ESID Newsletter

Contents

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:
Art in the Museum Insel Hombroich, Germany.

Dear ESID members,

Summer has just started as I write these words, but in Holland at least the rain is pouring down!

In this ESID Newsletter you can find the results of the second ESID poll in the President's and Secretaries' letters. Now, we have all the ingredients to make up the new ESID Constitution.

Helen Chapel asks all your help for the task to get SCIg on the WHO list, now that IVIG has been put back on after a successful campaign.

Selection of the candidates for the ESID Summer School will take place soon. We look forward to another very successful event. The Registries Working Party as usual gives you some follow-up on their very important work.

Furthermore, the Interesting Papers, Interesting Case, and the PID-care in development section about Malaysia offer you more on PID !

Wishing you all a very pleasant summer !

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 2,000 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 ESID members,

I am proud to say that the two rounds of election about the ESID constitution met a very interest in the ESID community, as attested by the frank and friendly discussions in the last months, and by the high participation rate in the two rounds (see the results of the poll in the Secretarial report). This democratic procedure was needed to ensure that the final decisions were endorsed by the entire community. The decisions made were not made by the ESID board during a secret meeting: they were made by the entire ESID community after an open discussion in Budapest and an abundant email correspondence since. We can be proud of this and we can be sure that this is the way to go in the future.

The results of the votes are extremely clear and there is no ambiguous interpretation. The ESID members have decided that the ESID president, secretary, treasurer, and heads of working parties (board members) may be citizens of any country world-wide but should work in Europe; they should also be MDs, PhDs in biology, Veterinarians, Pharmacists, or Dentists (or students in any of these areas), and they should declare any conflict of interest in writing to the ESID board. There is also a clear definition of Europe. In contrast, there is much less restriction on becoming an ESID member: the sole restriction is that, in addition to the above categories, they may hold a PhD (or be a student) in any other field (e.g. chemistry, sociology); patients and nurses may therefore be 'associate' but not full members.

I think the results of the election express that the ESID community has strong European roots but is widely open to the world. I now can say that I am personally delighted with these options. I did not campaign in favour or any option before the vote but expressed my personal opinion to those of you, within the board and among the broader community, who solicited my opinion. I am glad we could nicely solve the paradox of being a European and an international society, in the best interest of the patients, physicians, and investigators in Europe and world-wide.

Thank you all for your continued interest and involvement in the ESID.
All best wishes,

Jean-Laurent CASANOVA

Secretarial report

ESID Poll on changes to the constitution.

Dear ESID members,

The results of the second round poll on the ESID constitution in May 2007 is shown below. The percentage per answer is given with the actual number of votes in brackets.

1. Should the ESID President be:
1: a European citizen, working in Europe? - 37.70% (n=46)
2: a citizen from any country, working in Europe? - 62.30% (n=76)
Total: 122 participants

2. Should the ESID Secretary be:
1: a European citizen, working in Europe? - 31.67% (n=38)
2: a citizen from any country, working in

Europe? - 68.33% (n=82)
Total: 120 participants

3. Should the ESID Treasurer be:
1: a European citizen, working in Europe? - 44.17% (n=53)
2: a citizen from any country, working in Europe? - 55.83% (n=67)
Total: 120 participants

4. ESID board members shall be:
1: MDs, PhDs (biology), Veterinarians, Pharmacists, Dentists, or graduate students in any of these fields - 54.24% (n=64)
2: option 1 + PhDs (other fields) and corresponding graduate students - 45.76% (n=54)
Total: 118 participants

5. Should the head of an ESID working-party be:
1: a citizen from any country, working in Europe? - 60.83% (n=73)
2: a citizen from any country, working anywhere world-wide? - 39.17% (n=47)
Total: 120 participants

6. ESID members shall be:
1: option 1 first round (MDs, PhDs (biology), Veterinarians, Pharmacists, Dentists, or graduate students in any of these fields) + PhDs (other fields) and corresponding graduate students - 51.26% (n=61)
2: no restriction for membership - 48.74% (n=58)
Total: 119 participants

7. Europe shall be defined as follows:
1: no definition of Europe - 37.29% (n=44)
2: EU + Iceland, Norway, Switzerland, Serbia, Bosnia, Montenegro, Croatia, Albania, Macedonia and small states (Andorra, Monaco, Lichtenstein) + Ukraine, Belarus, Russia, Moldavia, Turkey, Israel - 62.71% (n=74)
Total: 118 participants

Some calls were close, but this is the beauty of democracy. Please remember that this is 'just' for our constitution, NOT for the legal act. Thank you for everybody who voted, I am sure we will have additional electronic polls coming up, for sure the next one will be on the election of new ESID board members prior to the ESID2008 meeting in s'Hertogenbosch.

Bodo GRIMBACHER

News & Views

WHO application for SCIg: your support is needed again !!

Dear Members,

The new application for SCIg to be included in the EML for Children is up on the WHO website http://mednet3.who.int/EML/expcom/CHILDREN/INDEX_children_07.htm

I would be glad if we could get some additional support - it was very successful last time when we achieved IVIg on the Essential Medicines list in March of this year. We need help again please - especially from paediatricians and those looking after adolescents too.

We need data on safety , efficacy and cost-effectiveness of SCIg in children and in adults please. The paucity of data, compared with IVIg, was the reason that SCIg did not make the main list in March - so here is a chance to get the EML committee to see that too.

The IUIS committee, on whose behalf I have sent this application, and IPOPI have been very helpful. If you can think of anyone else who could add some info and data - please do send this on. very many thanks

Helen Chapel

Report on the 6th ESID Prague Spring Meeting, May 14-15, 2007, Prague
Department of Immunology, 2nd Medical School, Charles University, Prague

On May 14 and 15, the sixth ESID Prague Spring meeting was held at the University Hospital Motol, Prague, Czech Republic. More than thirty participants from 12 countries, namely Czech Republic, Lithuania, Poland, Slovenia, Slovakia, Italy, Netherlands, Portugal, Finland, United Kingdom, Turkey and Iran attended and actively participated in the event; mean age of the participants was less than 35 years (ranging from 23 to 54).

Since its launch in 2002 the Prague ESID meeting has been devoted to the exchange of information on primary immunodeficiencies (PIDs) between Western and Central Europe. This year the main task was to bring together the youngest researchers and clinicians of ESID community. The aim was accomplished through an excellent attendance from EU member states, as well as from our close and further neighbours – Turkey and Iran.

The invited speakers were Andy R. Gennery from BMT Unit in Newcastle General Hospital, UK, Marita Bosticardo from San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET) in Milan, Italy and Miriam van der Burg from Department of Immunology, Erasmus MC, Netherlands.

