Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe

GRACE news

Spreading Excellence in Respiratory Tract Infections

April - July 2010, Volume 5 (2-3)

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Editorial

Dear GRACE Fans!

We did it! Yes we could!

Thanks to a tremendous effort of our 16 participating primary care networks we reached our most important and ambitious milestone: on April 12th 2010 we reached the target of 6000 inclusions for our observational and intervention study. Thousands and thousands of blood samples, nose & throat swabs, and urine samples are waiting in our freezers in European research sites for microbial and human phenotypic and genotypic studies. That will make this by a long way the largest trial and observational cohort for acute LRTI in typical primary care settings - and with good clinical characterisation and unprecedented microbiological and genetic information. The trial data set alone will be significantly larger than the existing systematic review - and that means that the data from this study will dominate the evidence for clinical management of LRTI for some time to come. This study shows better than any other we can think of, what great clinically relevant research is possible when we work together. What a great excitement to finally start analysing all these patient data and laboratory results.

The GRACE consortium is now developing the INternet TRaining for antibiOtic use (INTRO) trial, with tools that are acceptable across cultures in Europe. Another ambitious task but no doubt will the great GRACE team spirit result in another historical milestone. In this issue of GRACE News you can read more about INTRO on pages 5-6.

I hope you will enjoy reading this Newsletter and wish you a wonderful Summer holiday.

Herman Goossens
GRACE coordinator

News Flash: GRACE sustainability

As it would be devastating if after EU funding GRACE would be dismantled, we submitted a proposal to the European Science Foundation (ESF) Research Networking Programmes Call 2009. Now, our proposal for a five year and € 600.000 programme including science meetings, dissemination, coordination, ..., and all 15 EU countries hosting GRACE Work Packages or Primary Care Networks is shortlisted for recommendation. In July, ESF will sent it to ESF Member Organisations inviting them to consider à la carte support. Subject to receiving sufficient financial commitments, our programme will be launched in early 2011.

Samuel Coenen

News

WP9-10 Update: Recruitment has finished!

April 12th, an important day for GRACE: the deadline of 6000 inclusions was reached. After 3 winter seasons recruiting for WP9 and 10 we were proud the target was reached! After recruitment of the outstanding controls we ended up with 6093 patients & controls in total (see figures1&2).

An extra-ordinary achievement, only possible due to the dedication and hard work of all members of the GRACE Network of Excellence, recruiting and facilitating in all 16 participating networks. Many thanks to everyone who participated; all National Network Coordinators, National Network Facilitators, primary care clinicians, laboratory and administrative workers, and not to forget all the participating patients.

What do we have right now?
An enormous amount of data and samples (blood, nose & throat swabs, urine)! Of the 6093 patients, we have 2988 controls, 1050 WP9 only patients and 2055 WP9 and 10 patients. This means a WP9/10 ratio of 66%. In other words: 2 out of 3 patients agreed to be randomized to amoxicillin or placebo. Looking at the elderly: 31% of our patient population is older than 60 years.
Now starts the exciting period of harvesting from all our hard work in the last three years. All partners will participate in the analysis and reporting of the results in the coming year and beyond, and we will keep you informed!

Saskia van Vugt
For the GRACE WP9-10 Study Team

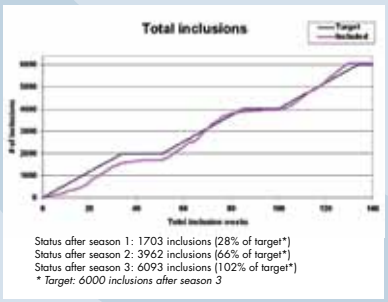


Figure 1

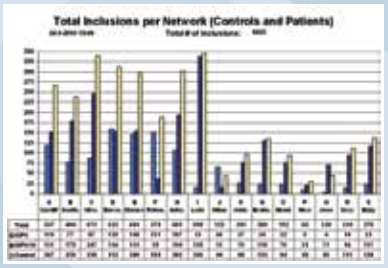


Figure 2

CHAMP Update: Great results and an extension

The CHAMP project main aim is to assess existing evidence, views and expectations of physicians, patients and experts on antibiotic use in respiratory tract infections in European primary care. The final reports of most workpackages are now finalised and have been extensively discussed during an expert meeting in Milan in November 2009 and the third yearly meeting in Warsaw in February of this year. It was found that patients' trust in their general practitioner (GP). Clear explanation and good communication between patient and doctor were regarded as the most important core values in all participating European countries. In addition there was clear common opinions among GPs in different European countries about how to improve antibiotic use. Interventions in primary care should aim on communication skills, and use of near patient tests look very promising.
Public campaigns were reviewed and found to be effective and most likely cost-effective in most countries. Determinants of success however were not clear and further studies should be done on for instance adverse effects of campaigns.
Ongoing and valid monitoring and assessing of prescription rates, side effects and resistance rates were mentioned as pivotal to support activities to rationalise antibiotic use in European primary care. Also the role of pharmaceutical industries should be further studied and discussed.
Both the Milan meeting in the centre of that beautiful and trendy town and the Warsaw meeting where we stayed in a very charming hotel and walked the snowy and historic centre of town were very well organised, very interesting and inspiring.
And some weeks after Warsaw we got the good news that our request for a one year extension was approved! This will enable us to study the feasibility and implementation of an intervention aiming at improving antibiotic use in patients with lower respiratory tract infections in Europe. We will do this in close collaboration with the GRACE project and preparations are in full swing as is explained elsewhere in this newsletter (see p.5-6). We have yet another exciting year ahead of us!

