ESID Newsletter

Contents

The ESID Newsletter is made for the members of ESID – the European Society for Immunodeficiencies.

It is published under the responsibility of the ESID Board, and at this moment it is edited by Esther de Vries.

Any ESID member who is interested in publishing his or her views, research, new ideas or other material in the ESID Newsletter is cordially invited to submit copy to the Editor. Suitability for publication is assessed by the Editor in consultation with the other members of the ESID Board.

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Front page:
Chinese Temple,
Melaka, Malaysia

Dear ESID members,

The tropical temperatures that we experience in Europe this summer are not very different from the temperatures you can find at the spot where the front page picture was taken!

This summer issue of the ESID Newsletter will bring you important information about the Board's initiative with financing a Registry with the help of PPTA. Please feel free to give us your opinion about this!

The 'Focus on a country' section shows you Turkey this time, with Prof. Ozden Sanal from Ankara as Established ESID member, and dr. Tuba Turul as Young Investigator, also from Haceteppe University.

If you feel like suggesting a country or person for the 'Focus on a country' section, want to attract attention to your symposium, express your opinion, write a review, or anything else of interest to the ESID community, **please don't hesitate to contact me at esther_de_vries_nl @ yahoo.co.uk**

Best wishes to all of you!

Esther DE VRIES, Editor

= ESID Information =

ESID is the European Society for Immunodeficiencies. It was formed in 1994. The forerunner of ESID, the informal European Group for Immunodeficiencies (EGID) was established in 1983. Anyone who is interested in primary immunodeficiency diseases can become a member of ESID. You can find the necessary information to contact the treasurer Esther de Vries at www . esid . org.

Within ESID, six Working Parties are actively engaged in coordinating the member's joined efforts in patient care and research in primary immunodeficiency diseases: Bone marrow transplantation (chair: Andrew Cant), Pathology (chair Fabio Facchetti), Patient registries (chair: Bodo Grimbacher), Clinical (chair: Jean-Laurent Casanova), Genetics (chair: Anna Villa), and Education (chair: Anders Fasth). Anyone who is interested in participating in one or more of these Working Parties is invited to do so. Please contact the chairman of the relevant Working Party (contact information is available at www . esid . org).

In 1994, a main registry of patients with various forms of immunodeficiency in Europe was established. Altogether, data from some 10,000 patients from 26 countries were received until now. In 1995, the first locus-specific immunodeficiency mutation database accessible through the internet was established (BTKbase for X-linked agammaglobulinemia – curators Mauno Vihinen and C.I. Edvard Smith). Since then, several additional locus-specific data bases have been established: ADAbase (adenosine deaminase deficiency – curators Mauno Vihinen and Michael Hershfield), BLMbase (Blooms syndrome – curator Mauno Vihinen), CYBAbase (autosomal recessive p22 phox deficiency – curators Dirk Roos and Mauno Vihinen), CYBBbase (X-linked chronic granulomatous disease (XCGD) – curators Dirk Roos and Mauno Vihinen), CD3Ebase (autosomal recessive CD3 epsilondeficiency – curators Mauno Vihinen and Jose R. Regueiro), CD3Gbase (autosomal recessive CD3 gamma deficiency – curators Mauno Vihinen and Jose R. Regueiro), CD40Lbase (X-linked hyper-IgM syndrome – curators Luigi D. Notarangelo and Mauno Vihinen), JAK3base (autosomal recessive severe combined JAK3 deficiency – curators Luigi D. Notarangelo and Mauno Vihinen), NCF1base (autosomal recessive p47 phox deficiency – curators Dirk Roos and Mauno Vihinen), NCF2base (autosomal recessive p67 phox deficiency – curators Dirk Roos and Mauno Vihinen), RAG1base (autosomal recessive severe combined RAG1 deficiency – curators Mauno Vihinen and Anna Villa), RAG2base (autosomal recessive severe combined RAG2 deficiency – curators Mauno Vihinen and Anna Villa), SH2D1Abase (X-linked lymphoproliferative syndrome (XLP) – curators Luigi D. Notarangelo and Mauno Vihinen), TCIRG1base (autosomal recessive osteopetrosis (arOP) – curators Mauno Vihinen and Anna Villa), ZAP70base (autosomal recessive severe combined ZAP70 deficiency – curator Mauno Vihinen), WASPbase (Wiskott-Aldrich syndrome – curators Mauno Vihinen and Luigi D. Notarangelo) (information is available at www . esid . org).

ESID organizes a biennial congress to facilitate international contact between primary immunodeficiency specialists. The last congress was organised in 2002 in Weimar, Germany; the next congress will be organized in Versailles, France in October 2004, and the one after that will be in Debrecen, Hungary, in 2006.

= ESID Information =

President's letter

Dear friends and colleagues,

When we are half way from a very successful Meeting in Weimar and what promises to be an excellent Meeting in Versailles under Alain Fischer's organization, ESID is continuing its efforts to foster collaboration in the field of Primary Immune Deficiencies (PID) across Europe.