The introductory lecture of the meeting served as an overview of current progress in haematopoietic stem cell transplantation for primary immunodeficiencies given by Andy R. Gennery, followed by interesting review on gene therapy protocols in Wiskott-Aldrich syndrome presented by Marita Bosticardo. Apart from these surveys relevant case reports flavoured this part of the programme.

Another section of the first day focused on antibody deficiencies. The participants could learn about European study on quality assurance of pneumococcal assays, molecular defects in CVID, clinical relevance of anti-IgA antibodies and clinical data extraction.

A review on recombination defects in PID was given by Miriam van der Burg at the beginning of the programme on the second day accompanied by instructive case reports on skin presentations in patients with SCID and a follow-up of a patient with Cernunnos deficiency introduced at this meeting last year. An overview of IPEX syndrome and atypical presentation of this syndrome in one family closed this section on severe immunodeficiencies.

A number of talks on chronic granulomatous disease were given by colleagues from Slovenia and Poland. Representatives from Iran informed the audience about phagocyte and complement defects in their homeland.

The first part of the afternoon programme was dedicated to a discussion on current and future activities of ESID Juniors that resulted in a few propositions enhancing future collaboration. Thankworthy projects of enthusiastic team of Prof Vihinen from Finland on information services in primary immunodeficiencies were presented, followed by an overview of PID diseases in Iran.

The last but one section concentrated on unusual and interesting case reports. These cases were highly appreciated and brought to the programme quite practical aspects connecting the bench work with the clinic.

All the presentations or abstracts of the talks accompanied with photos are available for download on a new website of Department of Immunology at: http://imunologie.lf2.cuni.cz

The social programme is an indispensable part of the Prague Spring ESID meeting, as it enables further fostering of close cooperation between all the participants. The relaxing stroll through Prague Castle, dinner in a restaurant in the historical quarter of Prague and a concert in a jazz club in the city centre were all enjoyed by the participants.

The meeting was organized as a part of the activities related to the Day of Immunology, declared by EFIS on 29th April, 2007. It was supported by the Charles University, 2nd Medical School, Prague and by University Hospital in Motol, Prague. Substantial contributions came from pharmaceutical companies Baxter, Grifols, Exbio, Immunotech, Olympus, Baria, ITA-BD, Schoeller and Binding Sites company that provided not only financial support but also books on diagnostics. Thanks to generous help of Talecris three travel grants approved by ESID board could be distributed to Crina Samarghitean (Finland), Lucia Bianchi (Italy) and Ömür Ardeniz (Turkey).

We thank all the participants for their contributions and we are looking forward to next meeting in 2008!

Anna SEDIVA
Ales JANDA

AT-meeting in Poland for patients and parents

Poland's THIRD nation-wide meeting of parents with children suffering from the ATAXIA-TELANGIECTASIA syndrome

On 12-13 May 2007, the 3rd Nationwide Meeting of Parents with Children suffering from the AT-syndrome was held at the Children's Memorial Health Institute in Warsaw. The meeting was organised by the Association of Friends to Children with Immunological System Deficiencies and the Clinical Department of Immunology at the Children's Memorial Health Institute in Warsaw.

There were fifteen families present from all over the country. Parents had a unique opportunity to share their experiences and express their doubts on everyday care and treatment of their children. Specialists on neurology, rehabilitation and oncology held lectures and parents could ask for professional advice. During the meeting a social care worker for disabled children answered the parents' enquiries.

Professor Richard Gatti from Department of Pathology and Laboratory Medicine of the California University in Los Angeles was the Honourable Guest of the meeting. Professor Gatti is a world-wide famous doctor and scientist. He has been successfully carrying out studies on ataxia-telangiectasia syndrome for many years. Professor gave the lecture on current experimental studies concerning A-T treatment. His presence and the content of the lecture gave the participants hope for the future.

In the meantime, when the parents shared their experiences and listened to the lecture, the children accompanied by a group of volunteers enjoyed a wonderful cruise along the Vistula river.

In the evening all families and lecturers were invited for a solemn supper

at the Sobieski' Hotel. The menu served was superb and the atmosphere was warm and friendly however the most exceptional moment of this evening was a piano concert given by Professor Gatti, who is not only a dedicated scientist but also a keen musician.

The parents were really grateful for the opportunity to participate in the meeting. They realised that they were not alone with their problems and that they could learn more about their children's disease. In appreciation of the effort put by the organizers and to continue the tradition of such meetings, they made a decision to establish the AT Foundation. Previous meetings resulted in launching the www.atel.org.pl web pages.

The treatment of AT patients has many aspects and requires clinical research based on co-operation of clinical specialists, immunologists, paediatricians, neurologists, rehabilitation specialists and many others. The AT Foundation will certainly help parents to solve their everyday problems.

We are very much obliged to sponsors of the meeting: Wyeth, Grifols and Vitis Pharma. We are also grateful for sweets donated by Mead Johnson. The organisers would like to plan further meetings and hope that sponsors will be found to make it possible.

I appreciate very much the commitment of Ms Maria Bukaty, the President of the Association of Friends to Children with Immunological System Deficiencies and Dr Edyta Heropolitańska-Pliszka who was the interpreter of Prof. Gatti's lecture. I also express my gratefulness for the enthusiastic contribution of nurses working in Gastroenterology and Immunology Department, especially Ms Bożena Kuśmirek. I would like to give my special thanks to Professor Ewa Bernatowska for her professional guidance and support during the organisation of the meeting.
(E-mail: oddzial.immunologia@czd.pl)

Barbara PIETRUCHA

Working Party reports

Educational WP

It has been a most encouraging spring. The ESID Spring Meeting and Educational Working Party (organised by Aleŝ Janda) took place from 14 to 15 May 2007 in Prague, and was very successful. Plans for the ESID Summer School are progressing well with over 60 applicants from a wide range of countries. The program has now been finalised and we aim to cover established areas such as SCID and CVID, as well as looking at the exciting recent advances in our understandings of defects of innate immunity. (Successful applicants will be notified by 1 July '07).

Andrew CANT

Registries WP

Improvement of Core Dataset entry forms.

As you already know, the ESID database is funded by five pharmaceutical companies in the PPTA (Plasma Protein Therapeutics Association). These companies are currently Baxter, Biotest, Grifols, Kedrion, and Octapharma. The project is also supported by the EU under project EUROPOLICY-PID, contract no. SP23-CT-

2005-01164. The contract with the PPTA is up for renewal in August and we recently have carried out negotiations with each of the individual companies to discuss the current status and future aims of the database. These talks were very valuable in helping us focus and coordinate the direction of the database to satisfy all parties involved. Many excellent suggestions on improving the database and data compilation arose from these discussions.

