ESID Newsletter

Reminder call for membership fee payment 2008-2009 !!

European Society for ImmunoDeficiencies

2008-2

ESID Newsletter

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

It is published under the responsibility of the ESID Board, and at this moment it is edited by Esther de Vries (editor in chief), Lucia Bianchi, Ales Janda, Gustavo Lazo, Nima Rezaei, and Crina Samarghitean.

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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Please only use my *new email address*: esid@ estherdevries.nl

Front page: flying in spring ...

Dear ESID members,

Spring has really started here in the Netherlands with lots of sun and pleasant temperatures! The seagull you see on the front page is enjoying it too. I hope we will have as much sun in October, when the ESID will meet in `s-Hertogenbosch, and where I hope to see you all.

Again, this ESID Newsletter shows you the activities of our Society, and more. Please read about the repeated call for candidates for ESID Board functions, and also, please pay your membership fee if you haven't yet done that. Without your payment, ESID cannot do what as much as it would want to.

In the PID-care in development section, you find an interesting contribution from Bosnia and Herzegovina, and the ESID junior editors have once more done their best in the Interesting papers, Interesting cases and Young Researchers' Corner sections of this issue.

Best wishes to all of you,

Esther DE VRIES

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. The aims of this society are, among others, to facilitate the exchange of ideas and information among physicians, scientists and other investigators who are concerned with immunodeficiencies and to promote the research on these diseases. Anyone who is interested in primary immunodeficiency diseases can become a member of ESID. Registration is possible online at www.esid.org/members.php.

Within ESID, seven Working Parties are actively engaged in coordinating the member's joined efforts in patient care and research in primary immunodeficiency diseases: Stem cell transplantation and gene therapy (chair: Mario Abinun), Registries (chair: Gerhard Kindle), Clinical (chair: Bobby Gaspar), Genetics (chair: Naomi Taylor), Education (chair: Andrew Cant), PID-care in development (chair: Laszlo Marodi), and ESID *juniors* (chair: Eleonora Gambineri). 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 /board.php).

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 was compiled until 2002. However, given various shortcomings of this registry, ESID decided to develop a new state-of-the-art database for primary immunodeficiencies. This online registry was launched in 2004 and contains subregistries for more than 150 primary immunodeficiencies. It combines both clinical and laboratory data of PID patients and offers the possibility to document genetic data as well. Up to date, more than 5,500 patients have been registered in that database. Information, database statistics and a demo version of the registry can be found at www.esid.org/registry.php, or send an email to registry@esid.org.

The new ESID Online Registry is connected to the mutation databases (IDbases) in Tampere, Finland. These were created since 1995, when the first locus-specific immunodeficiency mutation database accessible through the internet was established (BTKbase for X-linked agammaglobulinemia). Since then, more than 100 additional locus-specific databases have been established. Information is available at http://bioinf.uta.fi.

ESID organizes a biennial congress to facilitate international contact between primary immunodeficiency specialists. The last congress was organised in 2006 in Budapest, Hungary , and the next one will be October 16-19 in `s-Hertogenbosch, The Netherlands, in 2008. Information is available at www.esid2008.org.

= ESID Information =

President's letter

Dear All,

It is with great pleasure that I invite you all to submit abstracts to and attend the upcoming ESID meeting to be held in the Netherlands in October.

Esther de Vries and her colleagues of the scientific committee, together with the ESID board, have come up with an exciting and timely program that covers both conventional and novel topics in basic immunology and primary immunodeficiencies.

I would like to draw your attention to a novel workshop, "Primary Immunodeficiencies beyond Europe and North-America", i.e. in Latin America, Africa, Asia, and Oceania. This international workshop is one of the many novelties of the next ESID meeting.

Along these lines, we were delighted to learn that our African colleagues, under the leadership of Pr Aziz Bousfiha from Casablanca, Morocco, have organized the first international meeting of the African Society for Immunodeficiency (ASID).

The ASID is a sister society of the ESID and its first meeting will take place in Casablanca on October 30-November 1st, 2008. To foster the collaboration between ESID and ASID, it is essential that many ASID members attend the ESID meeting, … and vice versa!

I look forward to seeing you soon in the Netherlands and in Morocco.

All best wishes,

Jean-Laurent CASANOVA

Treasurer's report

— REPEATED MESSAGE —

Dear ESID members, it is time to pay your membership fee for 2008-2009. The amount you have to pay is the same as for 2006-2007. If you haven't yet paid 2006-2007, you will have to do this first!

It will not be possible to register as a member for the `s-Hertogenbosch meeting if your membership fee has not been paid in time. The congress organisation will check this before sending you your invoice, and will charge the non-members registration fee if you haven't paid your ESID membership fee 2008-2009. You can correct that, but if you do that after the early registration deadline, you will be charged the late registration fee for the meeting, albeit the fee for members.

So, don't forget to pay in time, and join us in October in `s-Hertogenbosch !!

— REPEATED MESSAGE —

Up to now (May 6) only 90 members have paid their membership fee 2008-2009. Please all take the time to pay your membership fee !!!

Esther DE VRIES

News & Views

ESID Elections for Board members are on the way — candidates needed !

According to our present Constitution, all candidates who are elected as officers of ESID are elected for a term of 2 years, once renewable. Only the treasurer can be elected for a total of 8 years. The president-elect is elected 2 years before his/her office starts, and biennial meeting presidents are elected 4 years before the meeting, and remain part of the board for 2 years thereafter. ESID Board members have to be ESID members, and the president has to be an ESID member of two years standing.

The following people can be re-elected for their office for another term of 2 years:
* President: Jean-Laurent Casanova
* Secretary: Bodo Grimbacher
* WP Registries: Gerhard Kindle
* WP Genetics: Naomi Taylor
* WP Education: Andrew Cant
* WP PID-care in development: Laszlo Marodi
* WP ESID*juniors*: Eleonora Gambineri

It is possible for alternative candidates to put themselves up for election.

The following people cannot be re-elected for their present office anymore:
* Treasurer: Esther de Vries
* WP SCT&GT: Mario Abinun
* WP Clinical: Bobby Gaspar

The following offices have to be filled:
* President-elect
* Meeting president 2012

All ESID members are heartily encouraged to put themselves up for election ! Please send your application with photo, for publication in the Newsletter and on the News section of the ESID website. ***Deadline is June 1, 2008.***

The ESID Board

April 13, 2008

Dear friends,

I ask your support for my candidacy as President of ESID.

Following my residency in Pediatrics, I did a fellowship in immunology in Philadelphia. Upon my return to Haifa I founded the first Primary Immunodeficiency Center in Israel. Currently I am the director of the Meyer Children's Hospital in Haifa and the Head of the Jeffrey Modell Foundation Center for Primary Immunodeficiency in Haifa. I'm a professor of Pediatric and Immunology at the Rappaport school of medicine at the Technion (the Israel equivalent for the American MIT), and the co-author of more than 200 peer reviewed articles, review papers and chapters in books exclusively on primary immunodeficiency subjects.

I'm a member of ESID for many years from the time it was called EGID (European Group for Immunodeficiency) and was the first chairperson of the therapeutic working party and a Board member from 1996 to 2000, a year in which I organized the ESID meeting in Geneva which was a successful meeting.

As the president of ESID, I would try to continue the wonderful work done by our previous presidents, Reinhard, Alain, Edvard, Luigi and Jean Laurent. My aim is to increase the awareness of PID in the European community mainly in those countries in which PID are not well recognized. I will work in close collaboration with the various working parties mainly genetic, data base and clinical. I will continue to increase contacts with other societies in Europe and the Americas which are interested in PID. I really believe that through ESID, Europe is the leading force in the field of PID, and I hope to be able to keep it that way in the future.

Amos ETZIONI

Hello to everyone!

I am Eleonora Gambineri from Florence, Italy and I would like to candidate for the ESID Treasurer post.

For those who don't know me: I am a physician and I've received my medical training at the University of Florence. I did my research fellowship in the States at the University of Washington under Professor Hans Ochs. Currently, I'm working as assistant professor at the Department of Paediatrics of the University of Florence, "Anna Meyer" Children's Hospital.

During the past 2 years, I have headed the ESID Junior working party. Needless to say that this was a great experience! Trying to gather a group of young people interested in PID and willing to get involved into ESID activities was really challenging, but lots of fun too! It was also a wonderful opportunity for me to learn interacting with several other junior members as well as seniors…a wonderful "growing up" experience!! As head of the ESID Junior working party I started to be engaged in the executive work of the ESID board. This was a unique chance that has enabled me to get introduced to a lot of new and exciting aspects on how to manage a Society. At first I was amazingly looking at the senior board members busy in the organization of the ESID meeting or establishing connections with sponsors and promoting the educational training and I was trying to gain as much as possible! Then I found myself to be actively part of it and I started to get moving on my own. I figured that the best way to raise the juniors' interest in the field of PID was to foster exchange of ideas and experiences and to establish connections among junior members around different countries. I started to look for sponsors to fund short-term exchange programs for young trainees to spend periods in other units in Europe. I have therefore talked to several industry representatives with the purpose of raising money to promote the "growth" of young physicians or researchers in the field of PID. While doing that, I have realized how exciting and important it is to constantly look for financial opportunities to support our excellent Society. In particular I think that the effort to encourage and sustain the educational activity is a good investment in the "future". Managing money and getting everything organized is a great responsibility and a lot of work and one really needs to be dedicated to it. However, I think that it is really appealing too! On this regard, I must say that Esther did a great job serving ESID as Treasurer and she has been and still is a great mentor for me.