Theo Verheij

The CHAMP Project Group

SATURN Update

The SATURN Project Group in front of a picture of famous French microbiologists including Pasteur et al. Will SATURN follow in the same path?

A very successful SATURN (Impact of Specific Antibiotic Therapies on the prevalence of hUman host ResistaNt bacteria; see GRACE News 2009;4;(4):4) kick off meeting took place the 12th and 13th February 2010 at Les Pensières Conference Center in Annecy, (France). This is a conference facility devoted to global public health created by Fondation Mérieux to promote exchange among leading scientists. And indeed, the great interaction between the participating scientists, managers, assistants and administrative collaborators generated productive sessions and allowed everybody to get to know each other better as well as the scientific and management aspects of the project.

Stephan Harbarth
Fabricio Da Liberdade Jantarada
For the SATURN Project Group

Genetic Link Between CISH and Susceptibility to Infectious Diseases Found

Anna Rautanen

Adrian Hill

Along with colleagues from the Wellcome Trust Centre for Human Genetics at the University of Oxford and from Singapore's Agency for Science, Technology and Research (A*STAR) and National University Health System (NUHS), we have identified a striking association between a gene called CISH and increased susceptibility to several infectious diseases including malaria, tuberculosis, and bacteraemia (bacterial infection of the blood stream). These findings have been published in a recent issue of the New England Journal of Medicine.[1] CISH encodes a protein that negatively regulates the signalling of a variety of cytokines and thereby plays a role in reducing messaging signals between cells of the immune system. Given the central role of cytokine signalling in the host immune response to infection, CISH was considered to be a good candidate gene that could influence susceptibility to common infectious diseases. Numerous genetic variants in the CISH region were analysed altogether in 8402 individuals including Kenyan children with bacteraemia, tuberculosis patients from Malawi, Hong Kong, and The Gambia, and patients with severe malaria from The Gambia, Kenya, and Vietnam. A panel of five different genetic variants within the CISH gene was shown to associate with increased susceptibility to the infectious diseases studied. We estimated that the overall risk of contracting one of these infectious diseases was increased by 18% among persons carrying a single CISH risk allele. The risk increased to 81% among persons with four or more risk alleles; a substantial effect size for a single gene. Functional studies carried out in Singapore showed that peripheral-blood mononuclear cells from healthy Chinese volunteers carrying a CISH promoter variant, the variant that accounted for most of the genetic association with studied diseases, had lower levels of the CISH protein overall than individuals with the more common form of the protein. This suggests that CISH exerts a significant genetic influence on human immune responses. However, it is not clear why having a reduced level of CISH associates with increased susceptibility to multiple infectious diseases. It is hoped that this finding will encourage more clinical research to better understand how the immune system responds to these infectious diseases, and could one day lead to better therapies and vaccines. These genetic variants are now high on our priority list to be genotyped in the GRACE cohorts.

Anna Rautanen

1. Khor CC, Vannberg FO, Chapman SJ, Guo H, Wong SH, Walley AJ, et al. CISH and Susceptibility to Infectious Diseases. N Engl J Med 2010; 362:2092-101.

Update HAPPY AUDIT: Overall results

A total of 618 general practitioners in five European contries (Denmark, Sweden, Russia, Lithuania, Spain) and Argentina have been participating in this study. The methodology of this study is published elsewhere.[1] Summarizing, in the first analysis the participating doctors filled in audit registration charts all the consultations with respiratory tract infections (RTIs) during 15 working days in winter 2008. Subsequently the physicians received partly their own result and partly the total result of their countries. The results were discussed at follow-up meetings, where the quality problems were defined and intervention activities initiated, consisting of training courses on management of respiratory tract infections, the handout of guidelines to the doctors with identical recommendations for diagnosis, but different, country-specific treatment guidelines, the handout of posters for the waiting room with the information to the patients that RTIs are often harmless and self-limiting diseases and that antibiotics are rarely needed, the handout of brochures to the patients with the same information and the acquisition of skill in the use of rapid diagnostic methods - rapid antigenic tests and C-reactive protein determination - in the medical office to make a more precise diagnosis in their office. A second registration was carried out in winter 2009 after this intervention and their results were also discussed in a last follow up meeting in the beginning of 2010. The general results about the number of physicians participating and the number of contacts registered are summarized in the table.