We recently implemented some of these suggestions together with other improvements in the Core Dataset of the database. The most important of these are the following (please look at the screenshot on the next page to get a visual impression).

1. Days missed at school/work and days in hospital: These fields have been changed to text fields. The old drop down menus, which we realized were not suitable for collecting reliable data, are no longer available but all previous entries will continue to be displayed next to the new field as "Entry made in old format" so you do not have to enter the old data again.

2. Infectious episodes and serious infections: These new fields are an additional indicator for quality of life questions. Therefore they have also been marked as red fields. Please note that infectious episodes also include serious infections. For further information on the fields, please click on the '?' buttons in the database to view the field definition.

3. Neurodegeneration: We added this question at the request of the EMEA.

4. Status of Therapy: Since this field does not represent Quality of Life data, it is now a separate box. Please note that it is a red field and should be filled in EVEN when the patient receives no therapy at all. In this case just tick the box "no (current) therapy" so that we know that the field was not just ignored.

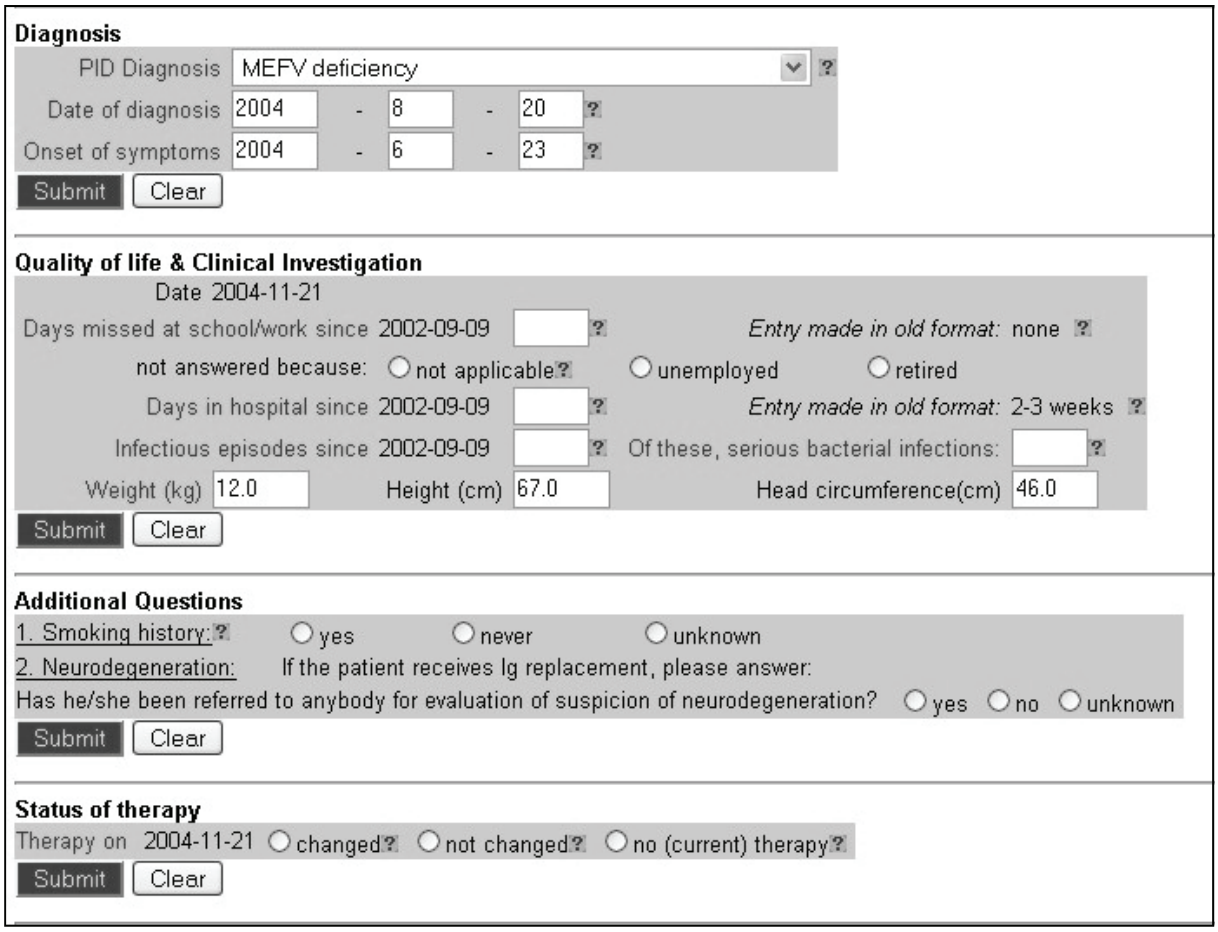
5. Drop-down menus in the therapy section, namely drug group, generic name, brand name (now a red field!) and unit: We have revised all of these during the last months and deleted or replaced all unnecessary entries. We are confident that this will make documenting a lot easier for all users.

Other minor changes concern the core laboratory page. IgM and IgA are now also part of the red fields. In addition, it had obviously not been clear that lab values should also be registered with the date when the blood was taken. Therefore, a new info button (ToolTip) has been added on this page next to the date field.

We have also noted that it is very important that the medication associated with infections as well as medication taken regularly such as for blood pressure or antihistamines should be documented in the therapy section. Please make sure that you document all medication in the therapy section as this could affect blood values. Things like vitamin supplements do not have to be (but may be) recorded.
The new red fields mentioned are mandatory from July 1st 2007. This means that they are not relevant for the bonus payments deadline on June 30th 2007.

Report generation.

We are in the process of developing a report generator so that all data form a single patient can be printed out in one report. The report in English will be available by the end of 2007 and can be generated by the documenting centres themselves rather than having to request a data report from the administrators in Freiburg or worse, printing screen shots for the patients. This report can be handed to patients to check that the data entered is complete and correct. Furthermore since data protection laws require that patients can access all data stored on them thus they can



also have a copy for their files should they request it.

Data analysis/warehouse project

The ESID database with data from over 4500 patients has now enough material for analysis. Up to now all analyses have to be carried out in Freiburg. It would be great however for the individual scientist to be able to do quick and simple analyses himself. An example of this would be, how many CVID patients are in the database who are on a certain brand of Ig replacement and who have smoked. A project to implement such reporting services has just been launched in collaboration with Prof. Mauno Vihinen and colleagues in Tampere and simple analyses like this will be available in early 2008.