My involvement with ESID over the past two years has fascinated me very much and after this experience I feel to be able to move forward in the field…I feel to be as a Junior "on the edge", maybe not as engaged as a senior, but senior enough to be steadily committed in PID. Therefore, since ESID has contributed a lot to my professional life, I would love to continue to serve this Society and have the chance to carry on the work as Treasurer. Looking for money is the most exciting activity, isn't it ??? Joking aside, the role of Treasurer will enable me to handle contacts, deal with sponsors and promote the future growth of the Society, somehow more firmly progressing what I have been working out for ESID Junior so far. I believe that looking for a financial support to specific programs is of great help to get actively involved and to fully believe in their development!

I am very motivated to work with enthusiasm and commitment and I am looking forward to participating on this aspect of the ESID life! Thus, I hope I can count on your vote and your support for the upcoming elections!

Eleonora
GAMBINERI

Dear Friends and Colleagues,

I ask your support for my candidacy as Chairman of the BMT and Gene Therapy Working Party

Following a clinical post in Immunology at Great Ormond Street Hospital in 1992, I became fascinated by severe congenital immunodeficiencies and their treatment by HSCT and the emerging discipline of gene therapy. I undertook a PhD in the Institute of Child Health and continued clinical and academic training at the same Institution. I was appointed to Senior Lecturer/Consultant in 2002 and to Professor of Paediatrics and Immunology in Oct 2007.

My clinical and academic interests are very intertwined and I am very involved in 1) the outcome of reduced intensity HSCT 2) the overall long term outcome including neuropsychological function 3) cellular therapies to improve transplant outcome and 4) the development of clinical trials of gene therapy for SCID. I have been an active member of the EBMT Inborn Errors WP over the past decade and have served for the last 3yrs as Chair of the ESID Clinical WP during which time I have directed a study on the outcome of HSCT for ADA-SCID and played an active role in the organisation of two ESID meetings including Budapest in 2006 and the forthcoming meeting in 's-Hertogenbosch.

If elected I would try to achieve the following objectives:

To establish HSCT outcome data for each specific molecular diagnosis as this may influence overall outcome. This will also determine not only where newer therapies such as gene therapy can offer improved alternatives and but also how transplant protocols can be improved
To establish common transplant protocols across different centres.
To develop and assess the role for cellular therapies including the use of virus specific CTLs, allodepletion strategies and MSCs
To standardise monitoring and outcome assessments such that follow-up data is compatible from different centres

I have recently been elected to the role of Chair of the Working Party for Inborn Errors within EBMT and if elected to this ESID post, then there would be a common chair person who could unite activities across both societies.

I thank you for your support!

Bobby GASPAR

Two important meetings for clinical immunologists have been held in Poland in 2007

The First meeting concerning the standardisation of cytometry in PID was organized on May 17 –18, 2007 in Poznan-Kiekrz. A project is under way to establish and evaluate harmonised guidelines for flow cytometric diagnostics in PID. This project is being implemented co-operation with Professor Jacques J.M. van Dongen from Erasmus University, Rotterdam. A standardised approach to the diagnostics of primary immunodeficiencies was presented at the meeting. The article on harmonising guidelines for flow cytometric diagnostics in PID was published in the *Central European Journal of Immunology, vol.32, 4 2007, 247-258.*

The 5th School of Clinical Immunology was held in Zakopane on December 13-15, 2007. The meeting was organised in accordance with grant PBZ-KBN-119-P05/2005from the Polish Ministry of Science, and with the Polish Academy of Science. It is a tradition, within the Department of Immunology at the Children's Memorial Health Institute, to invite young immunologists interested in clinical immunology from both Central and Eastern Europe. The School of Clinical Immunology has been a great success so far. The leading topics of meetings are the standardising of diagnostic and therapeutic guidelines in primary immunodeficiencies, and standardisation of flow cytometric immunophenotyping methods for PID. One of the sessions was dedicated to diagnostic and therapeutic standards in chosen primary immunodeficiency diseases. The highest number of participants from both Central/Eastern and Western European countries was recorded during this meeting. Young immunologists from ten European countries presented their own experiences concerning diagnosis and treatment problems in paediatric primary immunodeficiencies.

The School of Clinical Immunology has been organised every year since 2002, and is supported by the following European Union grants: PERFECT QLG1-CT-2002-90358 project, provided by the Paediatric Research Centre of Excellence – Focusing on Effective Child Treatment, 2002-2005; EURO-PID-NAS, 2002-2004, and EURO-POLICY-PID SP23-CT- 2005-006411, 2005-2008.

XIII Congress of the Polish Society of Experimental and Clinical Immunology will be held in Kracow, 14 – 17 May, 2008

With an outstanding list of foreign and Polish speakers in the field of basic mechanisms and clinical application, the XIII Congress of the Polish Society of Experimental and Clinical Immunology will be the key event of the year, as it is big enough for young immunologists from all Europe to learn from other disciplines. One the day after the meeting, on May 18, a meeting of the Polish Working Group for Immunodeficiency together with our colleagues from other European countries will be held, concerning the planning of future cooperation. There is no question that we need to come together and get inspiration. We warmly invite you to attend our congress. Information on the congress can be found at http://www.immuno2008.krakow.pl/, for more detail please contact us oddzial.immunologia@czd.pl

Ewa BERNATOWSKA

The first Spring School on Primary Immunodeficiency in China

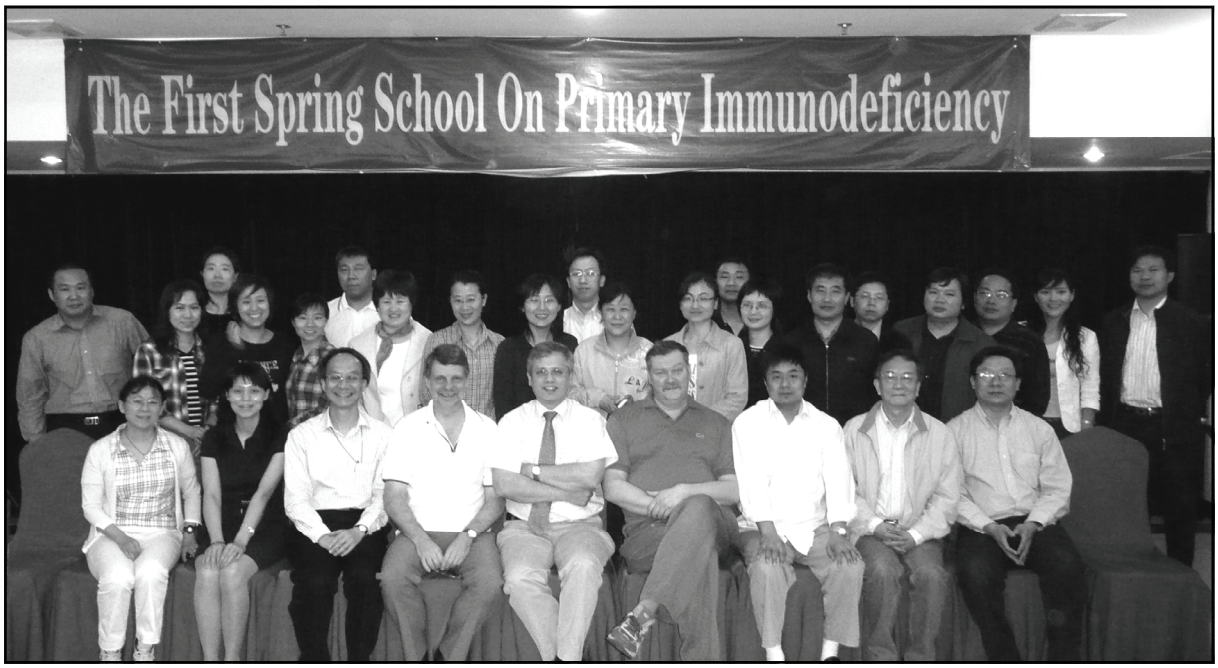
The ESID summer school has been a major success for a number of years. This has also led to the development of similar summer schools in the US, Australia and Latin America.

The PID field is still an underdeveloped area in China. Recently, two Jeffrey Modell centers have been inaugurated in China, the Beijing center, under the guidance of Prof. Xiaoming Gao and the Shanghai center, under the guidance of Prof. Xiaochuan Wang. However there is a great need for training of clinicians interested in PID.