Perhaps the most important achievement in this year of activity, an agreement has been reached to start a new on-line Registry for patients with PID. Through the development of a user-friendly interface, Bodo Grimbacher has set-up the system, so that each Center will be able to enter and review the data pertaining to its specific patients (and will be rewarded for this contribution!). This will allow on-line adjournment of data (something we were missing!), and will also facilitate large collaborative studies and trials. It is expected that the new Registry will start its activity already this year, using Common Variable Immune Deficiency as a model. Other diseases, such as XLA and CGD, will follow soon.

In the era of Internet, this represents a necessary tool to provide efficient monitoring of the status of research and clinical care for rare disorders, such as PID. Yet, Bodo and all of us will have to work hard in order to make sure that this effort does not jeopardize, but rather complement, already existing National Registries, some of which are already based on Web resources, and have indeed represented a model for the new ESID Registry itself. Furthermore, it is very important that the new ESID Registries find an appropriate way to integrate with already existing databases, that Mauno Vihinen, more than anyone else, has efficiently developed.

It is very important that, as soon as Bodo Grimbacher's initiative moves its first steps, the ESID Community provides adequate comments, so that we all move together.

We do need everybody's contribution. The efforts of many colleagues to develop new diagnostic guidelines (that were published in the last Newsletter) have received too little echo from our Community. **May I ask all of you to give your opinion?!?**

The scientific activity in the field of PID in Europe remains of high quality. While many people thought that with completion of the Human Genome Project there was little room for other scientific discoveries in the genetic bases of PID, this has proven to be a wrong assumption. To mention just one example, Jean-Laurent Casanova has recently shown that mutations in IRAK-4 may cause selective susceptibility to S. pneumoniae infection. Importantly, and not surprisingly, this contribution was made possible through an extensive collaboration among Centres in Europe, in the Middle East, and in the U.S.A., once again demonstrating that high-quality research knows no barriers.

Yet, within this reassuring scenario, some major problems have appeared. Very recently, the World Health Organization has decided that immunoglobulins no longer be considered a life-saving drug. While it is very likely that this decision was also contributed by the unjustified use of immunoglobulins for a variety of human disorders (with a major responsibility both of physicians and of companies), the consequences are difficult to predict, but might be severe for all of our patients, particularly in a moment of severe constraints worldwide onto funding healthcare. Consequently, together with IPOPI, ESID will react and complain about this decision.

Research and healthcare should proceed together. With this hope, we look forward to a great ESID Meeting in Versailles in 2004!

Luigi NOTARANGELO

Your opinion please ...

Secretary's report

From the last ESID Board meeting, as of June 30, 2003:

On March 14th, the ESID Board held its first meeting in 2003 at the Vienna Airport Congress Centre. Bodo Grimbacher started the meeting with a comprehensive overview on the plans for the new internet-based ESID patient database. In brief, this new ESID database should enable continuous update of anonymous patient information through improved communication with the local medical centers and/or physicians taking care of the patients. This ESID project is supported by the Plasma Protein Therapeutics Association PPTA, and IPOPI and other international and national patient organizations are informed from the very beginning. Bodo's presentation containing a detailed description of this project can be found on the ESID website (www.esid.org). In brief, patients can be entered by local centers in the different countries, and these centers are responsible for written patient consent and the duty to respect the local law. In order to avoid entrance of doublets, pseudo-anonymous patient data will still allow to connect data from the same patient to one another. Each center should have a person responsible for data monitoring, like in the European BMT registry. A financial reward for data entry is considered. Queries that are submitted to the ESID patient registry should go through the ESID Board, and if a researcher wants data about patients outside of his/her own center, a protocol has to be submitted. Emphasis will be given to interact with the many physicians that have already entered data into the existing database: they should be informed about the new development, given the new patient ids where applicable, and asked to either withdraw this patient, if no written consent can be obtained for inclusion into the online registry, or leave the patient in with consent and, better even, update relevant information. A pilot database project to see that the concept works will be the CVID subregistry. Ongoing studies of data from the patient registry will be published on the ESID website.

In addition, Anders Fasth reported on the ESID Summer School 2003 to be held in Portugal in September (25-29th); the main topic is thymus development and defects, and participants will present case reports. Faculty will include Esther de Vries, Susanna Müller, Gavin Spickett, Jacques van Dongen, Georges Holländer, Teresa Español and Anders Fasth. Following the successful experience ESID has with its Summer Schools, LAGID and CIS will also have theirs.

Among other topics, the ESID Board further discussed possibilities to submit an EU grant application within the 6th framework program; on first glance no topic seems to be suitable for ESID; Adrian Thrasher then suggested to apply for a specific program about integrating and strengthening the foundations of the European Research Area, and this will be pursued by the Board. From the ESID Clinical Working Party, the manuscript about the WAS treatment ESID/PAGID study was submitted to Clinical Immunology. A follow up should focus on the differentiation between mild vs. severe WAS phenotype. A questionnaire for an ADA survey is in preparation, and future surveys should deal with the different forms of HIGM as well as with XLA and CGD. In the Genetics Working Party, a project on quality control and quality management in genetic testing is started, beginning with a search among ESID members for genetic diagnostic labs participating in a quality control network. For other genetic diseases quality assurance networks already exist. In the BMT Working Party, the second paper on BMT in CD40L deficiency is in preparation. A study on 20 years experience in BMT for SCID recently was published in the Lancet.

