely well between attacks. With PID if you have a significant antibody deficiency, you are really never 100 percent. I think perhaps people with HAE can disappear from the radar. They will go to the hospital or to their doctor a few times and then, if they do not get any satisfactory response, they will just lie at home with their abdominal attacks. It is quite common that specialists say to me, “We have a family with this condition but they do not have much trouble with it.” And occasionally it has happened that these people have subsequently been referred to me. Actually, they are having a lot of problems, but they have not found it useful to access local medical care.

Encouraging Patients to Positive Empowerment

CHRIS: I think one thing that is quite important here is also patient empowerment, if I can use that phrase. In my experience with PID patients and HAE patients, probably less so with HAE patients than other PID patients, there seems to be a great reticence to push themselves forward to a large degree. To that end we are organising patient days where we are introducing a clinical psychologist, a dietician and a physiotherapist looking at the whole spectrum of treatment, including self-treatment, with the aim of the individual taking more control of their quality of life.

HILARY: Patients with HAE can be very stoical and despite feeling ill every month with a couple of days off work, they just go to bed and put up with it. With PID, I think the infections are often less acute so people actually look
Management Challenges

**EDDIE:** As a result of HAE and PID having small patient populations and expensive therapies, there are often moves to reduce the number of “approved” therapies or to limit access to treatment. What is the situation in the U.K.?

**RICHARD:** There are certainly complexities over this issue which have both a clinical and organizational focus. There seems to be variation in approach between hospitals and primary care trusts in England and, I have no doubt, there will also be significant differences in approach between the Department of Health centrally and the devolved administrations. In Scotland the treatment is centrally funded and access and therapies are available. In England there are issues around the primary care trusts (payors) pooling enough money for commissioning the specialist care generally and PID is no exception.

**HILARY:** Yes, certainly patients, through the Primary Immunodeficiency Association, have contacted me directly to say that they cannot get a referral to me. I have then needed to engage with the primary care practitioner directly. In the long term, payment by results (a tariff system of payment to the hospitals) should potentially be very good, because we should get reimbursed for the money we are spending. The danger is that we need to ensure that decent standards of treatment are incorporated in the tariff. If they are low then the payment will be commensurately low and we will not have enough money to provide proper care.

**EDDIE:** Are there other countries that we can learn from in the management of PID?

**HILARY:** Hungary has a system where everyone with HAE in Hungary goes to a specialist centre. In this case it is one specialist centre in Budapest—and will have access to C1 inhibitor concentrate for acute attacks. So for many years they have been much better off practically than patients in the U.K.

I think we can also look to places like the United States where we have an example of how not to do it where, because of lack of randomized controlled trials, we cannot give people the molecule that they are missing and we cannot actually treat them effectively with best treatment for acute attacks. That is really setting the standard really too high and not saying, “we are going to look at the best evidence we have although we need to collect more.” So I think the lesson is really we do need to have central...
funding for care and we do need to have specialist centres. I am not convinced that having one specialist centre for the whole of the U.K. would be right, because I do not think people would travel from Aberdeen to London or vice versa.

**EDDIE:** With all the issues around immunoglobulins, how does this impact on patient choice?

**HILARY:** I think that patients do not worry as much as we do in general about safety issues and I think that modern immunoglobulins are safe enough. I personally would be happy using any one of a variety of immunoglobulins and I think my patients, by and large, trust me enough to respect my advice.

In times of shortage there is some anxiety from the patients, but not a lot because if you go to a specialist centre the companies and the physicians work well together and our patients are prioritised. So I do not think it has been a major difficulty. I have had patients who have been under care of non-specialists actually come to me during times of shortage when they have been without their immunoglobulins and have subsequently got an infection. So if you are not in a specialist centre, the situation is not the same.

**CHRIS:** There is no question about it and patients certainly trust their consultant to give them a product and to give them all the reassurances they can. However, some patients have expressed a lingering thought, “I still have to put up with a product, a plasma-derived product, which can cause some concerns.”