We therefore organized the first Spring School on Primary Immunodeficiency in China, which was held in Sanya, Hainan Island, 22-25 Feb. The school was attended by 20 clinicians, part of the Chinese Pediatric Immunology Society, teachers from China including Professors Xiqiang Yang, Yu Lung Lau, Xiaoming Gao, Yingtong Xue and Xiaodong Zhao and teachers from ESID, including Professors Andrew Cant, Jacques van Dongen, Lennart Hammarström and Qiang Pan-Hammarström. The lectures focused on the diagnostic work up of patients with PID and numerous cases with PID were presented, showing a wide-spectrum of PID in China. The School was supported by a EU grant given to Professors Lennart Hammarström and Xiaoming Gao (PIDNET) and two pharmaceutical companies, Talecris (USA) and Biotest (Germany).

Judging from the course evaluation, the school was highly appreciated and was felt that it helped fill the void in knowledge. It was also felt that, like for the ESID summer school, there was a strong desire for repeating this exercise in the near future.

Qian PAN HAMMARSTRÖM



J Project Meetings in 2008 (23 to 27)

There will be another five J-project meetings in 2008: Ukraine (Odessa), Lyudmila Chernyshova, Apr 09-10, chernyshova@ukr.net; Bulgaria (Sunny Beach), Elissaveta Naumova , May 22-23, immun@sun.medun.acad.bg, Guergana Stoyanova, gal_ps@yahoo.co.uk; Bosnia-Herzegovina (Sarajevo) , Velma Mulaosmanovic, Oct 10-11, velmamulaosmanovic@hotmail.com; Republic of Moldova (Chisinau), Lyudmila Cerempei, Oct 31-Nov 1 , lcerempei@rambler.ru; Latvia (Riga), Tatjana Prokofjeva, Nov 27-28, monja@balticom.lv. You are all very welcome to join!

Laszlo MARODI

Primary Immunodeficiency Diseases Consortium CIS

The Primary Immunodeficiency Diseases Consortium will meet, organised by the Clinical Immunology Society on June 5, 2008, 8:30 am - 5:30 pm, in Boston, MA, USA. All ESID juniors are heartily invited to apply for a grant, for information send an email to Eleonora Gambineri at eleonora.gambineri@unifi.it.

EUROSCICON courses

At www.euroscicon.com you can find all kinds of interesting courses on immunological techniques.

Call for collaborations

Dear all, aAs you may know, our laboratory is interested in discovering novel primary immunodeficiencies. In particular, we believe that most pediatric infectious diseases result from novel primary immunodeficiencies. Thanks to your precious collaboration in the last 15 years, we have explored the following infectious diseases:

-mycobacterial diseases (BCG-osis, environmental mycobacteriosis, severe tuberculosis, corresponding to the syndrome of Mendelian predisposition to mycobacterial diseases and the IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1 and NEMO genes)

-salmonellosis (non-typhoidal in particular, corresponding to the same six genes)

-invasive pneumococcal disease (and/or staphylococcal disease, as seen in patients with anhidrotic ectodermal dysplasia with immunodeficiency, corresponding to the NEMO, IKBA and IRAK4 genes)

-and herpes simplex encephalitis (mutations in UNC93B1 and TLR3).

I write to you to inform you that we are expanding our field of investigation, by studying other infectious illnesses that attest of "holes" in protective immunity and strike otherwise healthy children normally resistant to most microbes. I have previously requested your collaboration for the first two following diseases, to which we recently added a few more:

-Congenital, isolated asplenia (without heart malformation)

-Chronic muco-cutaneous candidiasis (CMCC) without auto-immunity

-Classic, Mediterranean Kaposi's sarcoma of childhood (caused by HHV-8)

-Invasive, isolated and unexplained staphylococcal disease

-Whipple's disease of childhood

-Rhinoscleroma (caused by Klebsiella rhinoscleromatosis)

If you are following such patients, and if you are yourself very patient, I would be delighted to collaborate with you in the long search for the corresponding "infection-causing genes".

Thank you in advance for your trust and collaboration.

Jean-Laurent CASANOVA

ESID Registry Working Party Report

1. Novel features

1.1 Concomitant diseases and infections

So far, all subregistries in the ESID Database consist of a Core Dataset which contains data mainly on therapy, laboratory values and Quality of Life.

However, we have now realized that concomitant diseases as well as information on serious infections are essential for research on PID and should also be part of the standard entry forms available for all diseases.

We have therefore added these forms to the database in April 2008 (Fig. 1). Centers can now document their patients' concomitant diseases (neoplasms, autoimmunity, allergies etc.), infectious episodes (e.g. pneumonias) as well as the family history.

These new entry forms are not part of the "red" Core Dataset. This means they are not relevant for the annual bonus payments.

However, from a scientific perspective, ESID encourages all centers to document this data. Thereby, we will establish a valuable basis for identifying patient cohorts with common clinical features, which will benefit all participating researchers.

1.2 New design for the ICD-10 Tool

Concomitant diseases as well as infections are stored using the ICD-10 classification. The ICD-10 is the "International

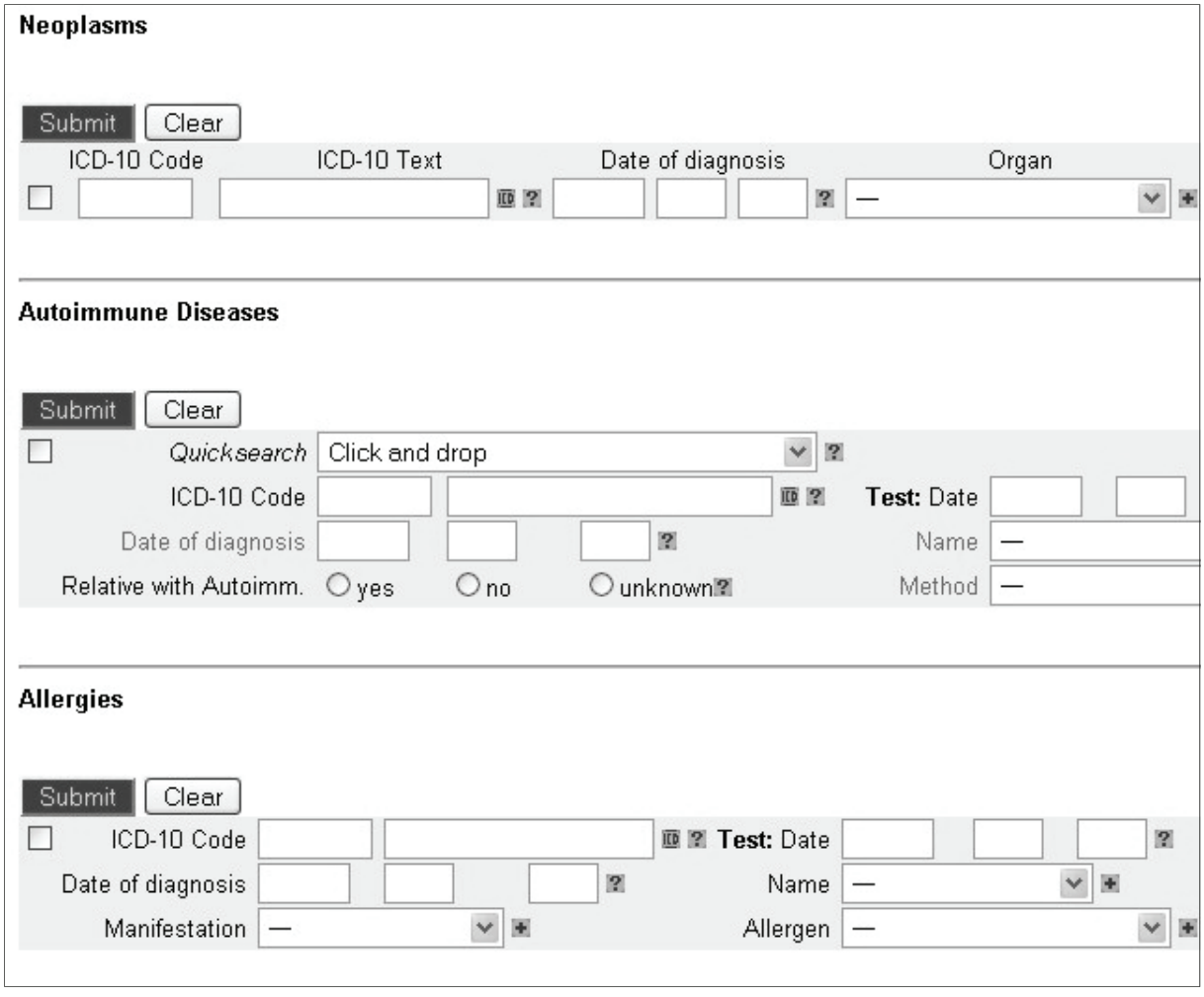


Fig. 1 Data entry forms for concomitant diseases

Classification of Diseases" set up by the WHO (www.who.int). It is the international standard diagnostic classification for all general epidemiological and many health management purposes. We have chosen this classification in order to standardise the documentation and facilitate evaluations.