Collaboration with patient organisations and patients

The ESID database documents patient data. Not all of this data is known by the physician so that we need to involve the patients more in the compilation of the data. In addition since the patient is the central point of this work, it is to our advantage to involve him more in documenting and verification of what has been documented. For example, the days missed at work or school as a result of the immunodeficiency since the last clinic date is not usually recorded by the documenting physician. This and the associated infection data is best known by the patient himself. Therefore we have created a "manual entry form for patients" so that patients can record or update their data when they attend a clinic. This is a questionnaire that can be handed out to patients while they are waiting for their appointment in the clinic/documenting centre. Most patients attend these clinics once or twice a year which is sufficient for recording their data. The attending physician collects the questionnaire when he sees the patient and puts it in the patient file to be used when

documenting data. If there are any questions on either side they can be answered at this stage. The questionnaire should not cause physicians, who are always on a very tight schedule, any delay as it serves to focus the patient on information required which is mostly already answered in the questionnaire. Each clinic can of course adapt the questionnaire to its particular needs.

Patient organisations will be requested to encourage patients to use the questionnaire or at least to record information such as frequency of infections, type and duration of infection, days missed at school, information which we are recording in the database with the aim of improving patient quality of life.

IVIG back on the WHO EML list.

We are delighted to hear that IVIG is back on the WHO list of essential medicines. The data used from the ESID database was probably only a very small contribution to the huge input made by many others but we are very happy to have been able to support this aim. In future the database will have more to contribute to further applications.

XLT survey.

There will be a survey on patients with X-linked thrombocytopenia (XLT) with mutations in WASP run by Dr. Michael Albert from Dr. von Haunersches Kinderspital in Munich starting within the next few weeks. Centres participating in the ESID Database can fill in the questionnaire online in the database. Please watch out for announcements on www.esid.org.

Current figures.

The numbers in the database are continuously growing, with an extraordinary number of patients from the French national registry CEREDIH. Still, other countries such as Turkey, Ireland and the United Kingdom have been contributing remarkable numbers over the last three months, too (see Figure 1). The total number of patients is currently 4636. With the bonus payments deadline two weeks away from the closing date of this newsletter, we are curious what the numbers will look like in the next ESID Newsletter! As always, the database statistics are regularly updated on the ESID website. Happy documenting.

Perspectives.

As stated at the beginning, the ESID database is currently funded by the PPTA and the EU with the EU project ending early next year. Since this is an international project it would make sense to continue with EU support. Therefore we would like to encourage members of documenting centres or other interested readers to put their heads together and organise an international project using the database as a basis for compiling information. We would be happy to help coordinate such a project, so would look forward to hearing from interested parties. (Email: registry@esid.org)

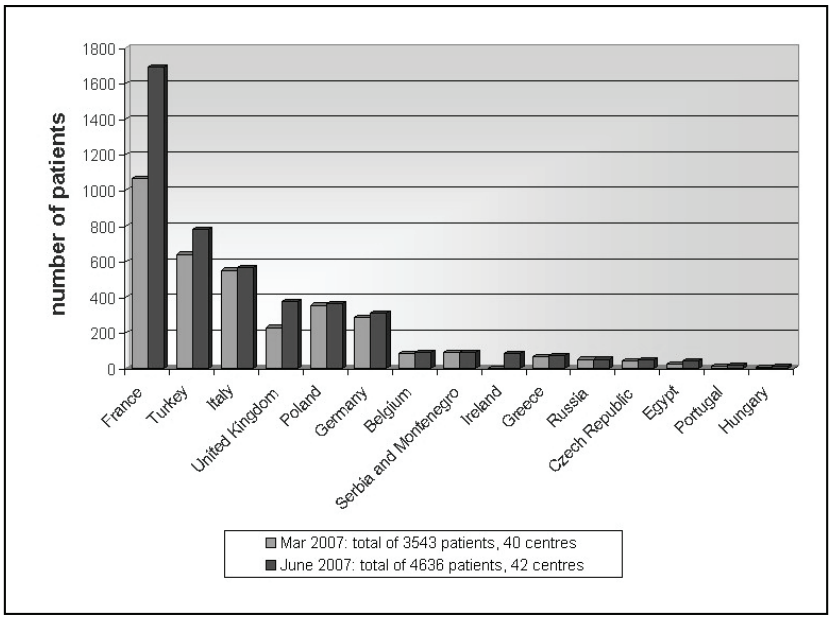
Gerhard KINDLE
Anne-Marie PERNER
Benjamin GATHMANN

On the next pages.

Figure: Patients registered in the ESID Database, March and June 2007 compared. Only countries with more than 10 patients are shown.

Table: Cohorts (sub-registries) with more than 20 patients in the ESID Online Database.

Questionnaire for patients attending a primary immunodeficiency (PID) clinic.



Disease	Entries
Common variable immunodeficiency (CVID)	1073
Isolated IgG subclass deficiency	363
Agammaglobulinemia X-linked (BTK)	342
Immunoglobulin A deficiency 1 IGAD	327
Ataxia telangiectasia (ATM)	267
Transient hypogammaglobulinemia of infancy	199
DiGeorge Syndrome	144
Wiskott-Aldrich syndrome with mutations in WASP	117
Other Hypogammaglobulinemias	103
Unclassified immunodeficiencies	99
Chronic granulomatous disease X-linked (CYBB)	94
CSR defects and HIGM syndromes with unknown genetic cause	88
Severe congenital neutropenia with unknown genetic cause	86
Cyclic neutropenia with unknown genetic cause	84
Schwachman-Diamond syndrome with unknown genetic cause	78
Hyper-IgE syndrome	74
Kostmann syndrome	72
CGD with unknown genetic cause	68
CD40 antigen ligand deficiency (CD154)	64
Nijmegen breakage syndrome (NBS1)	59
Wiskott-Aldrich syndrome with unknown genetic cause	54
T-B+ SCID with unknown genetic cause	51
Agammaglobulinemias with unknown genetic cause	50
Other unclassified T-cell disorders	49
Severe combined immunodeficiency X-linked (SCIDX1)	44
T-B- SCID with unknown genetic cause	31
Hereditary Angioedema (C1inh)	29
Familial mediterranean fever defect (MEFV)	27
Recombination-activating gene 1 deficiency (RAG1)	24
Deficiency of specific IgG	22

Questionnaire for patients attending a primary immunodeficiency (PID) clinic

Thank you for agreeing to allow your data relating to your primary immunodeficiency to be recorded in the ESID online database for PID (www.esid.org). This database is designed to help us record data on PID patients in order to improve diagnosis, prognosis and therapy of these rare diseases.This questionnaire will take a few minutes to fill in, and will give us an indication of how your condition affects your day to day life.If you are a regular patient here, just fill out new information since your last visit.