Finally, the ESID Board plans to contact immunological journals for reduced

subscription fees for ESID members; **members are invited to make suggestions for specific journals that should be addressed,** and journals that are less commonly represented in medical libraries should be preferred.

Hermann WOLF

Treasurer's report

Until now, July 2003, 313 ESID members have paid there membership fee for 2002-2003. Among those, there are many young people who have registered as new members. Unfortunately, 140 former ESID members have still not paid, after almost two years of receiving reminders … I hope some of them will still change their mind. If you know any colleagues who are wondering why you receive the ESID Newsletter and they don't anymore, ask them whether they have paid their membership fee!

Your treasurer is working hard at the moment to turn the paperwork into a computer-based system, which will make it all a lot easier to do. Hopefully, you will find the results of that in the next call for membership payment (2004-2005) which you will receive with the next issue of the ESID Newsletter towards the end of this year.

Esther DE VRIES

News & Views

Sponsorship for growing ESID registry

As the 'associated board member for industry liaison', I am proud to announce that we are going to sign our first contract with the industry providing sponsorship for the growing ESID registry.

As already mentioned in the ESID Newsletter before the last biennial meeting, the European Community is not sponsoring the database registry anymore, and we were looking for collaboration with the industry in order to provide new funding. We identified the registry as the most promising field, in that the data collected might – in the best interest of our patients - also be useful to the industry providing treatment for primary immunodeficiencies. It was Helen Chapel's idea to contact the Plasma Protein Therapeutics Association (PPTA), because we had worked together successfully on the European Blood Directive and many of its members already knew ESID and our clinical and scientific activities. Contact was made with Edward Hutt, their director on public affairs, who proved to be extremely helpful.

A first meeting was held between the ESID board and PPTA members during the meeting in Weimar last year, and PPTA members showed a general interest in sponsoring the registry in some way. Discussion continued thereafter among them, and next ESID was invited to participate at the International Plasma Protein Congress in Brussels in March 2003 that was organized by PPTA-Europe. Dr. Wolf as our secretary, Dr. Grimbacher as the head of the registry and myself went there, and used the opportunity to meet and discuss with many PPTA members and their directors explaining the rationale and the details of the project. The IPOPI representatives who participated in that

meeting supported us strongly, realizing that a clinical database, while respecting the patient's privacy, might provide answers to important open questions they have on quality of life and best treatment. The industry is well aware that good and updated data can not be obtained at zero costs, and is willing to provide the necessary means to guarantee reliable data. We were able to assure PPTA that ESID members are enthusiastic to collaborate on such an important issue, as they have already shown in the past. This lead to approval of the database project by the PPTA-Europe Board after the FOCIS meeting in Paris.

But the European Board wanted approval of the project also by the PPTA-Global Board, and invited us to present the project at the annual Plasma Forum in Reston, VA, USA in June 2003. I went there, and during a session dedicated to patient registries, I presented and discussed the project explaining once again the benefits an ESID database with clinical data could bring to the patients, the industry and the scientific community. Our experience with the mutation databases, the fact that almost 30 countries participate in the registry, and the expertise ESID has shown during the past years, for example in defining the diagnostic criteria for primary immunodeficiencies, as well as the enthusiasm of IPOPI, convinced the plasma industries leading people.

F.S.

At this time, a contract is being defined and a meeting will be organized to define the structure and items in the database. Starting with ESID's experience we will add data that are relevant to the industry (searching IPOPI approval), taking into account also items that may be suggested by the patients themselves (IPOPI), in order to answer their questions as well. With the team spirit of ESID members, I am confident that this will become another ESID success story!

Fabian SCHUMACHER

Call for collaboration: asplenia patients

We are looking for any kindred available for positional cloning for isolated congenital asplenia as an autosomal dominant cause of pneumococcal disease. Please contact me at casanova @ necker.fr!

Jean-Laurent CASANOVA

The ESID Prague Spring Meetings

Every May since 2002, the ESID Prague Spring Meeting has been organized in Prague, Czech Republic. The advantageous location of Prague between the Eastern and Western parts of Europe is used for the joint meetings of the specialists in primary immunodeficiencies from Eastern post-communistic countries and the scientists from the established centers in the West.

Both meetings organized so far were very successful, and already proved to provide the substantial help for both specialists and patients from the Eastern part of Europe. The report from the last

meeting, reprinted here, can be found on www.esid.org. The plans for 2004 are already in preparation. The meeting will take place in Prague, May 10-11, at the Institute of Immunology, Second Medical Faculty, Charles University, in Prague, Czech Republic. The major topics will be the early diagnosis and treatment of primary immunodeficiencies, the improvement of public awareness, the national registries in the countries of the participants, and latest developments in the field. All these topics, and the possibility of detailed discussion of difficult and unusual cases are of great importance to the improvement of the care for primary immunodeficiencies, particularly in Eastern Europe.

For information and to express interest to participate, please, contact me at annasediva @ hotmail.com.

Anna SEDIVA

P.S. The meeting will be followed by a bicycle trip Prague-Vienna under the leadership of Hans Ochs (this is not a joke, we definitely plan to do that, we 'll visit Martha Eibl's lab in Vienna, too!), so do come to Prague next spring!!