Of course, we know it is impossible to know all ICD-10 codes by heart. Therefore, we offer tools to make the documentation as easy as possible. As you see in Fig. 2, there are two fields that must be filled in. They are labelled "ICD-10 Code". The first field contains the code (e.g. J15.9), the second one contains the standardised text (e.g. "Bacterial pneumonia, unspecified").

The drop down "Quicksearch" offers a selection of the most frequently used entries. This is the easiest and most direct way to document a disease: By selecting an entry, the fields are automatically completed with the respective ICD10 data. For all other entries, the user must click on the "ICD" button next to the fields. A box called "ICD-10 Wizard" pops up. After the user enters a search string, the wizard offers all matching entries which can be entered into the empty fields by selecting one entry.

1.3 Status and twin in Core Dataset

We have added the field "Status" to the Core Dataset pages. The field status should especially be filled in if a patient dies or if he is lost to follow up. This will help us in clearly identifying all patients who are still being followed at the centres participating in the database.

Another field we added is "Twin". This field should always be filled in when the patient has a twin brother or sister. Thereby, we are able to see which patients are really twins and which ones could be double registrations. Double registrations can occur e.g. whenever a patient grows up and moves from a pediatric to an adult department or when a patient is referred to a specialized center for diagnostics or HSCT. If you know of patients who have moved to another center and are not being followed by you anymore, we would be grateful if you inform us at registry@esid.org

Please only send the patient ID and the name of the new center, not the patient names, please.

In any case, please remember to ask new patients if they have already signed a similar consent form at another center before. If so, you should get in contact with us to sort out which center the patient should be best registered with.

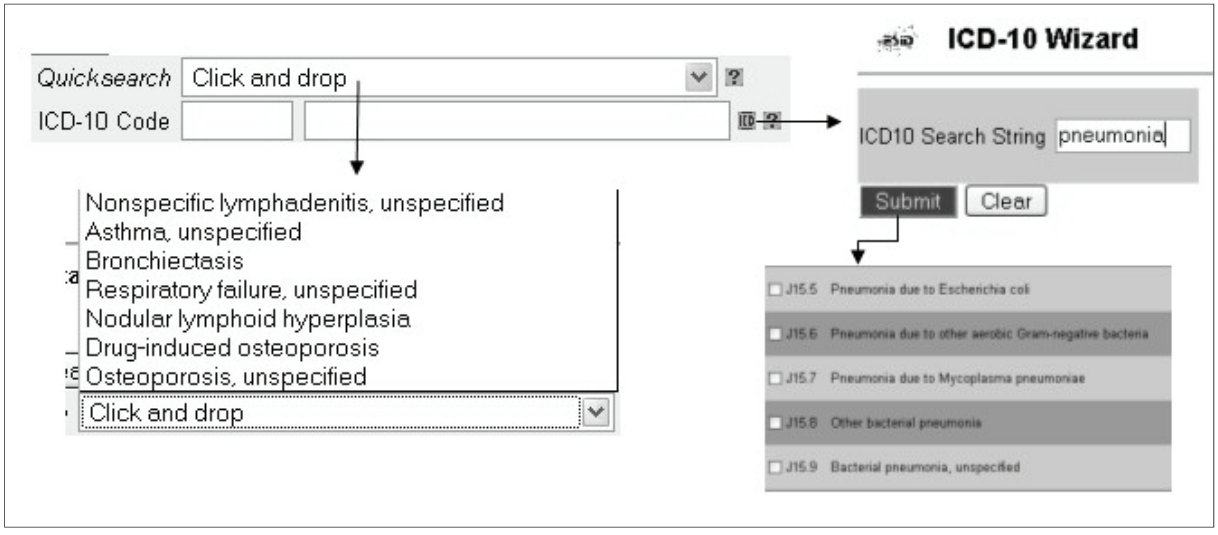


Fig. 2 ICD-10 search tools

1.4 New genetic defect: STAT3

Do any of your patients with Hyper IgE syndrome have a known genetic defect? We have recently added a new subregistry for HIES patients with STAT3 mutations, so all other HIES patients in the database are currently listed as "HIES with unknown genetic cause". Please inform us if any of your HIES patients should be moved to the STAT3 subregistry, or if there is another mutation that requires a new subregistry.

2. Documenting centers

2.1 New centers

Since the beginning of 2008, three new centers have joined the ESID Database. These are

· Antalya, Akdeniz University Faculty of Medicine Hospital (Coordinator: Olcay Yegin)

· Barcelona, Hospital Vall d'Hebron, Pediatric Infectious Diseases and Immunodeficiencies (Coordinators: Pere Soler-Palacin and Isabel Caragol)

· Ljubljana, University Children's Hospital (Coordinator: Tadej Avcin, Anja Koren Jeverica)

2.2 Overall situation

There are currently 72 registered centers participating in the ESID Database. Several of these centers represent national networks, such as AIEOP/IPINET (Italy), CEREDIH (France), Warsaw (Poland) and Brno (Czech Republic).

The centers in Frankfurt and Zürich have recently picked up documentation, which means there are now already 49 centers that have contributed patients.

More information on the centers, including contact details (for ESID members with a valid login) is available at www.esid.org/centers.php

2.3 Database training / workshops

These days, we are running several single-center workshops to train staff from participating centers in using the database. These workshops have shown to be very valuable and effective. They can take place both on site in the centers or in our

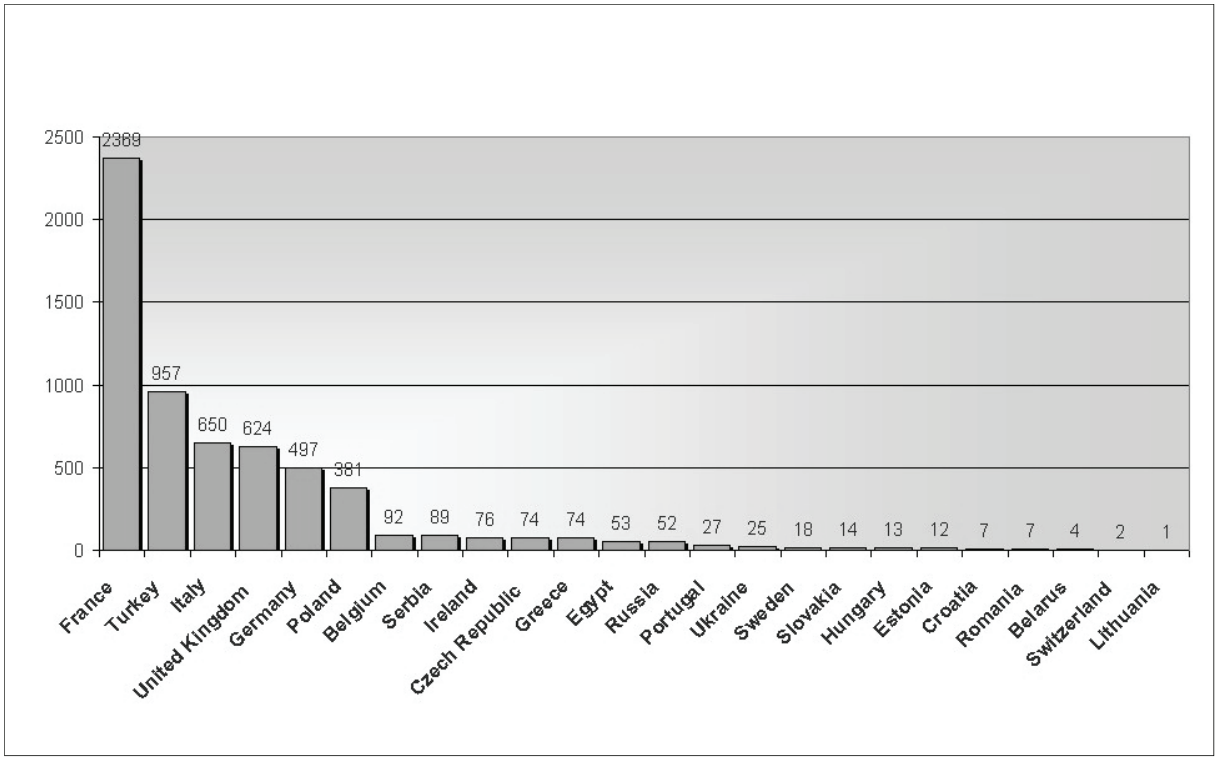


Figure 3: Patient distribution in the ESID Database by country

offices in Freiburg.

Centers which are interested in receiving database training should send a request to registry@esid.org

3. Current numbers

The total number of patients in the ESID Database as of April 28th, 2008, is 6118. Of these, 5520 are alive while 598 are deceased or lost to follow-up (i.e. there is no contact to the patient any more and so it is not known for sure whether the patient is still alive). Of all alive patients, 2334 currently receive Immunoglobulin replacement.