**EDDIE:** The shift to subcutaneous therapies, is that something you think that is going to continue? I presume it is good to have another option and another choice for the patients. How do you see that developing?

**HILARY:** I am a huge enthusiast of subcutaneous therapies for replacement. Certainly for us it helped us get people who you could never imagine being able to go on home therapy and look after themselves much more independently, it really has improved our patients’ quality of life.

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RICHARD: I am ambivalent. I will go with what patients want and the vast majority of our patients have opted in the past for intravenous therapy. However, there is another factor now which is the problem of supply, particularly with intravenous immunoglobulin. That being the case, I think there will be a shift towards subcutaneous, perhaps for slightly different reasons than no venous access and a flattening out of peaks and troughs and all the usual arguments. But I have to say that subcutaneous therapy, in my mind, especially for home therapy patients is fantastic. It is so much better than intravenous. I have slight difficulties wondering why patients opt for intravenous.

CHRIS: Believe it or not, there are other reasons. Some of it is a social reason. It is hard to imagine, I know, but a lot of people I have spoken to actually quite enjoy the experience of going to hospital and talking to other patients.

RICHARD: We should be aiming for higher trough levels, higher than 5-6, say 8.

EDDIE: There is a health gain argument there, too, is there not? The message should be that if we actually treat to the right level with the right amount, then we are actually going to prevent complications down the line.

HILARY: I agree absolutely. The difficulty is that this is the lesson we can only learn from experience. The best we can do is a consensus statement, although not based on concrete evidence, advocating higher levels of immunoglobulins.

The Future

EDDIE: What does the future hold for managing these conditions?

CHRIS: For HAE there are some very exciting medications for treating acute attacks of HAE, which are now undergoing detailed clinical trials. Four products, C1 esterase inhibitor, recombinant human C1 inhibitor, Icatibant and DX-88, are due for clinical trials in the U.K. over the next few months.

For PID, if you are looking at X-Linked Severe Combined Immunodeficiency, there has been the amazing success with gene therapy at the Institute of Child Health and Great Ormond Street. Hopefully that will continue. They are now looking at Wiskott-Aldridge Syndrome. These are the rarer PIDs admittedly, but we are looking at some pretty dynamic breakthrough treatments.
EDDIE: *In terms of CVID, what’s happening?*

HILARY: I think we have made some progress in diagnosis of full stop CVID. For a minority, a small minority; we have got a molecular diagnosis. And, because we know what the molecule is, which is faulty, potentially we could replace it with gene therapy. This approach could potentially be a much less toxic, less risky and less inconvenient way to have treatment. Of course, at the moment it is really very experimental. There are risks, particularly a risk of leukaemia, and some unknown risks. After all we are only eight years into gene therapy, but certainly in the long term I think that is something which we will see for some of the conditions we treat.

RICHARD: There are still some very basic questions to be answered about existing therapies. The safety of plasma-derived products is an issue. We are looking at, in the next two or three years, hopefully, a test for prion carriage in blood and for asymptomatic screening, which may also have a role in disease diagnosis in symptomatic patients in-vivo.

As we previously discussed, it sounds incredible, but we still do not know what the optimum dosage of immunoglobulin for a patient group is. You may be able to say in some way for an individual, but it is very difficult to say for a cohort of patients the dosage that is needed that will prevent the progression of complications such as lung disease.

There are some groups of patients, non-PID patients, who do not actually need immunoglobulin per se. They need something that it is in the immunoglobulin i.e., FC fragments. Presumably FC fragments would be amenable to recombinant production.

HILARY: I think that small advances are at least as important as the large advances. I would highlight that we are getting a little better at diagnosis. I can now measure more detailed B-cell phenotypes. We can now say, “actually this patient has very low immunoglobulins but they do not need replacement.” And we all see patients like that, some of whom have been put on immunoglobulins and it is very difficult to take them off.