Country	Number of doctors		Number of patients registered		Number of patients treated with antibiotics	
	2008	2009	2008	2009	2008	2009
Argentina	60	48	4,374	3,641	1,780 (41%)	1,170 (32%)
Denmark	102	78	3,904	3,706	1,351 (35%)	1,185 (32%)
Lithuania	31	28	2,706	1,976	1,152 (43%)	468 (24%)
Russia	39	37	3,685	3,284	1,215 (33%)	481 (15%)
Spain	309	281	16,751	12,760	4,675 (28%)	2,530 (20%)
Sweden	77	39	1,853	895	764 (41%)	333 (37%)
Total	618	511	33,273	26,262	10,937 (33%)	9,669 (24%)

TABLE. Number of doctors, patients registered and patients treated with antibiotics before (2008) and after (2009) the intervention

Unlike Sweden and Denmark, the use of rapid tests before the intervention was very low in the remaining countries. As is shown in the figure 1, StrepA was more frequently used in the first registration in the two Scandinavian countries while in the remaining countries it was more used after the intervention. Antibiotic prescribing was lower after the intervention in all the countries although this reduction was very slight in the Scandinavian countries. As shown in the figure 2, antibiotic prescription was 24% after the intervention vs. 33% observed in 2008. This difference was more remarkable in the Baltic countries (Lithuania and Russia) followed by Spain. The main results in Denmark were the reduction in the overuse of StrepA test, the decreasing use of antibiotics prescribed in acute bronchitis, the improved use of antibiotic in patients with exacerbation of COPD and the reduction in the use of macrolides. In Sweden no significant changes in the antibiotic treatment were observed in the second registration although a slight reduction was found in 2009. The accessibility to rapid tests reduced the antibiotic prescription in bronchitis, tonsillitis and sinusitis in Lithuania; furthermore, in that country cephalosporins were not prescribed any more for treating contacts with sinusitis and otitis, the prescription of amoxicillin + clavulanic acid decreased 3-7 times after the intervention and the prescription of antibiotics for children decreased from 44% observed in 2008 to 24.5% observed after the registration. In Russia an increasing use of rapid tests was clearly observed with a marked reduction in the antibiotic treatment for most RTIs and an improved choice of antibiotic when taking the decision to treat with antibiotics along with a reduction in the use of macrolides and cephalosporins. In Spain an important reduction in antibiotic prescription was also found after the intervention mainly in suspected viral infections with an improvement in the quality of antibiotic prescription, particularly in pharyngotonsillitis. A marked reduction in antibiotic treatment for most RTIs was observed in Argentina, with an improved choice of antibiotic when taking the decision to treat with antibiotics and a reduction in the use of macrolides and cephalosporins.

These results clearly show that the use of multifaceted strategies combining active intervention by general practitioners are really effective in reducing prescribing of unnecessary antibiotics for RTIs and improving the use of appropriate antibiotics in suspected bacterial infections.

Carl Llor

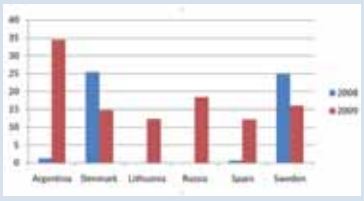
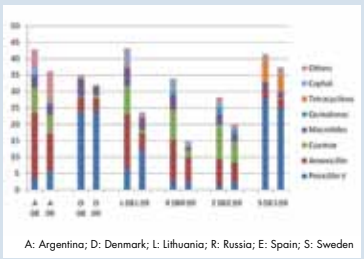


FIGURE 1. Percentage of Strep A performed in contacts with pharyngotonsillitis before (2008) and after (2009) the intervention depending on the country



A: Argentina; D: Denmark; L: Lithuania; R: Russia; E: Spain; S: Sweden

FIGURE 2. Percentage of the total amount of antibiotics and classes of antibiotics prescribed before (2008) and after (2009) the intervention

References

1. Bjerrum L, Munck A, Gahrn-Hansen B, Hansen MP, Llor C, Cots JM, et al. Health Alliance for Prudent Prescribing, Yield and Use of Antimicrobial Drugs in the Treatment of Respiratory Tract Infections (HAPPY AUDIT). BMC Fam Pract 2010;11:29.

WP10b *- The GRACE INTRO Trial (INternet TRraining for antibiOtic use)*

Acute lower respiratory tract infection (LRTI) will cost most EU countries several hundred million Euros in consultation costs let alone the annual antibiotic prescription costs. Evidence suggests that most GPs will prescribe antibiotics for a large proportion of acute respiratory infections (RTI) even in relatively low prescribing countries, and that there is probably very little benefit from antibiotics in LRTI[1, 2] - supported by recent evidence from the large observational study in GRACE (WP8).[3] Since LRTI is the commonest presentation of RTI, LRTI should probably be the first priority for rationalising antibiotic use.

Behavioural approaches to reducing prescribing. Systematic reviews and recent trials suggest an interactive approach possibly combined with audit is an effective way of reducing prescribing.[4, 5] To date literature reviews done within the sister CHAMP project showed that most interventions used in the different studies did have an effect, but the studies are too heterogeneous in setting and quality to conclude definitively which intervention is best; interventions seemed most effective when they contained education aimed at both professionals and patients; contained communication skills intervention; involved group discussions about guidelines with local modification; and or include delayed prescribing. There is recent evidence from the IMPAC^{3}T study - where two interventions (CRP, and communication skills) were tested in a factorial design - that training GPs in communication skills in a standardised way in the Netherlands (the lowest antibiotic prescribing country in the EU) can provide a 20% reduction in antibiotic prescribing for LRTI,[6] supported by results emerging from the STAR study in Cardiff (Chris Butler, personal communication). Another recent study from the Cardiff group demonstrated that a similar reduction in prescribing can occur with a web-based training programme based around the use of a patient information booklet for acute RTI in children.[7] Clearly these findings need replicating in wider settings, but if a web-based behavioural programme can achieve as much as training with additional outreach visits it is likely to be much more cost-effective. This trial in GRACE (WP10b) will assess whether a web-based behavioural intervention based around the most effective and hopefully cost-effective features of previous studies reduces prescribing for LRTI.