The French national center CEREDIH is still clearly showing the highest level of documentation with 2367 registered cases. More information on the distribution of patients is given in figure 3.

Further routinely updated statistical information on categories, diseases and age distribution as well as numbers on Ig-replacement are available at www.esid.org/statistics.php

4. Miscellaneous

The deadline for the annual bonus payment of 10 Euro per patient is June 30th 2008. As in the years before, we will evaluate the data on July 1st. All complete core datasets (red fields) for newly registered patients or follow-up visit dates will be rewarded with 10 Euro by ESID. We wish all centers happy documenting!

Last but not least, we would like to inform you that Anne-Marie Perner has left the Database team in January 2008 to take up a new position. Thanks for the great job over the years, Anne-Marie!

Gerhard KINDLE
Benjamin GATHMANN
registry@esid.org

Clinical Working Party

Dear All, as I may have mentioned in a previous ESID Newsleter, I am keen to understand the outcome of patients with XLP. It is over 25 years since the publication of a paper from Seemayer et al., which was the last documentation of the presentation and outcome of patients with XLP. That paper was published well before the SH2D1A (SAP) gene was identified as being defective in XLP (and before the identification of other genes repsonsible for an HLH phenotype) and well before the introduction of the HLH 94 protocol for treatment of patients with HLH. It is likely therefore that we can now make a more definite diagnosis of XLP and can identify patients who present in an atypical way. It would also be hoped that patients presenting with an HLH/FIM phenotype will have a better outcome than reported in the Seemayer paper (4% survival!). For these reasons we have produced the following questionnaire which hopes to understand the way in which patients present and are treated and also the overall outcome. We are also asking for HSCT details and outcome so that the transplant outcomes can be captured. This information will be invaluable for making evidence based decisions in managing these difficult patients and for informed counselling of families.

With time we hope to incorporate this questionnaire into the ESID registry but for the time being, a traditional paper questionnaire may yield more rapid data collection. Please send forms back to me by post/fax/e-mail. I have a very keen PhD student/clinical fellow, Claire Booth, working with me and she will help with data collection and analysis.

Many thanks for your participation!

Bobby GASPAR

Outcome of Patients with X-Linked Lymphoproliferative Disease (XLP)

Please send forms back by:

1) e-mail to: h.gaspar@ich.ucl.ac.uk

2) Fax to: +44 207 905 2810

3) post to: Prof Bobby Gaspar
Molecular Immunology Unit
Institute of Child Health
30, Guilford Street
London WC1N 1EH

Tel no: +44 207 905 2319/2289 (if required)

Completing physician:

Contact details:

Outcome of Patient with XLP

Centre: ……Patient identifier: …….

Sex: ……Date of birth: …….

1. PRESENTATION DETAILS

Age at referral/diagnosis: …….

Clinical History at diagnosis (please tick more than one if necessary):

HLH…….
With EBV……..
Without EBV……

Fulminant Infectious Mononucleosis (FIM)…….
Lymphadenopathy……
Hepatosplenomegaly……..
Bone Marrow hypoplasia……
Hepatitis……
Other organ involvement (please specify)……..

Dysgammaglobulinaemia……
Recurrent infection……..
Other……

Lymphoma……
Phenotype……
Site……

Aplastic anaemia……..

Vasculitis……

Other……

Diagnosed through family history …….

Immunology (at presentation)

Absolute lymphocyte count: …… Neutrophil count: …….
CD3+ : ……
CD4+ : ……CD8+ : ……
CD19+ or CD20+ : ……CD16+/CD56+: ……..

PHA stim (SI - if possible) : ……
Other mitogen responses (specify) : ……

IgG: ……
IgM: ……
IgA: ……

Antibody responses - Tet: Y/N…….Hib: Y/N…….Other (specify): ……..

Viral status: EBV Y/N…… Diagnosed by PCR Y/N…….
Other viruses…….

Diagnosis

SAP Gene Analysis……..
Exon involved……
Macro/microdeletion……
Nonsense mutation…….
Missense mutation……..

SAP Expression……
Method used…….

Clinical criteria……..
Definitive……
Probable……
Possible…….

Diagnostic criteria (for reference)

Definitive
Male patient with lymphoma⁄Hodgkin's disease, fatal EBV infection, immunodeficiency, aplastic anaemia or lymphohistiocytic disorder and who has a mutation in SAP.

Probable
Male patient experiencing lymphoma⁄Hodgkin's disease, immunodeficiency, plastic anaemia or lymphohistiocytic disorder, resulting in death following acute EBV infection. The patient had maternal cousins, uncles or nephews with a history of similar diagnoses, following acute EBV infection.

Possible
Male patient lymphoma⁄Hodgkin's disease, immunodeficiency, plastic anaemia or lymphohistiocytic disorder, resulting in death, following acute EBV infection.

2. MANAGEMENT

Prophylaxis

Replacement Immunoglobulin…….
Prophylactic antibiotics…….

Management of acute disease

Antivirals……
Drug.....
Length of treatment……

High dose Intravenous immunoglobulin……..
Dose…….
Length of treatment……

Interferon Therapy
Type and dose……..
Number of doses……..

Immunosuppression
Drug……...
Dose……..
Length of treatment……

Treatment of lymphoma……

Regime…….
Length of treatment……
Survived……

Treatment of HLH……

Drug……..
Dose…….
Length of treatment……
HLH 94 protocol…….

3. TREATMENT BY HSCT: Y/N……

No. of transplants:

Date of 1st transplant:……..Age at 1st transplant:……
Donor Type: MSD / MFD / mMFD / MUD / mMUD/ Parental Haplo
Stem cell source: BM / PBSC / Cord / other (specify) ……..
Donor compatibility: 12/12, 11/12, 10/10, 9/10, 6/6, 5/6, 5/10, other (specify)
…….

Active HLH/FIM at time of HSCT Y/N

Conditioning regime

Specify (drug+dose) : ……..……..
……..……..
……..……..
……..……..
……..……..
Serotherapy (drug+dose): ……..……..
……..……..
GvHD prophylaxis(drug + dose) ……
……..……..

GvHD Y/N……

Grade: ……
Skin: Y/N……
GI: Y/N……
Liver: Y/N……

Donor engraftment …Y/N……

Please give most recent result and time post transplant……

PBMC engraftment: % donor……
Myeloid engraftment: % donor…….
T cell engraftment: % donor…….
B cell engraftment % donor……..

Date of 2nd transplant:……..Age at 2nd transplant:……

Donor Type: MSD / MFD / mMFD / MUD / mMUD/ Parental Haplo
Stem cell source: BM / PBSC / Cord / other (specify) ……..
Donor compatibility: 12/12, 11/12, 10/10, 9/10, 6/6, 5/6, 5/10, other (specify)
…….

Active HLH/FIM at time of HSCT Y/N

Conditioning regime

Specify (drug+dose) : ……..……..
……..……..
……..……..
……..……..
……..……..
Serotherapy (drug+dose): ……..……..
……..……..
GvHD prophylaxis(drug + dose) ……

Outcome of HSCT

Deceased: Y/N……..
If Y – cause of death:……. time after HSCT:……
If alive – time of last f/u……..

Cellular immune reconstitution after HSCT

	6 mths post HSCT	**12 mths post HSCT**	**24 mths post HSCT**	**Most re-cent**
If diff time specify				
ALC				
CD3+				
CD4+				
CD8+				
CD19+ or CD20				
CD16+/CD56+				
TRECs (if available)				

Time to normal PHA response: …….
Time to normal antigen specific response: ……..

Humoral immune reconstitution after HSCT

Ig replacement discontinued: Y/N……
IgG prodn: Y/N……IgM prodn: Y/N……IgA prodn: Y/N……
Antibody responses - Tet: Y/N……Hib: Y/N…….Other (specify): …….

4. SURVIVAL AND OUTCOME

Is the patient alive?.....

If the patient is alive

Do they receive regular immunoglobulin replacement?.....
Do they receive prophylactic antibiotics?.....
Are they clinically well?.....

Date of death …….
Time from presentation……
Cause of death……
……..
……..

Survival length

After transplant…….

After other management (please specify other management)…….

Current Immunology

Time since diagnosis……

Absolute lymphocyte count: …… Neutrophil count: …….
CD3+ : ……
CD4+ : ……CD8+ : ……
CD19+ or CD20+ : ……CD16+/CD56+: ……..

PHA stim (SI - if possible) : ……
Other mitogen responses (specify) : ……

IgG: ……
IgM: ……
IgA: ……

Antibody responses - Tet: Y/N…….Hib: Y/N…….Other (specify): ……..

Viral status: EBV Y/N…… Diagnosed by PCR Y/N…….
Other viruses……

SEND TO : h.gaspar@ich.ucl.uc.uk

Interesting Papers

A short selection of interesting papers for this ESID newsletter number cover new genes and disease recently discovered, associations between autoimmunity and PIDs and different reviews on PIDs.