If you are new to this clinic, please fill out as much of the form as you can.

Thank you for your help. If you have any questions please ask your attending doctor.

Name	
DOB	

PID Diagnosis (if known):	
Date of diagnosis (approximate date/year if not exactly known):	
Date of onset of symptoms (approximate year if not exactly known):	

Quality of life	
Total number of infections (within the last year if you are a first-time patient or since your last visit if you are a follow-up patient):	
Of these please give the number of bacterial infections that required admission to hospital.	

Days missed at work/school: If this is your first visit, please put down the approximate number of days (weeks /months) missed within the last year (365 days). If this is a follow up visit, please put down the number of days (weeks /months) missed since your last visit.	o days o weeks o months
Days in hospital: If this is your first visit please put down the number of days (weeks /months) you spent in hospital within the last year. If this is a follow up visit, please put down the number of days in hospital since your last visit.	o days o weeks o months
Reason (s) for hospital admission	
Current weight:	
Do you smoke? o Yes never o used to	
How many per day (if you are a current smoker)?	

Medications (please enter all long-term medication such as Immunoglobulin replacement, heart medication, antibiotics, allergy etc) if not previously recorded by us. Therapy/Medication

(Explanations for the attending doctor/nurse/documentalist – not for patients!

Space is given for a detailed description of 1 type of medication/therapy. Please copy the therapy table on to a separate page for patients who have more medication to record. Compliance. Patients have to indicate how much of the medication they have taken. Always = >95%. Almost always = >90%,. most of the time = >75% . half the time = 50%. seldom = <50%. never = none. If you are taking part in a specific study associated with the ESID database, you may need to add more questions to this form.

Questions

This form is for patients to provide information necessary for you to document the core data set in the ESID online database. It contains questions that you would not normally ask as well as standard questions. Please take a look at the form and see how suitable it is for PID patients attending your clinic. The language should be as simple and clear as possible. Please improve as necessary. Are there too may questions? Is there enough space in the quality of life section to record all the infections or should we make multiple tables like in the therapy section. If you are taking part in a specific study associated with the ESID database, you may need to add more questions to this form. queries/comments to registry@esid.org or Tel. +49 761 270 3445. Anne-Marie PERNER)

Therapy started (date)	
Name	
Route: oral (tablet) intravenous. subcutaneous. topical (creams) inhaled unknown	
Dose and no. of times per day// week// month/ year	
Therapy stopped?	
Reason stopped	
Side effects (if any, irrespective whether or not treatment was discontinued)	
Do you take your medication regularly (i.e as prescribed by your doctor)? Tick one.	□ o Almost always, o most of the time, □ o half of the time □ o seldom □ o never

Juniors WP

As some of you might know, we recently had the ESID Spring Meeting in Prague on May 14 and 15. It was a great experience and a nice opportunity to meet and interact. Besides, this years more space was dedicated to the members of ESIDJuniors working party (Ales and I had the chance to chair all the sections and it was quite an experience! J). We also had broad discussion on the future activities of this working party during the meeting and the free time as well!

Here in brief are some of the issues we raised during the discussion and I would like to have your opinion about:
Age limit: we think it would be better to abolish the limit of 35 years old to join the WP. There are older people who feel to be still not "fully-grown" in the field of PID and would like to join the WP to have an opportunity to learn interacting with other trainees. I would like to have more opinions and then I will discuss that within the ESID board.

"Interesting cases" and "Young researchers' corner" from the ESID Newsletter: we would like to put those sections also on the ESID website to see if we can get more feedback from you all.
Establish collaborations on clinical or scientific projects to apply for European grants: any idea?

ESID Junior budget: I found sponsors who are willing to support our activities with particular focus on short-term stay programs (2-4 weeks) that allow young trainee to learn diagnostic/therapeutic procedures or lab techniques in other countries.
LAST but not LEASTJ: photo-book on the ESID website (maybe Benjamin could help).
Upcoming ESID SUMMER SCHOOL in Malaga, Spain: Application deadline was May 30. I hope most of you applied!!! It is a really challenging experience to learn and interact!

I am really looking forward to hearing back from everyone soon!

Eleonora GAMBINERI

Interesting Papers

- Successful treatment of lymphoproliferative disease complicating primary immunodeficiency / immunodysregulatory disorders with reduced-intensity allogeneic stem cell transplantation. Blood. 2007 May 14; Cohen JM, Sebire NJ, Harvey J, Gaspar HB, Cathy C, Jones A, Rao K, Cubitt D, Amrolia PJ, Davies EG, Veys P. Lymphoproliferative disease (LPD) is a recognized complication of primary immunodeficiency (PID) and immunodysregulatory syndromes with a very poor outcome. The authors describe eight patients with a range of PID and immunodysregulatory syndromes complicated by LPD. Following initial treatment of the LPD all patients underwent reduced intensity conditioned (RIC) SCT with prospective monitoring for EBV-viraemia. All transplanted patients survive free of LPD and cured of their PID, at median follow-up of four years (range one to seven years). The authors advocate this RIC SCT approach to PID patients with pre-existing EBV-LPD beside careful monitoring and pre-emptive therapy.

- A primary immunodeficiency characterized by defective immunoglobulin class switch recombination and impaired DNA repair. J Exp Med. 2007 May 14;204 (5):1207-16. Peron S, Pan-Hammarstrom Q, Imai K, Du L, Taubenheim N, Sanal O, Marodi L, Bergelin-Besancon A, Benkerrou M, de Villartay JP, Fischer A, Revy P, Durandy A.

The authours described here a new primary immunodeficiency, characterized by a defect in Ig class switching associated with a reduced memory B cell population and a skewed nucleotide substitution in SHM.

- Deconstructing common variable immunodeficiency by genetic analysis., Curr Opin Genet Dev. 2007 Apr 26, · Schaffer AA, Salzer U, Hammarstrom L, Grimbacher B, Recent genetic linkage studies have also identified possible loci for dominant CVID genes on chromosomes 4q, 5p and 16q. These findings markedly improved the genetic diagnosis of CVID and point towards new strategies for future genetic studies. In addition, some CVID genes might be relevant to more common diseases such as asthma and stroke.

The TACI story goes on in CVID:

- First explanations of how the C104R heterozygous mutations in TACI has dominant negative effects. However, the authors give no clue to explain hypogammaglobulinemia in patients that bear the heterozygous mutation. J Clin Invest. 2007 Jun 1;117(6):1550-1557. Dominant-negative effect of the heterozygous C104R TACI mutation in common variable immunodeficiency (CVID). Garibyan L, Lobito AA, Siegel RM, Call ME, Wucherpfennig KW, Geha RS.