Near patient tests. C-reactive protein (CRP) is the only commonly available near patient test for use in LRTI. Systematic reviews suggest that CRP when used alone has moderate negative predictive values for consolidation[8] - the major complication of LRTI - and that when added to clinical information the negative predictive value is improved further. The evidence from the IMPAC^{3}T study suggests that training GPs to use CRP in a standardised way can also provide a 20% reduction in antibiotic prescribing. This intervention needs to be assessed in a wider setting and to further clarify whether the additional use of CRP is additive to the best behavioural intervention available.

Method. We aim to randomise a minimum of 30 practices in each of the participating primary care networks (PCN; each practice documenting management and outcomes in 25 patients) to one of two basic groups.

1) Normal care
2) Web based training in communication skills and the use of natural history information and a patient booklet. We will develop web-based training modules incorporating the approaches of recent studies.[7, 9] The materials will be piloted in every country and modified according to feedback from focus groups in each country. Each participating practice will also be required to appoint a lead GP who will organise a group meeting where their in house audit of antibiotic prescribing and a version of the interactive patient booklet for each country will be discussed. We have chosen a web-based approach as it is likely to be easier to provide quality control, to allow individualisation, and to be as effective - and probably more cost-effective – as other approaches.

Half of each of the above groups (making four subgroups in all) will be randomized to receive training in the use of CRP, and the training will again be web-based. The precise guidance on the use of CRP will be developed based on systematic review evidence,[8, 10] and modified by consultation with the an expert group (including recognized leaders in the field within and outside GRACE (particularly Jochen Cals and Hasse Melbye) and by the results coming from GRACE WP9-10a. We propose using CRP equipment that was successfully used in the IMPACT study - generously supplied by Orion Diagnostica.

Primary Care Networks in INTRO

Paul Little

Networks. We would have very much liked to use all the GRACE PCNs, but due to the logistic difficulties of developing and modifying the website in different languages we have had to limit our choice to 8 PCNs sited in four sites, based on having two PCNs per country (or two PCNs sharing a language in different countries), and to make sure that different regions of Europe (North-South-East-West) are represented. Thus we selected PCNs in England and Wales, the Netherlands and Belgium, Poland (2 of the GRACE Polish Networks), and Spain (one of the GRACE Spanish Networks (one declined) and an additional Network lead by Carles Llor from the HAPPY AUDIT Consortium).

Quantitative Outcomes. We will measure changes in antibiotic prescribing, symptom resolution, quality of life, adverse outcomes (deterioration of the illness; complications), and resource use (for economic analysis).
Qualitative assessment. Qualitative work will inform the development of the interventions and modifications of the interventions following piloting. Time permitting at the end of the intervention winter, we will convene focus groups and/or individual interviews with participating clinicians in each country. Time permitting we will also interview patients to help understand their perceptions of the process for the same interventions and to help inform trial results.

If the GRACE WP10a trial was a difficult exercise, threatened by logistic difficulties the INTRO trial faces similar if perhaps not greater difficulties - to develop, pilot and trial two interventions among several thousand patients in less than a year is a very tall order indeed! Furthermore, a great wit has observed that getting GPs (and in this case GPs, clinical academics and microbiologists!) to agree is rather like trying to herd cats! However, despite the prodigious difficulties of trying to get agreement in a common approach and develop an intervention acceptable across cultures and countries, currently with both goodwill and great teamwork – which has typified GRACE to date - we have developed provisional versions of the website and are piloting them. GRACE INTRO is negotiating a difficult course through some major obstacles, but has made a flying start and is purring along nicely!

Paul Little
For the INTRO team

References

1. Little P, Rumsby K, Kelly J, Watson L, Moore M, Warner G, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomised controlled trial. JAMA 2005;293:3029-35.
2. Smith S, Fahey T, Smucny J, Becker L. Antibiotics for acute bronchitis. Cochrane Library 2009.
3. Butler C, Hood K, Verheij T, Little P, Melbye H, Nuttall J, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. BMJ 2009;b2242.
4. Arnold S, Straus S. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database of systematic reviews 2005.
5. O'Brien M, Rogers S, Jamtvendt G, Oxman A, Odgaard-Jensen J, Kristoffersen D, et al. Educational outreach visits: effects on professional practice and health care outcomes . Cochrane Database of systematic reviews 2007.
6. Cals J, Butler C, Hopstaken R, Hood K, Dinant G. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. BMJ 2009;doi:10.1136/bmj.b1374.
7. Francis N, Butler C, Hood K, Simpson S, Wood F, Nuttall J. Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. BMJ 2009;339:b2885.
8. van der Meer V, Neven AK, van den Broek PJ, Assendelft WJJ. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. BMJ 2005;331:26.
9. Cals J, Scheppers N, Hopstaken R, Hood K, Dinant G, Goettsch H, et al. Evidence based management of acute bronchitis; sustained competence of enhanced communication skills acquisition in general practice. Patient Education & Counseling 2007;68:270-8.
10. Falk G, Fahey T. C-reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies. Fam Pract 2009;26:10-21.