The 2nd ESID Spring School in Prague

Another delightful meeting of the ESID Spring School was held in Prague at the Motol Hospital in May 2003. There were 20 participants from 8 countries, namely the 3 primary immunodeficiency centres in the Czech Republic, Estonia, France, Macedonia, Lithuania, Slovakia, Sweden and the UK.

Topics ranged from the current status of the PID registers in Europe as well as the participating countries, safety and types of therapy including bone marrow transplantation and immunoglobulin treatment and several presentations on patients with unusual features and findings. The interrelationship of basic science and clinical findings in XLA, XLP and ALPS were also considered. Dr Anna Berglof presented an outline of the EUROPID project and explained the opportunities to benefit from this funding. The highlight of the 2 days was the plenary talk by Dr Anne Durandy on the defects in inherited models of class switch recombination and somatic mutation. She brought us up to date with the recent findings in HIGM 2, HIGM 4 and HIGM 5 in under an hour; a remarkable feat.

This meeting provides a forum for discussions of methods of diagnosis and protocols for treatment in which many participated. The lively discussion underlines the need for ESID-based, consensus protocols for these aspects of PIDs and the requirement for consolidation of the evidence basis as well as generation of new data.

The nature of this small meeting was once again friendly and informative, thanks to our hosts at Motol, Anna Sediva, Andrea Polouckova and their team. The extension of this spring school to new countries is most encouraging and the widening of the breadth of discussion indicates that these meetings are appreciated and useful. It is to be hoped that this excellent format will be repeated next year; what can be better than Prague in the spring.

It was disappointing that there was no commercial sponsorship available this year but we were grateful to the Ministry of Health, Czech Republic [Research programme 00000064203] and the EUOROPID grant [NAS QLRT 2001 02742] for support.

Helen CHAPEL
May 2003

Chyba! Záložka není definována.

Working Party reports

Registries Working Party

On May, 17th, 2003 the ESID Registry Meeting was held in Paris, France. Major issues were the presentation of further concepts concerning the ESID Online Database Project and discussing (brainstorming) several issues of interest.

Participants: Fred and Vicki Modell (NY, USA), László Maródi (Debrecen, Hungary), Bernd Belohradsky (Munich, Germany), Carrock Sewell (London, UK), Sean Rimington (Head of Patient registry of Australia and New Zealand), Gulbu (Chicago, USA), Hans Ochs (Seattle, USA), Jennifer Puck (NIH, USA), Charles Waller (PPTA), Menso Bult (PPTA), Paru (London, UK), representatives of Baxter including Karen Wijant, Bodo Grimbacher (head of ESID-registry), Dominic Veit (Freiburg, Germany)

For that day and meeting excused were: Helen Chapel (London, UK), Lennart Hammarström (Stockholm, Sweden), Alain Fischer (Paris, France), Nuria Matamoros (Mallorca, Spain), Stefan Ehl (Freiburg, Germany), Klaus Schwarz (Ulm, Germany), Graham Davies (London, UK) and Luigi Notarangelo (Brescia, Italy).

Agenda:

1. Presentation of the database project (Bodo Grimbacher)
2. Statement of the Patient Organizations (Fred Modell)
3. Statement of the PPTA (Charles Waller)
4. Statement of the American colleagues concerning IRB issues (Hans Ochs)
5. Discussion (brainstorming)

Ad 1) the PowerPoint presentation held by Bodo Grimbacher has been published on the ESID website (www.esid.org).

Ad 2) the Modell Foundation is in full support of the project, however, financial support can not be granted for the time being but may be available as early as September 2003.

Ad 3) PPTA Europe has approved to finance major parts of the project. However, approval of PPTA World is expected for the last week of June. Any contract of PPTA with ESID can go from there on.

Ad 4) Hans Ochs pointed out that one way to address recent IRB issues is to have patients register to any given database, and have their physicians 'just' approve their entries and add the laboratory values.

Ad 5) Steering committees for each disease specific patient registry shall be founded. A preliminary list of volunteers is attached (see below). Interested physicians: please contact Dr. Grimbacher at Grimbacher @ mm61.ukl.uni-freiburg.de!

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please let us know if anyone volunteers in addition to these people!

A discussion of the "5 c's" (confidentiality, control, cost, continuity and compliance) has been initiated. The confidentiality issues have been addressed in the project. The database will be pseudo-anonymized (only the patient's physician can match a specific dataset with his/her patient – however, longitudinal analysis of the data can be achieved) and the patients consent will be obligatory. Moreover, each documenting center will need to get ethical approval from their local IRB-board.

The control will be addressed by regular updates on the ESID website to ensure transparency to the public.

The cost shall be distributed between the pharmaceutical companies and the patient organizations (Modell and PIA, IPOPI). Any financial contribution from research programs (e.g. EU) is welcome.

The continuity is secured for the upcoming 4 years. However, it is the specific aim of the project to be in place for an indefinite time.

To address compliance, the idea came up to audit the participating physicians practice. Moreover, certain incentives for the documenting centers have been discussed, including financial compensation for the secretarial work to enter the data.

It has been proposed that the registry may also be designed as "patient's registry", where patients can register and access their own therapy data.