A newly described disorder termed RIDDLE (radiosensitivity, immunodeficiency, dysmorphic features and learning difficulties), whose cells lack an ability to recruit 53BP1 to sites of DNA double-strand breaks was published in Proc Natl Acad Sci U S A., 2007 Oct 23;104 (43):16910-5. The authors demonstrate the existence of an additional unknown biochemical event which is required for 53BP1 relocalization to sites of DNA breaks and which also has an impact on BRCA1 recruitment.

The growing number of identified sporadic cases of periodic fever syndromes and the lack of discriminatory clinical criteria impeded the identification of new disease-causing genes. Using a candidate gene approach the authors identified mutations in NLAP12 in two families with periodic fever syndromes. These data open up new ways to manage these disorders and also demonstrates the crucial role of NALP12 in inflammatory signaling pathways Proc Natl Acad Sci U S A. 2008 Feb 5;105 (5):1614-9.

In a recent article in Blood. 2008 Jan 1;111(1):209-18, the authors describe reverse mutations in patients with leukocyte adhesion deficiency type-1 (LAD-1). The discovery of 3 cases at one center suggests that this may be a relatively common event in this rare disease.

An interesting series of articles in the special issue of the Journal of Clinical Immunology are dedicated to autoimmunity and PIDs. One of them shows that PIDs associated with autoimmune manifestations provide insights into the pathophysiology of autoimmunity as well as into the genetics of autoimmune diseases (AID). The authors interpret such stringent disease associations, together with a wealth of observations in experimental systems. They indicate that natural tolerance to body components is an active, dominant process involving many of the components that ensure responsiveness, rather than, as previously believed, the result of the mere purge of autoreactivities J Clin Immunol. 2008 Feb 22. Another article from the same series shows associations between systemic lupus erythematous and PIDs. As human models of autoimmune disorders, PIDs represent unique and not fully explored opportunities for a better comprehension of SLE J Clin Immunol. 2008 Apr 11.

An elegant review appeared recently in Curr Opin Immunol. 2008 Feb;20(1):39-48, showed novel primary immunodeficiencies revealed by the investigation of paediatric infectious diseases. The genetic puzzle of immunity to infection is only beginning to be assembled and more PIDs affecting leukocyte activation are likely to be discovered.

Another interesting review on PIDs was published in Nat Rev Immunol. 2007 Nov;7 (11):851-61. This review focuses on the characterization of new primary immunodeficiencies and disease-related genes. A series of primary defects of innate immunity have recently been discovered and are discussed here. New defects in pre-B-cell and B-cell differentiation and antibody maturation are summarized and recently discovered monogenic immunodeficiencies that disturb the homeostasis of both the innate and the adaptive immune systems are discussed.

We are welcoming any new interesting papers, comments or suggestions you may have.

Crina SAMARGHITEAN
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Case # 6: Severe enterocolitis with combined immunodeficiency of unknown cause.

Discussion

Intractable ulcerating enterocolitis (IE) is a quite rare entity in infancy. It is seen in less than 0.5 % of paediatric cases of inflammatory bowel disease (1). It was first described by Sanderson et al. (2), defining its diagnostic criteria: (A) familial consanguinity, (B) onset of symptoms in neonatal period, (C) marked oral and perianal disease with ulcers, inflammation and fistulae, (D) small bowel enteropathy, (E) transmural colitis with deep flask-shaped ulcers with overhanging edges, and (F) poor response to immunosuppressive therapy in a long term perspective. Underlying immunodeficiency or immunodysregulation is suspected as there is high prevalence of abnormities in immune parameters in these infants similarly as in children with Crohn disease, ulcerative colitis or autoimmune enterocolitis (3).

The largest cohort of these patients was described by Thapar et al. (1) documenting 8 cases treated at Great Ormond Street Hospital in London. The patients were of Pakistani, Romany, Arabic and Portuguese origin, the median age at onset of symptoms was 2 weeks, all of them did not respond well to long-term immunosuppressive treatment (steroids, azathioprine, cyclosporine, tacrolimus) and required colectomy to control the symptoms of enterocolitis (performed in median age of 1.7 years). Evidence of immune dysfunction was apparent in all the patients, however besides non-specific elevation in serum IgA levels no other unifying defect was described. Two patients developed lymphomas one suffered from EBV- related lymphoproliferative disease later in life. It was suggested that IE represents the severe end of a spectrum of mucosal immunodeficiency predisposing the patients to development of lymphomatous proliferation as well.

Based on this presumption bone marrow transplantation was performed in two brothers with favourable outcome. It resulted in prolonged clinical remission and abrogated the need for aggressive immunosuppression; follow-up of 3, respectively 5 years (4).
Despite the fact that the course of our patient differs from the Thapar's patients in milder form of oral involvement and more pronounced immunodeficiency we believe that the disease is due to a common underlying defect within the immune system.

Have you ever treated similar patients? What is your experience? If you do so, please, contact Dr. Neil Shah at Great Ormond Street Hospital who is involved in research of this disease.

Aleš JANDA
Anna ŠEDIVÁ

Thapar N, Shah N, Ramsay AD, Lindley KJ, Milla PJ: Long-term outcome of intractable ulcerating enterocolitis of infancy. J Pediatr Gastroenterol Nutr, 2005 (40): 582-8.

Sanderson IR, Risdon RA, Walker-Smith JA: Intractable ulcerating enterocolitis of infancy. Arch Dis Chil, 1991 (66): 295-9.

Ojuawo A, St Louis D, Lindley KJ, Milla PJ: Non-infective colitis in infancy: evidence in favour of minor immunodeficiency in its pathogenesis. Arch Dis Child, 1997 (76): 345-8.

Thapar N, Lindley KJ, Kiparissi F, Elawad MA, Ashworth M, Veys P, Gaspar HB, Hill SM, Milla PJ, Shah N: Treatment of intractable ulcerating enterocolitis of infancy by allogeneic bone marrow transplantation. Clin Gastroenterol Hepatol, 2008 (6): 248-50.

APOPTOSIS, PRIMARY IMMUNODEFICIENCY DISEASE & AUTOIMMUNITY

Apoptosis or programmed cell death is a physiological form of cell death, very important for cellular homeostasis, embryogenesis, metamorphosis, and removal of mutated or unwanted cells. In the immune system, apoptosis plays an important role in the selection of T cell repertoire, deletion of self-reactive lymphocytes, killing of target cells by cytotoxic T cells and natural killer cells. Moreover apoptosis signaling cascades are believed to be involved in maturation of the immune system (T- and B-cell development) and its further homeostasis, thus being key to regulate both acquisition and maintenance of self-tolerance. Defects in apoptosis pathways contribute to initiate and perpetuate the autoimmune process through a destructive immune response to autoantigens in many ways, including either ineffective deletion of autoreactive lymphocytes during negative selection