Conversely, we all see patients who have got really not bad immunoglobulins, who when you finally do end up putting them on replacement in despair, actually do extremely well. So I think with B-cell phenotyping we may find that it might be a better way of telling which patients need immunoglobulin and which ones do not.

EDDIE: *Thank you all for a stimulating and animated discussion.*
About the Participants

**Dr. Hilary Longhurst**  
*Consultant Immunologist, Barts and The London NHS Trust, London, England*  
*Member, Medical Advisory Panel, Primary Immunodeficiency Association*

Dr. Hilary Longhurst trained in Cambridge and London. She began specialist training in general medicine but during her Ph.D. she developed an interest in immunology. She is currently Consultant Clinical Immunologist at Barts and the London NHS Trust. She is also responsible for immunology laboratory services for North East London and Essex.

She is an enthusiastic supporter of patient empowerment, aiming to enable patients to lead independent, productive lives. Her unit was one of the first in the U.K. to offer subcutaneous immunoglobulin therapy and home therapy for C1 inhibitor deficiency.

**Dr. Richard Herriot**  
*Chair, U.K. Primary Immune Network*

Richard Herriot studied medicine at Aberdeen University and trained in General Medicine and Immunology in Aberdeen, Glasgow and Oxford. He has been Consultant Immunologist since 1992 with responsibility for providing specialist care services, in hospital and at home, for patients with primary immune deficiency and allergic disorders across Grampian and Highland regions in the North and East of Scotland.

He is keen to support the development of Immunology service provision to patients throughout the U.K., particularly in respect of infrastructure, quality, training and interaction with service commissioning structures.

He is Chairman of the U.K. Primary Immunodeficiency Network, past Chairman of the Association of Clinical Pathologists Committee on Immunology, specialty adviser on Immunology to the Scottish Office Department of Health and a committee member of the Joint Royal College of Physicians Postgraduate Training Board Speciality Advisory Committee in Immunology and Allergy and the Royal College of Pathologists Specialty Advisory Committee on Immunology and Joint Committee on Immunology and Allergy.

**Chris Hughan**  
*Chief Executive, Primary Immunodeficiency Association (PIA), London, England*

Chris Hughan has been involved in the charitable sector for nearly twenty years, initially as a Trustee and Chairman of a national charity supporting children with Inflammatory Bowel Disease (IBD) and their families, and more recently in CEO posts in IBD charities in the U.S. and U.K. He has been Chief Executive of PIA for the past two years.

In his earlier career in the commercial sector Chris held a number of senior posts in major advertising and communications companies, as well as establishing, developing and leading three public relations companies—including Ogilvy & Mather PR in the U.K. and his own consultancy—Communications in Business.

**Eddie Owens**  
*General Manager, U.K. and Ireland, CSL Behring*

**CSL Behring**

CSL Behring is a global leader in the plasma protein biotherapeutics industry. Passionate about saving lives and improving the quality of patients’ lives, CSL Behring manufacturers and markets a range of plasma-derived and recombinant products for rare diseases.

**The Primary Immunodeficiency Association**

PIA is the only U.K. charity that supports people living with one or more of the over 80 recognised PID. The charity works closely with specialist immunology centres to help provide optimal treatment for all PID patients; provides a wide range of information and activities to support, inform and benefit children and adults with PID; advocates for the rights of its members with government; and funds important research, often leading to breakthrough treatments—such as gene therapy and bone marrow transplants.

**The U.K. Primary Immune Network**

The U.K. Primary Immune Network was established to improve PID patients’ care through the development of common approaches to management by means of setting agreed standards of care. To further this aim, help is provided in the form of model protocols (policies, procedures and guidelines), based on common practice and available on the Web site for downloading by individual centres who wish to use them as the basis of local protocols.
From left to right, Eddie Owens, Chris Hughan, Dr. Richard Herriot and Dr. Hilary Longhurst