Relating to Patient's consent it has been suggested that legal issues may be solved Europe-wide. E.g. in Australia no consent must be given for a date prior to the new rules established recently.

As of fund raising, EU money may be applied for in the future.

For cases not classifiable into the known PID diseases, there should exist an "unknown" registry to collect the data.

Finally, the support for the registries should be bottom-up: it should raise from patients over patient organizations to industrial companies.

Freiburg, June 16th 2003
Bodo GRIMBACHER

Dear Colleagues,

the ESID registry working party has made major steps towards an "ESID Online Patient- and Research-Registry".

We are about to develop a multi-centred data collection system in European and Non-European countries for patients with Primary Immunodeficiencies. The data collected in the participating centres shall be pseudonymized and thereafter be entered and made accessible in a central online registry. The registry will consist of multiple 'disease-specific subregistries'.

Data from e.g. national registries will be automatically tranferrable to eliminate

the need of a second registration. The system will enable the user to enter any data at any time for any visit.

We are asking for yearly updates of the records. With PPTA, the major financial sponsor of this project, we are about to arrange a financial compensation for the use of secretarial help for the documentation.

For this project, ESID is asking for support from all physicians and researchers involved in the diagnosis, care, treatment, and support of patients with PID!

The bonus system is set up as follows:

*ESID suggests to compensate for secretarial assistance with 5€ per documented patient for whom a core dataset (red fields) has been documented and 10€ for each documented patient for whom an extended dataset (blue fields) has been documented.

*In addition, there shall be an annual award for the five best publications of the five disciplines (Antibody deficiencies, T-cell or combined deficiencies, Phagocytic disorders, Complement disorders, Other PIDs) within PID using data of the ESID registry of about EUR 2.000,00 per publication and an extra award of EUR 5.000,00 for the best publication over all.

*Furthermore, a center which has reached a specific number of documented patients shall be rewarded by travel grants to either the ESID summer school or the biannual ESID scientific meetings. Free registration to the meetings is also being discussed.

*Each center may install the database locally to be able to work with personalized data, since the application will be able to generate patient reports to be sent e.g. to the home-physician. In addition, the database will support features like 'recall functions' which will remember the physician if a patient has not shown up for his/her regular follow-up visit.

*There will be a patient consent to be signed to ensure that the patient supports the initiative. It will be the centers' responsibility to obtain the patient's consent. However, all PID patient organizations so far supported this project since it is designed to increase awareness and diagnosis of PID and to facilitate research in the field.

We are prepared to provide you with all documents you will need for patient's consents and ethical approvals!

Please reply to this email whether or not you are still working in the field of PID and willing to contribute your patients to such a registry:

YES / NO
I am still working with PID patients.

YES / NO
I am prepared to document my patients into a new ESID Online Registry after obtaining the patient's consent. I understand that it is my privilege to decide what data I would like to share with other researchers and what data shall be only viewed by my center.

Please reply as soon as possible, but before October 1st, to the following email address:

frisch@medizin.ukl.uni-freiburg.de

Thank you for your collaboration!

Bodo GRIMBACHER,
head of the ESID registry

& Barbara FRISCH,
Database-Monitor for the
ESID registries working party

Education Working Party

The ESID Summer School will soon take place in Portugal again (September 25-29). There were a lot of applicants, and selection was not easy. We tried to be as fair as possible, and selected the following applicants: Carmen Bonfim from Brazil, Chiara Caldiani from Italy, Beata Derfalvi from Hungary, Rasa Duobiené from Lithuania, Melinda Erdös from Hungary, Eleonora Gambineri from Italy, Manuella Gomes from Germany/Brazil, Maria Ana Gonzalez del Castillo Campos from Spain, Filomeen Haerynk from Belgium, Manfred Hönig from Germany, Christoph Königs from Germany, Emanuela Laicini from Italy, Bénédicte Neven from France, Jena Pachlopnik from Switzerland, Olga Paschenko from Russia, Carolina Prando-Andrade from Brazil, Ellen Renner from Germany, Pavel Rozsival from the Czech Republic, Elisabeth Sarmiento from Spain, Anna Shrimpton from the UK, Radek Špíšek from the Czech Republic, Tuba Turul from Turkey, Pim van der Vossen from the Netherlands, Adilia Warris from the Netherlands, Anna Yurasova from Russia, Carmen Zarate from Mexico, Paula Klemetti from Finland, and Susana Lopes da Silva from Portugal.

We hope and trust the Summer School will this year be as much of a success as it was in previous years!

Anders FASTH
Teresa ESPAÑOL
Esther DE VRIES

Clinical Working Party

Guidelines for diagnosis of patients with primary immunodeficiencies, jointly established by Amos Etzioni and Luigi Notarangelo in Europe and Mary-Ellen Conley in the United States, have been greatly appreciated worldwide. It now appears that guidelines for therapy would be appreciated by many colleagues in the field. However, such guidelines are more difficult to establish, not only because therapeutic decisions are generally best taken on a case by case basis, but also because "official" guidelines may cause ethical and perhaps legal dilemmas, for those of us who may wish to follow different options.