GRACE Related Projects: *ARPEC*

Antibiotic prescribing is a major paediatric problem both in the community, where too many children are receiving broad-spectrum antibiotics for viral infections, and in the hospital, where long courses of broad-spectrum antibiotics drive antimicrobial resistance. There is an urgent need to strengthen the prudent use of antibiotic prescribing for children in Europe. It is well recognised that there are very few new classes of antibiotics under development. We have, as yet, no systematic data collection for community antibiotic prescribing, hospital antibiotic prescribing, and antimicrobial resistance rates for common pathogens in children in Europe.

A new study in this field has now been funded by DG SANCO and will start in late 2010. ARPEC (Antibiotic Resistance and Prescribing in European Children) will use established methodologies from ESAC (European Surveillance of Antimicrobial Consumption; www.esac.ua.ac.be) and EARSS (European Antimicrobial Resistance Surveillance System; www.rivm.nl/earss/) and community prescribing databases to develop a prospective surveillance system to monitor rates of antibiotic prescribing and resistance in European children.

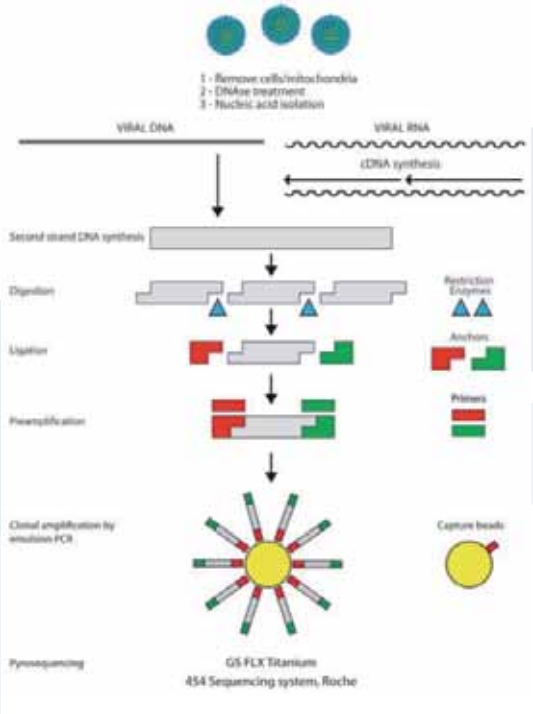
The study has 5 main goals. The first is to identify and investigate all existing paediatric prescribing databases across the EU to determine the different rates of antibiotic prescribing, by drug and where possible, by age and indication. The second is to work with ESAC to develop a novel paediatric PPS (Point Prevalence Survey) methodology and to pilot it in 15 large paediatric hospitals across the EU. The third part of the study is to use EARSS methodology to develop a prospective data collection of paediatric bacteraemia and identify variation in rates of antimicrobial resistance in 6 key pathogens in the partner institutions and countries. The fourth part of the study is a systematic data collection of community and hospital antibiotic prescribing guidelines.
All these results will be collated into a country specific web based training tool for use in paediatric trainees in collaboration with specific European Paediatric Training programmes.

The study will then aim to set formal benchmarks for prescribing and resistance rates, working through membership of ESPID (European Society of Paediatric Infectious Diseases) and clinical experts within that group to develop more unified EU-wide antibiotic treatment guidelines. The project will feed back the rates of the surveys to encourage through national opinion leaders and networks and educational programme to encourage prudent antimicrobial use.

For any further information please do contact Dr Mike Sharland Chair of ARPEC on mike.sharland@stgeorges.nhs.uk

Spreading Excellence in Respiratory Tract Infections:

The best option for virus discovery, VIDISCA combined with high throughput sequencing



In approximately 20% of the adults with respiratory tract illness no known pathogen can be detected. A yet unknown virus could be the cause of the illness and a sequence independent amplifications method such as virus discovery cDNA-AFLP (VIDSICA), can be used to identify the virus. The VIDISCA method uses restriction enzyme recognition sites to digest all nucleic acids in a sample, a ligation step to add adaptors, and a PCR with primers that anneal to the adaptors to amplify the input viral DNA or viral RNA.[1] The method was successfully used to identify human coronavirus NL63 (HCoV-NL63) [1] and picornaviruses.[2] These discoveries were all from cultured virus isolates and not from clinical samples, since the VIDISCA assay is not sensitive enough to detect viruses from uncultured material. In theory the latest high throughput sequencing techniques may enhance VIDISCA sensitivity and enable virus identification in cases where conventional VIDISCA may not.

In conventional VIDISCA a virus specific amplification product has to be visible and recognizably different from the negative control PCR products. This means selection of virus specific amplification by eye, whereas VIDISCA combined with high throughput sequencing does not need recognizable visualization. With next generation sequencing large amounts of sequences are generated, thus it allows everything in a sample to be sequenced, including background (mainly rRNA amplification products) and potentially unknown viruses.

We evaluated this theoretical sensitivity improvement by sequencing VIDISCA amplified products with the Roche 454-FLX system (VIDISCA-454, see figure). As input twelve randomly chosen nasopharyngeal washings of patients all containing known respiratory viruses were used. The outcome of the standard VIDISCA was compared to the results with VIDISCA-454. All samples were analyzed double-blind to prevent biased analyzing of the sequences.