- The C104R allele has been found in control population in larger studies. Deleterious role of this allele has thus to be confirmed in patient with CVID, eventhough the frequency of the mutated allele is higher in CVID population than in control cohort. Nat Genet. 2007 Apr;39(4):430-1. Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Castigli E, Wilson S, Garibyan L, Rachid R, Bonilla F, Schneider L, Morra M, Curran J, Geha R.

- Nat. Genet. 2007 Apr;39(4):429-30. Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Pan-Hammarström Q, Salzer U, Du L, Björkander J, Cunningham-Rundles C, Nelson DL, Bacchelli C, Gaspar HB, Offer S, Behrens TW, Grimbacher B, Hammarström L.

Interesting Cases

Case #3 *A 7 y-o girl who has been treated for multiple osteomyelytic foci and skin abscesses of unknown aetiology.*

At the age of 6 y (in 2006) the girl was admitted to a hospital due to pain in her knees and both ankles, subsequently accompanied with local swelling. She was initially afebrile, later there were intermittent febrile periods, markers of inflammation (CRP, ESR) fluctuated, however, her overall condition was not significantly altered. X-ray, CT and MRI scans revealed osteomyelitic/osteolytic foci in distal parts of tibia, fibula, femur bilaterally (mainly in metaphysis and epiphysis of the bones), on scintigraphy increased activity was seen at these regions, fluid secreting from fistula on left tibia was sterile, TB was excluded, blood culture was repeatedly sterile, no causal infective organism was found. Bone marrow aspirate was non-remarkable, diffuse osteoporosis on X-ray was documented.

Lab investigation showed microcytic anaemia, thrombocytosis, fluctuating hypergammaglobulinaemia (max values: IgG 18 g/l, IgA 2.9 g/l, IgM 2.4 g/l), IgD normal, screening for autoantibodies, HLA B27 negative, lymphocyte subpopulations normal, response to mitogen (PHA) stimulation normal, NBT and chemiluminescence repeatedly normal, no increased alpha-1-antitrypsin, other biochemistry unremarkable.

Regarding her personal history: Perinatal period was non remarkable. However, in infancy she repeatedly suffered from abscesses in gluteal region after vaccination, she had suppurative ulcer with chronic fistula on her left cheek, she had blepharitis of her right eyelid 2 times, the secret was always sterile or with Staph. aureus. Her denture has been in a bad condition, probably due to insufficient care. She is shorter for her age. Otherwise she was healthy.

She has noteworthy family history. The aunt of our patient (sister of her father), born in 1984 suffered from similar problems – repeated osteomyelitis without disclosed infectious foci. Her parents were related (her father was a cousin of her mother's mother). She underwent long-term treatment with steroids, methotrexate, and suffered from serious side effects of steroid therapy - generalized osteoporosis, retardation of bone growth, extreme obesity, gastropathy, Cushingoid face and secondary diabetes mellitus. She died at the age of 16 y during enterococcal sepsis. The father of our patient has been suffering from similar troubles as well. Since the age of 12 y he has been repeatedly admitted to the hospital due to acne, pyodermia and abscesses in the face, chronic gluteal skin abscesses, one post-vaccination abscess with good response to steroid administration. In 2003 (24 y-o) he suffered from muscle aches for several months, fatigue, nausea, abdominal pain, repeated febrile episodes, oedema of his knee and loss of weight (11 kg in 2 years). He was admitted to the hospital where hepatosplenomegaly and ascites were found, due to ileus, surgical revision was needed; multiple enlarged mesenterial lymphnodes were seen in the abdominal cavity; blood culture was continually negative. After immunosupressive treatment with steroids his status improved, he has been using low doses of steroids since then and besides the skin affection no clinical problems have been encountered. He has never had bone lesions. Cousin of the patient' s father suffers from psoriasis. The family originates from Eastern part of Slovakia, they are Romanies.

Our patient was treated with several antibiotics for a few weeks with minimal effect on the bone and skin lesions. Slight improvement (decrease of oedema and pain) was seen after repeated boluses of steroids. Biological therapy with infliximab at dose 5mg/kg in 4 wks interval was started together with supportive therapy (Ca, Fe substitution, bisphosphonate). The first few infusions brought significant relieve, the patient was almost without any symptoms. However, subsequent doses has had less impressive effect, that is why the interval of administration was shorten (2 wks), then cyclosporine A (3-6 mg/kg/day) and IVIg (1-1.5g/kg/3wks) were added. A prompt, however, only transitory improvement was seen.

We are now considering enhancement of the therapy by using other biologicals (etanercept, adalimumab or anakinra) as the effect of the current therapy seems to be slowly vanishing.

Differentials and discussion

We suspect that this condition is an auto-inflammatory syndrome with autosomal recessive (AR) or autosomal dominant (AD) inheritance with variable penetrance (1). From this group of diseases we consider Chronic Recurrent Multifocal Osteomyelitis (CRMO); Maajed Syndrome (MS) - CRMO+anaemia+dermatosis; PAPA - pyogenic sterile arthritis, pyoderma gangrenosum, acne; and possible overlap with SAPHO syndrome - synovitis, acne, pustulosis, hyperostosis, osteitis.

CRMO is described as rare relapsing chronic illness manifesting with multiple bone lesions that look like defects described at our patient. The diagnostic criteria are as follows: multiple bone defects (most often in metaphysis of long bones, eg. tibia, femur), prolonged course of the clinical symptoms (more than 6

months), periods of remission, uselessness of antibiotic treatment; inflammatory markers do not have to be always increased. In some cases the syndrome is associated with palmoplantar pustulosis or skin pustulosis, Crohn disease or Sapho syndrome. Takayashu arteritis has been documented in some patients with CRMO (2). Inheritance of CRMO is AR and AD as well (3).

MS is a rare disease found mainly in Arabic, predominantly Jordanian population. In the cases found in the literature there were chronic hypochromic and microcytic anaemia requiring transfusions. The course of CRMO is more aggressive in MS and there is growth retardation as well. Recently mutation in LIN2 gene (important in metabolism of fat) has been found. In our patient and her aunt there has been microcytic anaemia, however, it has never required transfusions. The described skin lesions in MS are labelled as pustulosis, often palmoplantar, similar to affection seen in psoriasis. The skin defects seen in our patient differs from these in MS, however family history is positive for psoriasis.