The Clinical Working Party of ESID initially piloted a study of treatment guidelines for Wiskott-Aldrich syndrome and this received a very good response from ESID members. The survey showed that different centers vary considerably in the way that they treat patients with WAS but it also emphasised the need to establish robust prognostic features before more consistent treatment guidelines can be produced. The results of this survey have been collated and a manuscript acknowledging all contributors has been submitted for publication.

The Working Party has now decided to conduct a survey on the treatment of ADA-SCID. Unlike most forms of SCID, where the ultimate treatment option is haematopoietic stem cell transplantation (HSCT), ADA-SCID can also be treated by PEG-ADA therapy and more recently by gene therapy. Thus, a variety of choices are available to treating physicians, and it would be of great use to understand what options are chosen by different centers, and the reasons for those choices. Therefore, **we want to ask you again to fill in a questionnaire**, which we hope will not take up too much of your time...

Based on your responses to the questionnaire below and the opinion of selected experts on ADA-SCID in Europe and the Americas, we will write a report of what is currently being done. Again we hope this report will be published in the ESID Newsletter or submitted to an international journal (e.g. Clinical Immunology). We expect that we will carry out similar surveys for other conditions in the near future.

Thank you in advance for your contribution!

Jean-Laurent CASANOVA
Bobby GASPAR

Questionnaire re: guidelines for ADA-SCID

These questions concern the treatment of a child with clinical and immunological features of typical ADA-SCID (85-90% of all cases), as defined by peripheral blood autologous lymphocytes below 100/mm3 and lack of response to mitogens. We are assuming that all children will be placed on immunoglobulin, and anti microbial prophylaxis as for all SCIDs. With regard to transplant, the questions relate to whether you would perform a transplant or not; please do not address what sort of transplant would be performed (i.e. conditioning/T cell depletion, as those questions/guidelines will be dealt with by the BMT Working Party)

To start with, please answer the following questions:

How many ADA patients have been followed at your PID clinic since it was established ?

How many ADA patients are currently being followed at your center ?

ADA-SCID guidelines questionnaire
(please choose "Y or N" within each question if you feel this is appropriate)

1. If a match sibling donor (MSD) was available, would you:
A. proceed to haematopoietic stem cell transplant (HSCT) Y/N
B. treat with PEG-ADA Y/N

2. If no MSD but a phenotypic matched family donor (MFD) was available, would you:
A. proceed to haematopoietic stem cell transplant (HSCT) Y/N
B. treat with PEG-ADA Y/N
C. look for an unrelated/cord blood donor Y/N

3. For questions 1 and 2, if the child was in a poor clinical state (defined by serious infection *or* failure to thrive *or* organ damage), would you initiate PEG-ADA prior to transplant?
Y/N

4. If the answer is no, what is the reason:
A. concerns regarding effectiveness of PEG-ADA Y/N
B. concerns regarding side effects Y/N
C. concerns regarding expense Y/N
D. concerns regarding impact on success of HSCT Y/N
E. other reason: .....

5. What criteria would you use to define a successful response to PEG-ADA:
A. good clinical response with weight gain, clearance of infection Y/N
B. increase in absolute lymphocyte count > 1000 cells/mm^3 Y/N
C. CD3 count >500 cells/mm^3 Y/N
D. CD4 count >300 cells/mm^3 Y/N
E. proliferation to mitogens Y/N
F. production of IgG/A/M Y/N
G. production of T cell antigen specific responses Y/N
H. production of B cell antigen specific responses Y/N

6. If no MSD or MFD is available, would you initiate an unrelated or cord blood donor search? Y/N

7. While waiting for an unrelated, cord blood or a parental donor transplant would you start the child on PEG-ADA? Y/N

8. If the answer is no, what is the reason?
A. concerns regarding effectiveness of PEG-ADA Y/N
B. concerns regarding side effects Y/N
C. concerns regarding expense Y/N
D. concerns regarding impact on success of HSCT Y/N
E. other reason .....

9. If a fully matched unrelated donor (MUD) (inc. unrelated cord) was available, would you:
A. proceed to HSCT Y/N
B. start/continue with PEG-ADA Y/N
C. wait for a better donor (eg MSD/MFD/MUD) Y/N
D. enroll into gene therapy trial Y/N

10. If only a mismatched unrelated donor (mMUD) was available, would you:
A. proceed to HSCT Y/N
B. start/continue with PEG-ADA Y/N
C. enroll into gene therapy trial Y/N
D. wait for a better donor (eg MSD/MFD/MUD) or proceed to a haploidentical parental donor transplant Y/N

11. If only an unrelated mismatched cord blood was available, would you:
A. proceed to HSCT Y/N
B. start/continue with PEG-ADA Y/N
C. enrol into gene therapy trial Y/N
D. wait for a better donor (eg MSD/MFD/MUD) or proceed to a haploidentical parental donor transplant Y/N

12. If only a parental donor was available, would you:
A. proceed to HSCT Y/N
B. start/continue with PEG-ADA Y/N
C. wait for a better donor (eg MSD/MFD/MUD/mMUD/cord blood) Y/N
D. enroll into gene therapy trial Y/N

Thank you for completing the questionnaire!