With Roche-454-FLX a total of 83135 sequences were generated of which 68 were viral (HCoV-229E, HCoV-OC43, RSV, HRV, hMPV). Standard VIDISCA revealed the identity of only 1 virus (HCoV-229E) in the 12 nasopharyngeal samples, whereas with the VIDISCA-454 the viruses in 6 of the 12 samples could be correctly identified.

In conclusion, high throughput sequencing and VIDISCA increases the sensitivity of the discovery method to a level that allows virus discovery directly from nasopharyngeal aspirates.

Lia van der Hoek
For the WP5 team

References

1. van der Hoek L., Pyrc K, Jebbink MF et al. Identification of a new human coronavirus. Nat Med 2004;10: 368-73.
2. de Vries M, Pyrc K, Berkhout R et al. Human parechovirus type 1, 3, 4, 5, and 6 detection in picornavirus cultures. J Clin Microbiol 2008;46:759-62.

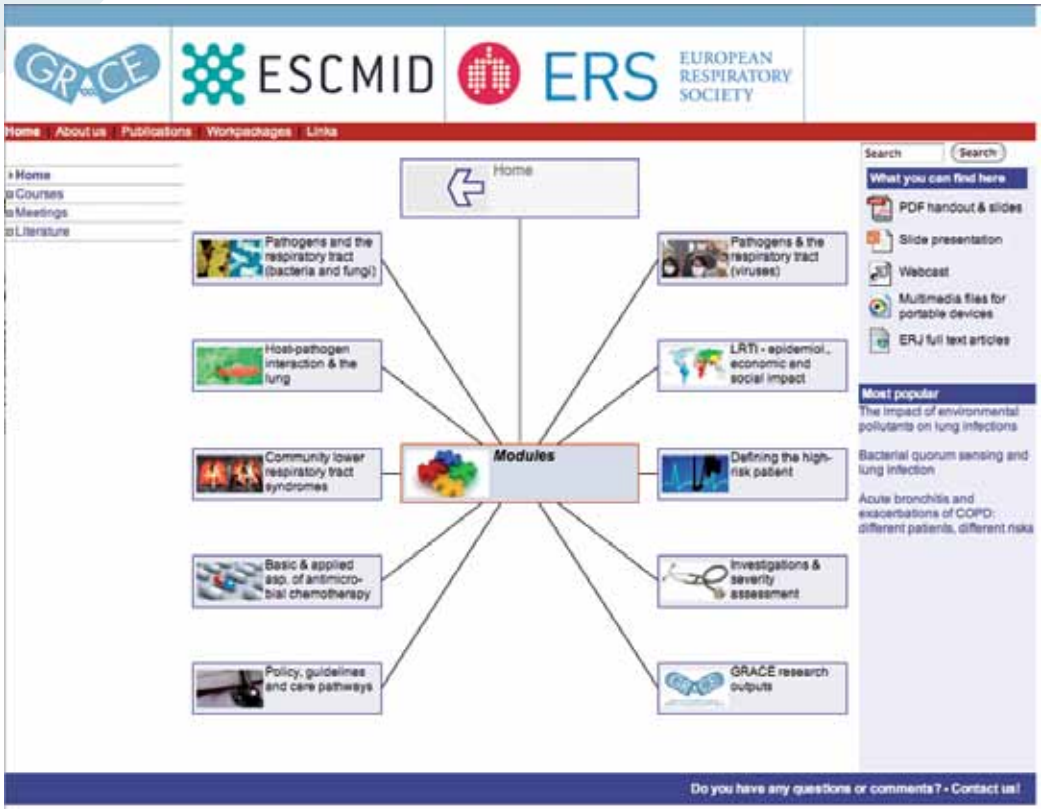
WP12 News

The GRACE Education and Training Curriculum and e-Learning Portal

The GRACE research Network of Excellence is designed and delivered through an integrated and collaborating series of Work Packages (WP). Work Package 12 (WP12) consists of representatives from two leading European professional societies namely, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Respiratory Society (ERS). The work package leaders for WP12 are Francesco Blasi (ERS) and Roger Finch (ESCMID). WP12 has responsibilities for developing and delivering a novel programme of education and training based on the topics and research themes pertinent to the GRACE project.

In order to deliver its programme of education and training, WP12 decided to design an innovative curriculum of themes and topics relevant to the science and practice of the collaborating disciplines within the GRACE project. This curriculum would form the basis for informing content and design of the educational activities of GRACE; these have been delivered through a combination of postgraduate courses (PGCs) and workshops (WSs). The curriculum has been designed in a modular format. These modules cover basic science, specialist knowledge and relevant elements of clinical practice for the management of community-acquired lower respiratory tract infections. The 10 modules (Table) and their individual topics have informed the content of the GRACE PGCs and WSs. Since the GRACE project is also delivering on a programme of research, it was agreed to allocate one of the modules to cover topics of a research nature presented by the GRACE team of investigators.

The PGCs have been delivered by linking to the annual Congresses of the two partner societies (European Congress of Clinical Microbiology and Infectious Diseases and ERS Annual Congress). These were structured as either whole or half-day events. The workshops have been organised as independent events lasting for one or two days. To date these have been held in Prague, Cambridge and Rome. The content of these PGCs and WSs has been drawn from the GRACE curriculum. Both the curriculum and the outputs of the PGCs and WSs are available through the GRACE e-Learning Portal.