Another possible diagnosis is PAPA syndrome inherited in AD pattern. The skin defects similar to the ones in our patient and her aunt (abscess formation after intramuscular injection) and father of our patient (severe acne, pyoderma gangrenosum). In the clinical picture of this syndrome prevails arthritis not osteomyelitis as it is in our case. Proteinuria, late onset IDDM (in the case of patient's aunt the diabetes was most probably steroid-induced). The syndrome has AD inheritance, the affected gene is PSTPIP1 (product of the gene binds directly to pyrin, protein associated with Familiar Mediterrean Fever; it plays a role cytoskeletal architecture of a cell.

Symptoms seen in our patient and her relatives show signs of over-lap syndrome encompassing the above mentioned nosological entities.

Regarding the therapy of CRMO it has been documented that antibiotics are ineffective besides azithromycine that showed some positive outcome in a few cases. IFN-alpha, IFN-gamma, sulphasalazin, pamidronate, infliximab (4,5) or calcitonin (6). Coticosteroids are effective (7), however due to their effects they are certainly not suitable for long-term treatment. In the case of PAPA syndrome colchicine might be another option due its effect on cytoskeleton.

Questions

Do you think that our differentials are correct? Would you suggest any other option? What other diagnostic procedures can be done? What would be your suggestion for the management of this patient? What is your experience with the treatment of patients with this diagnosis?

We are looking forward to your opinion and to YOUR CASES as well!

Aleš JANDA

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PID-care in development:

For this issue we had a very valuable contribution from:

Prof Madya Dr. Amir Hamzah Abdul Latiff, Clinical Immunology Unit within the Department of Paediatrics, University Putra Malaysia

Dear professor:

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

My name is Amir Hamzah bin Abdul Latiff. I graduated from University of Malaya in 1989. I started work as house officer and medical officer at Hospital Kuala Lumpur before pursuing postgraduate training in paediatrics. I obtained my Master of Medicine in Paediatrics in 1996 from the National University of Malaysia. A year later I was in UK to pursue sub-specialty training in Immunology, and subsequently appointed Specialist Registrar in Clinical Immunology in 1998 based at Leeds General Infirmary and St. James's University Hospital, Leeds. The training programme also included a stint at the Department of Paediatric Immunology and Infectious Diseases, Newcastle General Hospital which was also the Supraregional BMT Centre for Primary Immunodeficiency Diseases in UK.

After returning to Malaysia in 2005, I joined the Faculty of Medicine and Health Sciences, University Putra Malaysia (UPM) and together with Professor Dr. Lokman Mohd Noh, established the Clinical Immunology Unit within the Department of Paediatrics in August 2006.

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

Malaysia which is situated in South-East Asia is made up of West (Peninsular) and East (Borneo Island) Malaysia. The size of Malaysia is approximately 330,252 sq km. with a population of 26,127,700 (in 2005). The annual population growth is 2.1% and the life expectancy is 76.4 years for females and 70.6 years for males. The crude birth rate is 19.6/1,000, crude death rate 4.4/1,000 and the infant mortality rate is 5.1/1,000. The doctor to population ratio is 1:1,300. Both the public and private sectors play important roles in Malaysia's healthcare delivery system. The public sector is substantially subsidized and focuses on healthcare promotion as well as rehabilitative and curative care at the primary, secondary, and tertiary levels.

Can you give some information about PID in your country?

The prevalence of PID in Malaysia is yet to be established and currently efforts are being made to ascertain this. However, given that PID is not thought to be as rare as had been perceived, I am convinced the prevalence is similar to figures in other parts of the world. Whilst the earliest report of PID in Malaysia was made in 1977, PID clinical services were not established until 1986 by Prof Lokman, when he was with the National University of Malaysia, assisted by the Immunology Department of the Institute of Medical Research (IMR), Kuala Lumpur providing the laboratory services. Since then the number of PID cases accumulated to more than 70 cases till 2005 under Prof Lokman's care. Subsequently, referred cases for suspected PID increased substantially when I came back to Malaysia.

Currently our cohort of PID cases (together with those from University of Malaya Medical Centre, UMMC) is over 100, although these could well be more in number, as other centres in Malaysia may have not reported or diagnosed PID clinically. The distribution of types of PID is comparable to

other countries, although we observed that patients with phagocytic defects are of higher frequency than other cohorts. The cases of PID in our cohort are not definitively diagnosed i.e. confirmed by genetic defects, due to lack of molecular diagnostic services for PID at the present moment.

These patients are managed jointly with the general paediatricians, and especially with infectious diseases and respiratory specialists. Intravenous immunoglobulin (but not subcutaneous) replacement therapy is available for PID patients requiring them, and is given in hospitals. Bone marrow transplant for PID has been performed in a few cases at UMMC, but a structured national stem cell transplant services for PID has yet to be established.

What has your role been in PID in your country until now? What do you hope to achieve in the future?

Since coming back to Malaysia, I have been heavily involved in establishing the Clinical Immunology Unit (the first in Malaysia) together with Prof Lokman, whilst enhancing the clinical services for PID patients (including adults). I have also been working closely with IMR to improve the laboratory services for patients suspected of having PID, whilst waiting for our unit's laboratory to materialise in UPM. Other activities include giving lectures on PID to medical students (Paediatrics and Immunology courses) as well as the public via seminars and meetings. I am editing the Malaysian PID clinical guideline which is due for publication in 2007. I am in the steering committee for establishing a national PID network in Malaysia; currently three regions (of West Malaysia) have been tentatively suggested – Northern (where Prof Lokman is currently based), East Coast and Southern (which would encompass East Malaysia for now). My unit, together with IMR, will lead the Southern region. The Northern and East Coast regions will be managed by University Sains Malaysia through the Advanced Medical and Dental Institute, and the School of Medical Sciences, respectively.

Many areas in the care of PID in Malaysia need to be addressed for the future:

1. Establishing the prevalence of PID in Malaysia which will assist our efforts to comprehensively structure an optimal streamlined PID clinical and laboratory services and thus obtaining the necessary financial and human resources from the government and other agencies.

2. To create much greater awareness of PID and disseminating the necessary knowledge via various media including publications/newsletter, 'roadshows'.

3. Creating an online PID registry (to be based in my unit) to compliment the first issue above, and to promote interaction between doctors, nurses and other healthcare workers involved in PID patient care, together with patients and their families. This will also prompt research into various aspects of PID, in both basic and clinical sciences.

4. Increase the number of specialists in Malaysia in the field of Clinical Immunology in general, and especially in the area of PID.

5. Establishing a PID network between regional areas in Malaysia (as stated earlier) for both patient care and research opportunities.

6. Streamlining immunodiagnostic services for PID, including quality assurance in Malaysia and identifying centres to perform tests for molecular diagnosis of PID.

7. Establish a centralized national bone

marrow/stem cell transplant services for PID.