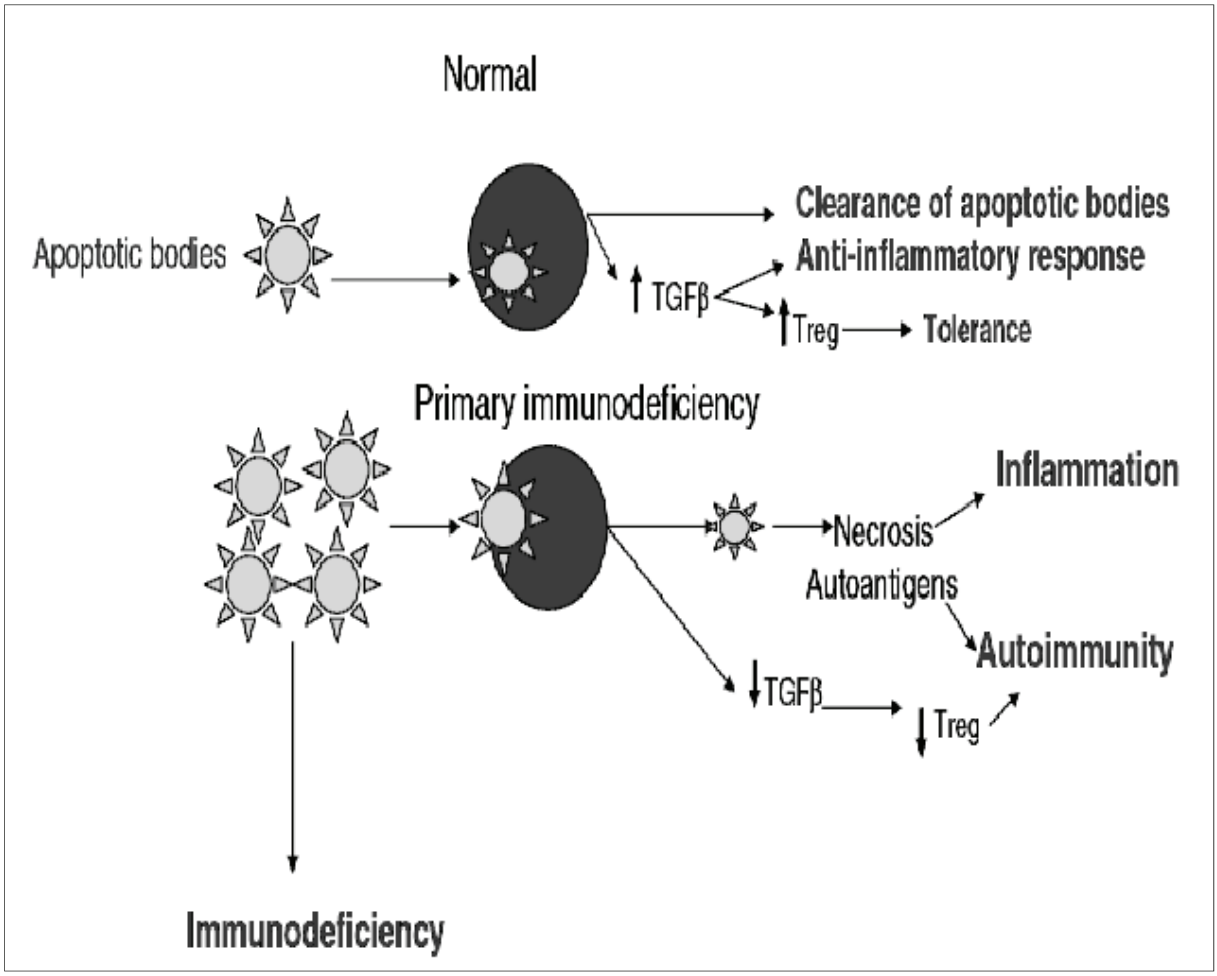

Fig. 1 Proposed model of autoimmunity in Primary immunodeficiency (PID): Under normal circumstances, apoptotic cells and bodies are taken up by the neighboring phagocytic cells, resulting in their removal and production of anti-inflammatory cytokines, including TGFβ. TGFβ induces regulatory T cells (Treg), resulting in tolerance. In PID, increased apoptosis and/or defect in the clearance of apoptotic cells results in decreased production of anti-inflammatory cytokines (including TGFβ) and lysis and necrosis of apoptotic bodies releasing self antigens contained within them. Lysis of apoptotic bodies along with a deficiency of generation of Treg, as a consequence of decreased TGFβ, results in autoimmunity and inflammation.

process, creating new immunogenic selfpeptides or insufficient clearance of autoparticle-containing phagocytic cells during an immune response. One of the hallmarks of apoptosis is a lack of inflammation, which is a reason why, when a cell dies by apoptosis, it leaves no trace behind, whereas when a cell dies by necrosis, it is associated with an inflammation. The lack of inflammatory response in apoptosis involves a rapid uptake of apoptotic bodies by the neighboring phagocytes and the induction of intracellular signals resulting in a downregulation of inflammatory response and induction of anti-inflammatory response, including production of TGFβ. Phagocytosis of apoptotic bodies (which contain self antigens, DNA, histones, RNA, RNP, etc.) is facilitated by "eat me" surface molecules, which are recognized by an array of receptors on phagocytice cells (e.g., C1q, phosphatidyl serine and other proteins recognized by CD14, WASP proteins). TGFβ is an important molecule in the generation of regulatory T cells. Therefore, if there is a defect in apoptosis, it may result in both immunodeficiency and autoimmunity (Figure 1).

An increased apoptosis may result in the depletion of functional lymphocytes and a defect in uptake of apoptotic bodies (e.g., mutation in C1q associated with SLE; mutation of WASP is associated with autoimmunity in WAS) may lead to (a) late necrosis of apoptotic bodies and the release of self antigens and (b) failure to induce anti-inflammatory response (including production of TGF-β, which is important in the generation of Treg) resulting in immunodeficiency, auto-immunity, and inflammation. In contrast, an inefficient apoptosis may lead to a failure to delete self-reactive lymphocytes and expansion of immature and functionally defective lymphocytes (e.g., autoimmune lymphoproliferative syndrome, ALPS) (Table 1).

Apoptosis primarily involves activation of cysteine proteases, the caspase, that has affinity to cleave its substrates at a particular aspartase residue. These caspases act cleaving a number of nuclear, cytoplasmic, and structural substrates, including cell cycle enzymes, DNA repair enzymes, caspases themselves and transcription factors, to induce classical morphological and biochemical features of apoptosis (e.g. DNA fragmentation). In addition, in certain cell types and under certain conditions, apoptosis may be mediated by a caspase-independent pathway. Apoptosis is signaled by two major pathways, an intrinsic pathway, which is mediated via mitochondria and the endoplasmic reticulum and an extrinsic or death receptor-mediated pathway. Death receptors belong to a large family of tumor necrosis factor receptors (TNFR), which contain a death domain motif in their cytoplasmic tail. The most studied death receptors include CD95 (or Fas) and TNFRs. CD95 is mainly expressed on the cell membrane of lymphocytes. CD95-mediated Apoptosis stimulus is the ligation of CD95 with CD95 ligand (CD95L or Fas ligand, FasL) and resulting in a caspase dependent pathway predominantly in T cells. Abnormal regulation of apoptosis, particularly involving the Fas/ Fas ligand (FasL) pathway, has been considered to play a role in the pathogenesis of autoimmune diseases. Mutations of the fas gene and the fas ligand gene, which lead to defects in apoptosis, have been found in autoimmune strains of mice and in ALPS. The most typical alternatively spliced variant of the wild-type fas gene transcript is known as soluble fas. Because this variant transcript lacks 63 bp of the transmembrane domain, its product (soluble Fas) can be secreted from cells to suppress membrane Fas-mediated apoptosis by blocking the binding between membrane Fas and Fas ligand in the extracellular region. If there is high level of soluble Fas in the extracellular regions, lymphocytes in these regions may avoid apoptosis and survive longer.

Table I Disorders of Apoptosis in Primary Immunodeficiency

Disorder
Increased apoptosis
ADA-deficiency-mitochondrial pathway (p53-mediated)
Cartilage hair hypoplasia syndrome-CD95-mediated
Omenn syndrome-CD95-,TNFR, oxidative stress-mediated
Ataxia telangiectasia-mitochondrial pathway (ATM-p53)
Wiskott–Aldrich syndrome (CD95-, mitochondrial, defect in clearance of apoptotic bodies)
DiGeorge anomaly (CD95-mediated)
Common variable immunodeficiency (TNFR-mediated)
Selective IgA deficiency (BCR-induced caspase-1-mediated)
Kostmann syndrome (*HAX1* gene mutation)
Decreased apoptosis
Autoimmune lymphoproliferative syndrome mutations of CD95, CD95L, caspase-10, NRAS mutation
Caspase-eight deficiency state mutations of caspase-8

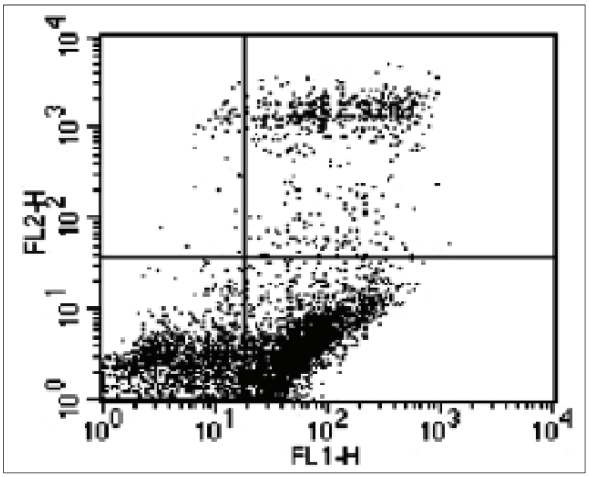

Fig. 2. Dot plots of annexin V/PI staining. Annexin V is represented on FL1-H and PI on FL2-H.

The gold standard for identification of apoptotic cells is ultrastructural evidence of chromatin condensation, the earliest characteristic morphological feature but the costs of electron microscopy for this purpose are prohibitive because it is extremely labor intensive, and therefore it is not recommended for routine work. However, not every alternative method is suitable for tissue sections and individual cells; and all of them possess limitations, especially regarding sensitivity and specificity that make them less reliable than the ultrastructural approach. Thus, to avoid or at least to minimize, diagnostic or methodologic errors, combinations of two or more of these diagnostic resources should be used.

The following list comprises some of the available apoptotic assays approach:

• The terminal deoxynucleotidyl transferase (TUNEL) method is the most widely used technique, most probably because its use is facilitated by commercial availability of special kits and because microscopic evaluation of the number of positive cells is not difficult. It is a DNA fragmentation-based method. Or until the TUNEL method gives a positive signal? Finally, TUNEL has been reported to label not only apoptotic but also oncotic nuclei as well as nuclei in DNA repair.

• Southern hybridization of DNA resulting in a smear on the blot when DNA is fragmented. This is a reliable parameter bur it is useful only when larger amounts of tissue/cells are available.