GRACE e-Learning Portal

The GRACE e-Learning Portal has been developed in collaboration with the ERS who have a well established e-Learning facility for its membership.

The e-Learning Portal has been constructed as a searchable resource. The design is based on the modular arrangement of the GRACE curriculum and their individual topics. The material can be interrogated in several ways, either via the curriculum which is structured like a mind-map by module and topics, or by accessing the PGC and WS material directly. These outputs are freely accessible and include downloadable PowerPoint presentations, lecture handouts and webcasts of the presentations and other reference resources. To date, eight PGCs and four WSs have taken place and have provided more than 90 webcast presentations and much more supporting material.

The GRACE e-Learning Portal is now a valuable resource not only for individual learning but also to support group educational activities that might include workshops and even symposia. Users can thus design their own educational events by selecting and downloading relevant material. Furthermore, there is no restriction on translating the material, which should further extend its accessibility.

Conclusion

The GRACE e-Learning Portal has been designed and built up over the past four years to ensure that it provides key material relevant to the science and practice of investigating, managing and preventing community-acquired LRTI and in the process support the control of antibiotic resistance. The range of topics within the modular arrangement provide a rich resource to support education and training. These materials are all freely accessible and downloadable at www.grace-edut.org. You are therefore encouraged to access, use and recommend the material.

Roger Finch

Table: The GRACE Education and Training Curriculum

Module	Title	No. of topics in module
1	Pathogens and the respiratory tract (bacteria and fungi)	13
2	Pathogens and the respiratory tract (viruses)	9
3	Host-pathogen interaction and the lung	7
4	LRTI – epidemiology, economic and social impact	8
5	Community lower respiratory tract syndromes	13
6	Defining the high-risk patient (host, microbe and environmental factors)	6
7	Basic and applied aspects of antimicrobial chemotherapy	16
8	Current approaches to investigations and severity assessment	8
9	Policy, guidelines and care pathways to support community and hospital practice	9
10	GRACE research outputs	11

GRACE @ ECCMID 2010, Vienna, Austria

GRACE Postgraduate Courses (PGCs) held at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) have already some tradition: Munich in 2007, Barcelona in 2008, Helsinki in 2009 and Vienna this year.

This year's PGC on **Viruses and the respiratory tract – current and future issues** took place on 10 April 2010 during the 20th ECCMID in Vienna. With approximately 160 participants, it was one of the GRACE courses with the highest attendance. Like previous GRACE events, this course was rated highly by delegates and faculty alike. The course topics spanned from epidemiology via pathogenesis, diagnosis and surveillance to vaccination. All material - webcasts and presentation slides - can be accessed freely online at the GRACE e-learning platform (www.grace-edut.org).

In addition to the PGC, the following GRACE activities provided further opportunity for GRACE to share its research programme and educational outputs with delegates attending the Congress:
- a general GRACE poster in the European Network Corner (see next page)
- an oral presentation on diagnosis of community-acquired LRTI (M. Ieven et al.)[1]
- two scientific posters on diagnostic topics (Loens et al.) [2,3]

Roger Finch
On behalf of WP12

References

1. Ieven M, Lammens D, Vanderstraeten A, Loens K, Verheij T, Little P, Goossens H and the GRACE study team. Usefulness of sputum Gram stain and culture for S. pneumoniae and Haemophilus spp. in the aetiologic diagnosis of community-acquired lower respiratory tract infections and predictive value of serum PCT levels for these bacterial LRTI (Abstr. 2649)
2. Loens K, Lammens C, Vanderstraeten A, Coenjaerts F, Claas E, Van Loon A, Verheij T, Little P, Goossens H, Ieven M on behalf of the GRACE study team. Is there a role for CRP or PCT as inflammatory parameters in the management of outpatients with community-acquired lower respiratory tract infections? (Abstr. 2282)
3. Loens K, Vanderstraeten A, Lammens C, Ursi D, Dettlaff S, Verheij T, Little P, Goossens H, Ieven M and the GRACE study team. Sensitivity of both PCR and serology for diagnosis of Mycoplasma pneumoniae and Chlamydophila pneumoniae in a primary care setting (Abstr. 2695)

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GENOMICS TO COMBAT RESISTANCE AGAINST ANTIBIOTICS IN COMMUNITY-ACQUIRED LRTI IN EUROPE (GRACE)

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LIFE SCIENCES, GENOMICS AND BIOTECHNOLOGY FOR HEALTH

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Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe

www.grace-lrti.org

Background: Community-acquired lower respiratory tract infections (CA-LRTI) are the leading reason for seeking medical care and consuming antibiotics.

Objectives: The overall aim of GRACE is to combat antimicrobial resistance in CA-LRTI through integrating and strengthening centres of excellence for studying the application of genomics with primary care practitioners.

Budget: 11.500.000€

Period: March 1, 2005-February 28, 2011 (6 month extension has been requested)

Methods: The research program has been divided into four platforms (fig. 1): **GRACE-COMIT** for coordination, management and information technology, **GRACE-TECH** for technological developments, **GRACE-PAT** for patient studies and **GRACE-EDUT** for education and training. More information can be found in the GRACE Leaflet (fig. 2) and on the GRACE website (www.grace-lrti.org).