8. Initiate home immunoglobulin replacement therapy (including the use of subcutaneous immunoglobulin preparations).

9. Create a patient support group for PID patients and their families.

10. Co-operation with international centres of involved in PID care to exchange information on clinical services and opportunise research collaborations.

How could ESID help to achieve this goal?

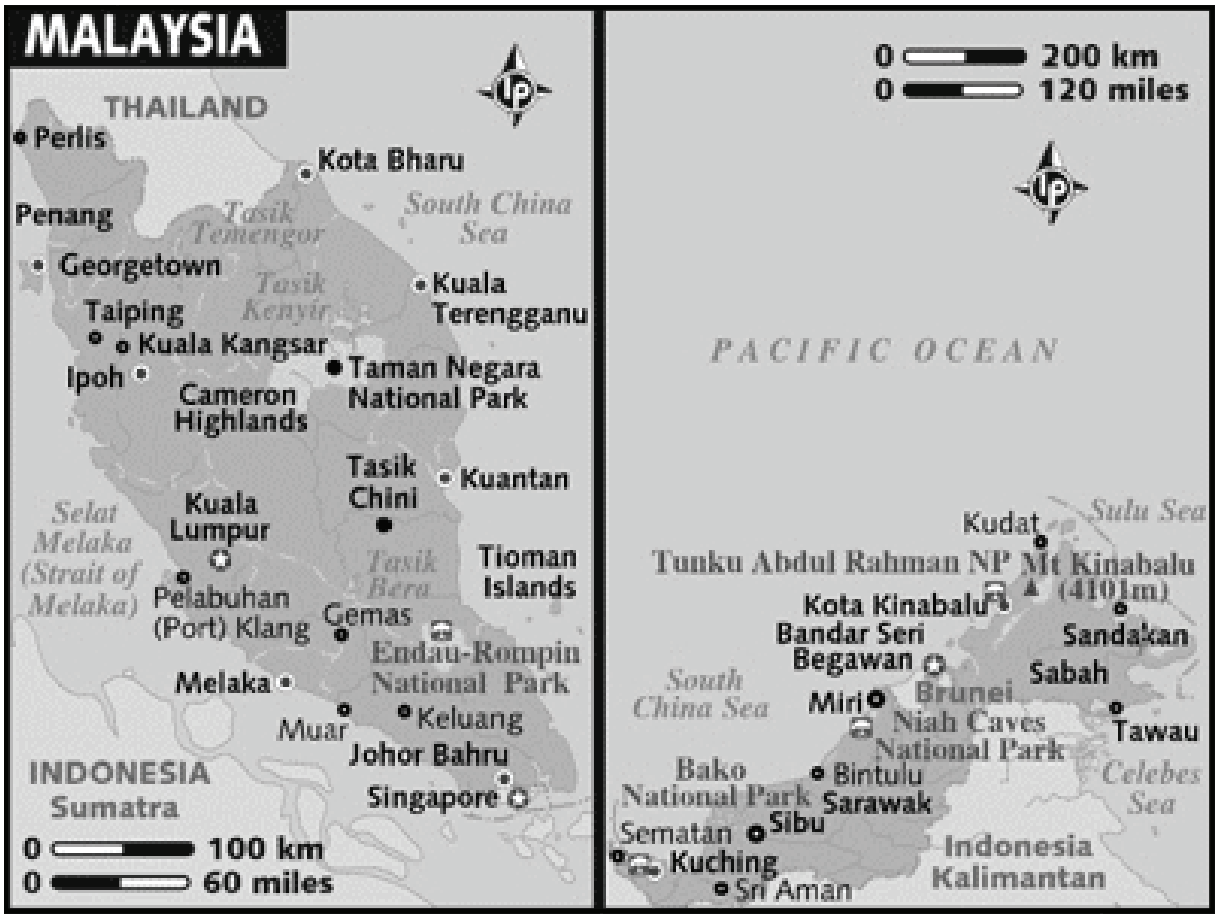
The many activities of ESID have generated interest and keen participation among all those involved in PID care. The idea and philosophy emerging from globalization would suggest that ESID has an important role in delivering and sharing their experience for a united cause in PID care to all. Whilst this may in itself pose a challenge, given the various economic, political and cultural issues among various nations outside the EU, but the common theme of 'caring for patients' would prevail, and ESID can make major steps in establishing a global network among these nations, including Malaysia. These would create opportunities for an open channel where communications can freely flow between ESID and us in many aspects of PID care. These would include consultation and patient referral and research collaborations in basic and clinical sciences of PID, as well as laboratory aspects.

(E-mail: amir@medic.upm.edu.my)

Some pictures from beautiful Malaysia.

Prof Madya Dr. Amir Hamzah Abdul Latiff,

Malaysia


MALAYSIA
THAILAND
Perlis
Kota Bharu
Penang
Tasik Temengor
South China Sea
Georgetown
Kuala Terengganu
Taiping
Tasik Kenyir
Kuala Kangsar
Ipoh
Taman Negara National Park
Cameron Highlands
Tasik Chini
Kuantan
Selat Melaka (Strait of Melaka)
Kuala Lumpur
Tasik Bera
Tioman Islands
Pelabuhan (Port) Klang
Gemas
Endau-Rompin National Park
Melaka
Muar
Keluang
Johor Bahru
INDONESIA
Sumatra
Singapore
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0 200 km
0 120 miles
PACIFIC OCEAN
Sulu Sea
Kudat
Tunku Abdul Rahman NP
Mt Kinabalu (4101m)
Kota Kinabalu
Sandakan
Bandar Seri Begawan
Sabah
South China Sea
Brunei
Miri
Niah Caves National Park
Tawau
Bako National Park
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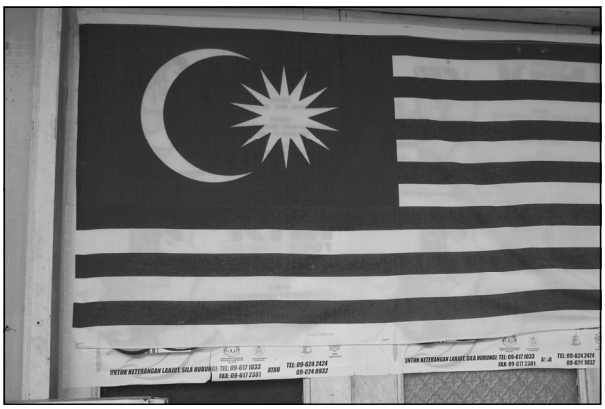
Celebes Sea
Sibu
Sematan
Kuching
Indonesia Kalimantan
Sri Aman


DAULAT TUANKU



Malaysia