• Staining of the nuclear configuration typical of apoptosis using nuclear dyes, e.g. Hoechst 33342 DAPI,YOPRO-1, etc. This seems to be useful but has to be evaluated with caution because of low specificity and it should be combined with other methods.

• Cleavage of substrates (e.g., gelsolin, polyADP-ribose polymerase and caspase-3) of the caspase dependent pathway. This has been determined with Western blot techniques. Moreover, assays that are based on caspase activation or cleavage of substrates do not detect caspase-independent pathways.

• Disappearance of lamin proteins from the nuclear membrane. This is a highly reliable parameter useful in immunohistochemical preparation of tissue sections or in cultured cells. These proteins are involved in the maintenance of nuclear membrane integrity and they disappear after activation of the apoptotic cascade.

• Analysis of Fas and Fas ligand proteins and genes. Detection of the percentage and mean fluorescent intensity (MFI) of Fas-positive lymphocytes (membrane Fas expression) by flow cytometric analysis. Detection of alternatively spliced variants of fas and mutational screening of fas and fas ligand genes.

Here below two protocols in brief details:

1. Fas Ab-induced apoptosis protocol: On the day preceding the apoptosis determination experiment, the T cells were fed with fresh IL-2-containing medium. For each sample, 100 µl of cells were plated in triplicate in 96-well plates at a density of 2 × 106 cells per well. Apoptosis was induced by the addition of 100 µl media containing 1 µg/ml anti-Fas antibody (APO-1-3, Kamiya Biomedical) with 1 µg/ml protein A (Sigma). No antibody was added to control wells. The cells were incubated at 37°C for 24 hours and then assayed for quantification of apoptosis, as reported previously in literature. Briefly, cells were harvested on ice and propidium iodide (final concentration 3.3 µg/ml) was added. Fixed time flow cytometry was performed for 15 minutes to count live cells using a flow cytometer.

Apoptosis was calculated as: % cell death = (1 - live cells after antibody treatment/live cells in control tubes) × 100.

2. Cell death detection using labelledAnnexin V. One of the hallmarks of cell death is the cell surface–expression of phosphatidylserine. Expression of phosphatidylserine at the cell surface can be measured in vitro with the phosphatidylserine-binding protein annexin V (or annexin A5) conjugated to fluorochromes. The assay is based on a simple 15 min incubation of cells in a solution containing Ca2+ ions and annexin V–FITC (at a final concentration of 1 lg/ml). The annexin V-binding buffer consists of 10 mM Hepes–NaOH, pH 7.4, 150 mM NaCl, 5 mM, KCl, 1 mM MgCl2, and 1.8 mM CaCl2 and should be stored at 4°C. After the incubation period, a vital dye such as propidium iodide (PI) or 7-amino-actinomycin D (7AAD) can be added to the cell staining solution in order to identify different stages of apoptosis, or cells undergoing secondary necrosis. Analysis of the cell staining can be made either by flow cytometry (Figure 2) or by confocal scanning-laser and fluorescence microscopy. Analysis of annexin V/PI-stained cells by flow cytometry allows quantitation of the fraction of living cells that are annexin V and PI negative (double negative), of secondary necrotic cells that are annexin V and PI positive (double positive) and of cells in the early phases of cell death that result annexin V positive and PI negative (single positive). The annexin V-binding assay is a very simple, rapid and reliable assay that does not require fixation or processing of cells, thereby reducing manipulation and loss of sample material. This assay has been successfully used on a variety of cell types.

What do you think about these methods? Which one or which combination of two or more is better suitable for detection apoptosis?

I'm waiting for any interesting topic, protocols, comments you would like to suggest!

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PID-care in development:

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

Name : Velma Mulaosmanovic
Age : 35 yrs
School : High school "Prva gimnazija", Sarajevo, Bosnia and Herzegovina
University degree : School of Medicine University of Sarajevo 1998, B&H
MSc : 2005, Postgraduate Studies School of Medicine University of Sarajevo B&H
Pediatric Board Exam : 2006, Children Hospital Sarajevo B&H
Family : not married (still)
Becoming a Pediatrician : While I was medical student I had a dream to become Obstetrician. I was impressed seeing first signs of life of newborns in delivery room. Amazing isn't it?
But, while I was doing my practical year 1998, I simply met an amazing person Senka Dinarevic, pediatric-cardiologist and Assistant Professor of Pediatrics. Those days changed my life forever. The contact with pediatric patients, listening heart sounds, evaluating haemodinamics, heart morphology and physiology - became my new dream indeed. That was the main reason why I changed my job position from my first employment at the Centre for Human Genetics in the Medicine School of Sarajevo to Pediatric Resident at the Sarajevo Children's Hospital. I never regretted it. I felt that I found myself in a professional sense – I fell like a "natural born" clinician.

While I was still a Resident Pediatrics, I finished my Master's degree in 2005. Focus of my research was the correlation between blood pressure and birth weight in children born during Sarajevo siege.

One year later, successfully approved Pediatric Board Exam and next 9 months I was worked at the Nephrology Department in our Children's Hospital. Immune mediated renal disease, systemic lupus erythematosus and finally one child with X-linked agammaglobulinemia changed my professional interest. Questions like why all those diseases are happen, how to treat them and follow them up, changed my way of professional "dreaming". Then, I spent March/April 2007 at Department of Allergology, Rheumatology and Clinical Immunology, Children's Hospital Ljubljana, Slovenija with another great person – Tadej Avcin, pediatric immunologist/ rheumatologist, Assistant Professor of Pediatrics. It was my first contact with primary immunodeficiencies and novel approach in diagnosis and treatment of rheumatic and autoimmune diseases. So, that was final step to make my last decision : To become immunologist and rheumatologist.

Can you give me some information about health care in your country?

Well, I am not quite sure that I can answer those questions appropriately. You can call health care in B&H as "health care in a transition country". It has very specific background : it was highly positioned in scientific sense in former country before 1992. Then we had one of the biggest disasters that human mind can ever imagine – war from 1992 till 1996. I wish nobody in the World to experience it never. Since

then, B&H has been recovering slowly but surely. Main characteristics are enormous enthusiasm and optimism – I hope I will have some free time in my life to write a short article about it. We need continuing medical education – here and abroad, and a network similar to Institutions around Europe and North America.

The Child Health care is provided by Government mostly, far less by private practitioners. Primary care is widespread all over the country as well as secondary health care for children. Tertiary level is provided in several Hospitals in the country. The level is good and appropriate.

Facilities and money matters – It is a problem as everywhere in developing countries, I think.

Differences between city and countryside – doesn't seem to be such a big problem from my point of view. Bosnia and Herzegovina is a small country. Maybe the biggest problem is transport of critically ill children to our tertiary level Hospital. I can't remember anything more important at the moment.

Can you give me some information about PID-care in your country?

PID care in B&H is very inadequate at the moment. One of the aims of opening our new Department of Allergology, Rheumatology and Clinical immunology at the Sarajevo Children's Hospital in April 2007, was to provide early diagnostics and treatment of PID patients as well as other kind of patients. It has been a hard work but we are happy to have such a challenging goal. Currently a few children with PID are treated in our Department and some other centres in the country, Tuzla for example.

Immunoglobulin therapy
IVIG therapy is expensive but we are managing that problem so far. Expenses are covered by the local government funds. IVIG are imported since we don't have local manufacturers. It is maybe rather easy due to the fact that we don't have too many PID patients. In the future, we are planning to introduce subcutaneous immunoglobulins also when appropriate. Treatment of infections is possible since we have all needed drugs so far.

Stem Cell Transplantations Project for children is planned, but not introduced yet. Till now, I am not aware of children with PID that needed it. In brief : we are at the very, very beginning of all that process of establishing PID centre in the country.

What has been your role in PID-care in your country until now?

Challenging question and my answer is simple : I still don't know, but for sure I will do my best in cooperation with my colleagues to develop it as much as possible and as soon as possible. Maybe it will be more interesting to answer this question in one or two years. Thank you. We are planning to organise J Project Meeting at the end of this year. It would be a pleasure for me to inform you how the things concerning PID care development are going in the future.

What do you hope to achieve in the future?

My new dream is to become licensed pediatric immunologist/rheumatologist and to make a successful network of similar professionals in my country and to link it with PID centres abroad. Main goals : are well being of our patients and improvement of our "best clinical practice". Well, I am aware that I am too optimistic and that I see only bright future, but that's the only way I could live like.

Bosnia and Herzegovina

How could ESID help to achieve this goal?

ESID can help us in many ways, I am sure. The most important things are : education and sharing knowledge, collaborative work, exc. Obviously I am very fresh in this field, so I need more time, experience and knowledge to give a more detailed answer.

Bosnia and Herzegovina

XIIIth meeting of the European Society for Immunodeficiencies

ESID

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October 16-19, 2008

together with

the Xth Meeting of the International Patient Organization for Primary Immunodeficiencies

IPOPI

and the VIIIth Meeting of the International Nursing Group for Immunodeficiencies

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