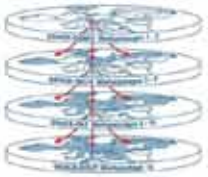

Figure 1: The GRACE Platforms

Figure 2: The GRACE Leaflet

Results:

GRACE-COMIT, platform for coordination, management and information technology:

- A 3-monthly newsletter is reporting on the progress of GRACE activities (fig. 3).
- A GRACE Online System (GOS) was set up by Robert Veen and his team at the University Medical Centre in Utrecht (fig. 4).

Figure 3: GRACE News 2006 - 2009

Figure 4: GRACE Online System: WP9-10 inclusion rates (24 March 2010)

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GRACE-TECH, platform for technological development:

WP3, led by Greet Ieven and her team at the University of Antwerp:
- A network of laboratories with expertise in real-time molecular amplification procedures, of CA-LRTI agents was established. The network developed, validated and implemented these assays. The assays are being applied to the nasopharyngeal flocked swabs collected in WP9/10.

WP4, led by Adrian Hill and his team at Oxford University:
- Genetic risk factors for community-acquired pneumonia will be identified. An ability to distinguish susceptible from resistant individuals with simple genotyping tests will provide a long-term capacity to target particular antibiotics selectively to more susceptible individuals.

WP5, led by Alexander Gorbalenya and his team at Leiden University:
- Analysis of patient samples was initiated with the aim of detecting new viruses. A technique exploiting the genome conservation among viruses and a 2nd technique relying on the ubiquitous presence of restriction sites in virus genomes are being used.

WP6, led by Birgitta Henriques-Normark and her team at Smittskyddsinstitutet:
- The pan-European spread of antibiotic resistant and susceptible pneumococcal clones causing CA-LRTI will be studied as well as clonal properties correlated to disease.
- The development of antibiotic resistance in *S. pneumoniae* causing CA-LRTI will be monitored and genotypic determinations will be performed of new resistance determinants.

WP7, led by Derrick Crook and his team at Oxford University:
- The prevalence, mechanism and evolution of antibiotic resistance in *Haemophilus influenzae* will be investigated. All the methodology for conducting the studies has been completed, new methodology is being developed.

GRACE-PAT, platform for patient studies:

WP8, led by Chris Butler and his team at Cardiff University:
Anno 2010 the network of primary care networks (PCNs) established for WP8 includes 19 PCNs in 15 European countries of which 16 currently are active in WP9-10 (fig. 4).
The first GRACE papers has been published (BMJ 2009;338:b2242). It describes the first results of GRACE-01, registered at www.clinicaltrials.gov as NCT00353951, the largest observational study of current practice in CA-LRTI ever undertaken, including 3,402 patients from 14 PCNs. More papers are published, in press or in review.
The opinions and expectations of physicians and patients regarding CA-LRTI (management) were assessed in GRACE-02, a qualitative study with over 200 interviews in 9 PCNs.
Evidence-based definitions of major LRTIs were produced in GRACE-03.

WP9, led by Theo Verheij and his team at the University Medical Centre in Utrecht:
Up to 3000 adults with CA-LRTI and 3000 healthy controls are being included to study the microbiological etiology of CA- LRTI and bacterial resistance rates in collaboration with GRACE-TECH.
With the 3000 cases diagnostic models will be developed to help physicians better predict bacterial infections and pneumonia, and a prognostic model that would help physicians to discriminate between patients with a high and patients with a low risk for poor outcome.

WP10, led by Paul Little and his team at the University of Southampton:
A trial nested in the observational studies of WP9 will study the effects of antibiotic treatment (amoxicillin 1g TID) compared with placebo in 3000 subjects with CA-LRTI.

For WP9-10 inclusion rates see figure 4 (daily updates at www.grace-lrti.org/wp9-10).

WP11, led by Jo Coast, Richard Smith and their teams at the University of Birmingham and the London School of Hygiene and Tropical Medicine, respectively:
According to very preliminary results on resource use, treatment costs and quality of life (based on GRACE-01 data and information about sources of costs provided by the PCNs) already clearly showed that treatment of LRTI varies hugely across Europe both in terms of the resources used in different settings and the cost of those resources.

Figure 5: The 19 primary care networks involved in GRACE

GRACE-EDUT, platform for education and training:

WP12, led by Francesco Blasi (ERS) and Roger Finch (ESCMID):
- A professional educational programme, including web-based teaching resources, is organised through 2 leading European scientific societies (ESCMID and ERS) with the objective of widely disseminating current scientific and clinical knowledge, and the emerging research outputs of the Network of Excellence.

The GRACE e-learning platform at www.grace-edut.org, contains the GRACE curriculum and educational material from all GRACE Postgraduate Courses (PGC) and Workshops (WS) for free. Currently this is material from 7 PGC and 4 WS, i.e. 85 webcasts, 62 presentation slide sets and 111 PDF documents.

Figure 6: The e-learning platform

Future courses and workshops

9th PGC: Antimicrobial chemotherapy in daily practice (ERS Congress, Barcelona, 18 September 2010)
5th WS: Hot topics in lower respiratory tract infections (Budapest, 4 – 5 November 2010)