Please send your responses to Bobby GASPAR
by Fax (44 207 831 4366) or e-mail (h.gaspar @ ich.ucl.ac.uk)

Focus on a country:

Established member Q & A
Ozden Sanal
Immunology Division
Hacettepe University Children's Hospital
Ankara, Turkey

Can you give me some information about your background and can you tell something about your carrier history?

After I graduated from Medical School in Ankara, I started my pediatric training and finished it in the Pediatrics department of the same Medical School. I started my Pediatric Immunology training at Immunology Division, Hacettepe University Children's Hospital in Ankara headed by Dr. A.I. Berkel. After working there for about a year, I continued my education between 1974-76 with Dr. Rebecca Buckley at the Division of Allergy & Immunology, Dept of Pediatrics, Duke University Medical School. During my training at Duke University, I carried out research on lymphocyte subsets and ADCC in patients with primary immunodeficiencies (e.g. XLA, CVID, SCID, HIGM and WAS) and investigated which population was responsible for the cytotoxicity using different targets and different lymphocyte populations. This study, along with another one (which was related to three infants with SCID whose features show that SCID may result from several different biological errors), made me realize how heterogeneous the lymphocyte subsets and immunodeficiencies may be as far as the underlying defects and clinical and laboratory phenotypes are concerned. These studies also gave me the opportunity to follow-up several different immunodeficient patients.

After I went back to my own country, I continued to work at Immunology Division of Hacettepe University Children's Hospital with Dr. A.I. Berkel and Dr. F. Ersoy. I actively participated in the study on the localization of the AT gene at UCLA working with Dr. R.A. Gatti between 1989-90.

We have been running a pediatric immunology clinic and a lab at Hacettepe Children's Hospital all this time.

How did you become interested in immunodeficiencies?

I spent quite a long time in the Hematology-Oncology department during my training in Pediatrics. My interest in immunodeficiency began with my interest in the neoplasms of the immune system, mostly ALL. At that time, lymphomas and leukemias had traditionally been classified on the basis of morphology and clinical features. As the clinical features and the outcomes could be determined by the type of the cell affected, the effect of the type of the involved cells on the clinical and laboratory features and prognosis was my first project during my pediatric training. The broad range of immune mechanisms being involved in a wide range of diseases was also receiving my attention.

After I began to see patients with immunodeficiencies (ID), I realized that the number of defects underlying these diseases might be numerous, and I got interested in mostly primary IDs. I thought each patient would teach us something, and the study of immunodeficiencies would give a clue about the mechanism of development and function of the immune system.

What have been your achievements in research and patient care in the field of immunodeficiencies?

My research interest has been mainly clinical investigation, diagnosis and treatment of primary immunodeficiencies, although I carried out or participated in some basic research also.

Hacettepe University Children`s hospital has been a major referral center. As the consanguineous marriage rate is rather

high in my country, we had the chance to see many ID patients in our Immunology Division, even the very rare ones, particularly of course concerning the AR forms. Ataxia-telangiectasia (AT) patients comprise the majority among our primary immunodeficiencies and we have several publications on this disease.

I think I and my colleagues (Dr. A.I. Berkel, Dr. F. Ersoy, Dr. I. Tezcan) contributed to the identification of genes responsible for rare immunodeficiencies by diagnosing and noticing the differences in presentation and unusual features, in collaboration with centers equipped with basic science research tools for individual immunodeficiency diseases. The first case of C1q deficiency, Griscelli diseases with MyoVa, Rab27, mlpl, MyoVa exon F defects, IL-12Rb1 defect, different forms of HIGM, ALPS, variant AT, and CD3g deficiency were described in this context.

I remember a patient when I was working at Duke University, who had disseminated atypical mycobacterial infection without a demonstrable ID; he died of infection despite antimycobacterial and transfer factor therapy. That patient impressed me a lot, and I wished that the defect could have been detected and the patient cured. About 15 years later, I had a chance to see a patient with a similar clinical course, this time having a problem with BCG and whose defect has turned out to be IL-12Rb1 deficiency.

During the late 70s and early 80s, most of the primary immunodeficiency patients died without a diagnosis, since these disorders were rare; they comprised a minor portion of health problems ,and immune deficiencies were not well known by physicians. I remember a patient who was the 16th child in a family with 14 siblings dying in the first few months of life. Now, there are many referrals from peripheral hospitals. I believe our center played a significant role in training physicians to suspect and recognize immunodeficiency disorders.

Now, our BMT unit - which was established and is run by Dr. Tuncer, Dr. Tezcan, and Dr. Uckan - give our ID patients (particularly those with SCID) a chance for cure since 1996.

What kind of developments in immunodeficiency do you expect in the near future?

Although gene defects associated with the majority of IDs are known, the pathogenesis of many immunodeficiencies is still unknown at the molecular level. Understanding the mechanisms of immunodeficiency diseases will enable us to treat the patients better, and will lead to novel therapies.

I think the effects of the modifier genes and the genetic compositions in the place of the phenotypes of the patients will be better understood. Patients who are vulnerable to various infectious agents with normal results of routine immunologic workup will reveal new molecular defects. Lastly, being a physician who sees and follows hundreds of AT-patients with neurological deterioration, the most serious feature both for patients and parents, I hope neuronal stem-cell therapy for AT patients will make cure possible, even for those who have already developed neurological defects. Knowledge about regulators of stem-cell proliferation factors controlling cell lineage determination, differentiation and stem-cell based transplantation therapy will show rapid development and may help in this.

What is your advice for young people who want to launch their carrier in ID?

Knowing that immunodeficiency diseases profit from advances in basic sciences and being an MD, I would have advise for MDs:

·Learn the spectrum of each ID-disease and the underlying mechanisms well

·Have training in basic science and be involved

in full-time research for several years at least during your early years of training,
·Continue to extend knowledge in basic science attending basic science courses whenever possible
·Teach the collaborating PhDs some clinical sides of the IDs

And -last but not least- what does ESID mean to you?

ESID is an excellent forum in the field of immunodeficiency: to find colleagues experienced on a subject you are interested in, to discuss with them in a friendly atmosphere on mutual subjects, and to learn the new developments.

In the late 80s-early 90s every EGID meeting I attended led me to identify new ID patients with unusual features or very recently recognized (even unpublished) ones!

O.S

Young Investigator Q & A
Tuba Turul
Immunology Division
Hacettepe University Children`s Hospital
Ankara, Turkey

Can you give me some information about yourself and your background?

My name is Tuba Turul and I am 33 years old. I was born in Antalya, Turkey.

Can you tell me something about your career history?

After I graduated from Hacettepe University Medical School, I started my residency in pediatrics at the Children's Hospital in İzmir and continued my residency at Hacettepe University Children`s Hospital and finished it in 2001. Since 2001, I've been working as a fellow in pediatric immunology at the Pediatric Immunology Department of Hacettepe University.

How did you become interested in immunodeficiencies?

When I was a 3rd year medical student I was greatly impressed by the microworld of the immune system. However, I wanted to be a pediatrician first. I decided to specialize in immunology during my rotation at the immunology department, which was part of my residency program. I thought that the pathways of complex interactions between different cell types could be highlighted by studying immunodeficiency diseases.

What have been your achievements in patient care and /or immunodeficiency research up to now?

I studied in vitro lymphocyte proliferation responses against different stimulatory agents, to define lymphoproliferative response patterns to various stimuli in T-lymphocyte deficiency diseases as my residency thesis.

After starting as a fellow in immunology, I participated in several projects - among them antibody responses to conjugated pneumococcal vaccine in patients with A-T, the screening of patients with disseminated BCG infection, tuberculosis and non-tuberculous mycobacterial infections for IL-12Rb1 or IFNgR expression.

During my fellowship program, I had the chance to follow many patients with SCID, and got familiar with performing and interpreting the various tests used for evaluation of immunodeficient patients (e.g. flow cytometric analysis of lymphocyte subsets including IL-12Rb1 expression, lymphocyte proliferation, detection of cytokine polymorphisms).

I am also involved in the follow-up of stem-cell transplanted immunodeficiency patients, and the changes in their immune parameters. I have submitted a project on Toll-like receptor 4 polymorphisms in children with gram negative infections.

What do you hope to achieve in the future?

At the present, I am practicing mostly clinical immunology. After I have completed my fellowship program I would like to have more training in immunology genetics.

How are you planning to reach this goal?

Hard work is the first requirement. The guidance of my senior and experienced colleagues will be very constructive. As soon as my fellowship program has finished, I would like to spend some time on immunology genetics and to participate in a research in a laboratory specialized on this subject.

What does ESID mean to you?

I learned from my senior colleagues that ESID presents a great opportunity to exchange ideas, to discuss the subjects you are interested in and to learn new developments. I haven't had a chance to attend an ESID meeting yet. However, I have already applied to attend the Summer School of ESID that will be held in Portugal in September 2003 (and her application was successful – editor).

What would you want to change if you were president of ESID?

I have no idea yet. I may be able to answer this, when I get to know how it works.

T.T.

Preparation for the upcoming ESID/INGID/IPOPI meeting to the held in Versailles, October 21 to 24, 2004 is ongoing !

According to a recent visit to the site, the scene should be great .

The scientific program will be built next fall, then call for abstracts will be launched at the very beginning of the year 2004. So you still have some time to perform the work you wish to present .

A local scientific committee* will make proposals for the program to be discussed with the ESID Board. We'd like to see presented a combination of physiopathology and clinical studies, based as often as possible on collaborative ESID projects.

The company selected for meeting organisation is "Albine Conseil". The person to contact if you wish is Mrs Florence POUPLOT – 67, Rue Anatole France – 92309 LEVALLOIS PERRET Cedex – Tel : 33 1 41 05 94 16/Fax : 33 1 41 05 94 19 – e-mail : florence@albine-conseil.fr.

Any suggestion for the meeting organisation is most welcome !

** Scientific Committee listing :*
Stéphane BLANCHE, Jean-Laurent CASANOVA , Marina CAVAZZANA-CALVO, Henri DE LA SALLE, Geneviève DE SAINT BASILE , Jean-pierre DE VILLARTAY , Anne DURANDY, Olivier HERMINE, nçoise LE DEIST, Yves LEVY, Eric OKSENHENDLER, Frédéric RIEUX-LAUCAT, Claudine SCHIFF, Reinhard SEGER, Naomi TAYLOR.