Editorial

**GRACE: extended until August 2011, but ... the spirit will prevail until 2016!**

Our request to extend GRACE with another 6 months ([from March 1 to August 30, 2011](#)) was granted by DG Research of the EC. With this extension, we will be able to finish the INTRO trial and organise a memorable Final GRACE Meeting in June (p.8).

GRACE will leave a trace because our proposal submitted to the European Science Foundation for funds to continue the translational work of the GRACE Network was granted (p.3)! This new project is called **TRACE** (Translational Research on Antimicrobial resistance and Community-acquired infections in Europe) and it will be launched in June 2011 in Antwerp, just prior to the Final GRACE Meeting.

GRACE INTRO (p.2) has kicked off in 8 Primary Care Networks in 6 European countries. The last improvements are being implemented in the predominantly web-based intervention. The intervention is linked with the European Antibiotic Awareness Day (held annually on November 18) and the logo and visuals (e.g. kicking hedgehog) will be used in the booklet. Another unique study has started in primary care in Europe.

On page 3 and 4 we invite you to read more about two new EU funded projects, **APRES** and **RAPP-ID**. The RAPP-ID project will hopefully result in the development of point-of-care diagnostic tests by 2016. In this Newsletter we also report on the role of CRP, the impact of aging on susceptibility to infection and pathways in the management of LRTI.

The **Final GRACE Meeting** will be held in Antwerp on June 16 - 18, 2011 (p.8). The objectives of the GRACE project will be revisited during this conference and we will discuss where GRACE made a difference in the field of CA-LRTI. I am confident that we will tick all the boxes of the GRACE objectives!

We expect a “**GRACE dissemination boom**” in 2011. GRACE will be presented at ECCMID, ERS, WONCA, EGPRN, and GRIN.

We hope you enjoy reading this GRACE Newsletter!

**Best wishes,**

Herman Goossens

GRACE Coordinator

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**Announcement**

We are recruiting one Project Manager for both TRACE (see p.3) and RAPP-ID (see p.4). Starting date: April 2011.

Interested?

Please contact Herman Goossens, herman.goossens@uza.be, before March 15, 2011.
News

GRACE INTRO: Update of Progress (WP10b)

This trial is a practice-based trial assessing the impact of internet based training packages in communication skills and the use of CRP to modify antibiotic prescribing for patients presenting with LRTI in primary care (see GRACE News 2010;4(2-3):5-6, and GRACE News 2010;5(4):2-3).

The GRACE INTRO trial has reached an important milestone: the baseline audit of antibiotic prescribing is now complete. The first patient was recruited by Antwerp on 22nd September 2010, and by 17th December, 6,174 patients had been included by 8 participating networks in 6 European Countries (Spain, Poland, England, Wales, Netherlands, and Belgium). The final figure for inclusions in the baseline audit will be even higher as networks complete their data entry in the next few weeks.

With the baseline audit complete, the 246 participating GP practices were randomised to one of four groups, 1. Usual care 2. CRP device training 3. Communication skills training 4. Both CRP and communication skills training. The GP practices have a few weeks mid-winter to complete their training.

For CRP Point of Care Training, training will entail a visit to demonstrate the CRP device with web-based material including
- Background to the CRP test.
- Information on the use of the test in an LRTI consultation.
- Guidance on interpretation of CRP values.
- Short video clips demonstrating how the test result can be obtained within 4 minutes

For Communication Training, training will entail a practice team seminar to discuss issues around antibiotic prescribing and web-based material including
- An overview of the booklet, and how it can help you explain to patients when they do or do not need antibiotics.
- An outline of three key elements of effective consultations that will help to ensure that patients are satisfied with the consultation, even if you do not prescribe antibiotics.
- Short video clips demonstrating effective use of the booklet in a consultation in the general practice setting

Following training and prior to post-intervention data collection there will be a period for GPs to practice their new CRP and communication skills.

Preparations are now underway to prepare the packs to supply the practices for the post-intervention audit. As well as measuring GP antibiotic prescribing, patients will also complete a validated diary, used in the previous GRACE work packages, to measure symptom severity and duration. The recruitment of another 6,000 patients is planned in this phase. Notes review in the four weeks after presentation will document significant deterioration of illness and resource use.

At the end of the intervention winter we will convene focus groups and/or individual interviews with participating doctors in each country. We will also interview patients to help understand their perceptions of the process for the same interventions and to help inform trial results.

Funding permitting we will also perform a follow-up audit of antibiotic use in the autumn of 2011, to estimate what the longer term consequences are of the interventions. After the trial, participating practices will also have access to the intervention(s) not randomized to in the trial.

The GRACE team has been working together to deliver this project and this has been possible due to the coordinated efforts by the Web team, Data Management team, statisticians, scientific advisors, network coordinators, leadership and all team members, and over 240 GP practices.

Gilly O’Reilly
For the INTRO team
**APRES update**

APRES (see GRACE News 2009;4(2-3):10; www.nivel.eu/apres) is a four-year research project (2009-2013) funded by the European Commission (FP7) that is being carried out in nine European countries, led by NIVEL (the Netherlands Institute for Health Services Research). The study assesses the appropriateness of prescribing antibiotics in the primary health care setting, where more than 90% of all antibiotics are prescribed. The study has the following aims:

1. to assess antibiotic resistance patterns in the community;
2. to assess antibiotic prescription patterns in primary care;
3. to formulate evidence-based antibiotic treatment guidelines in primary health care.

The resistance data are collected by taking a nose swab from patients (N=4,000 per country) visiting a primary care practice for a non-infectious disease. Two bacteria are isolated (Staphylococcus aureus and Streptococcus pneumoniae) from these swabs and tested for antibiotic resistance on a range of antibiotics in a central laboratory (University of Maastricht). The table shows the number of swabs taken so far.

A pilot study was carried out over the summer of 2010, which included a quality assessment of laboratory testing, and it showed the study design was feasible. Data on antibiotic prescriptions over the previous 5 years will also be extracted from the practice data systems of the GPs. Considering data collection for the resistance data will continue until March 2011, the first results and conclusions will be available in 2012.

**GRACE will leave a TRACE**

In August 2011, funding by the European Commission (EC) of GRACE will end. Already in June of this year, the Final GRACE Meeting will be held (see p.8). In an effort to sustain GRACE beyond EC funding, in November 2009, the GRACE Management Team submitted a proposal for a Research Networking Programme (RNP) to the European Science Foundation (ESF). It was called Translational Research on Antimicrobial resistance and Community-acquired infections in Europe or in short TRACE (see GRACE News 2010;5(1):3, (2-3)1, and (4);1).

In June 2010, we were notified that TRACE was shortlisted for recommendation and would be send to the ESF Member Organisations (MOs) inviting them to consider à la carte support. We could not have agreed more with the specific feedback comment that “EMRC very strongly recommends TRACE for funding with the highest priority”. Early December last year, we received an overview from ESF of the support for TRACE by the ESF MOs. At that time already eight MOs had agreed to support TRACE (see Table), bringing the level of funding for TRACE at 62% of the requested budget. However, reaching 80% of the target budget is the condition for launching an RNP.

In an final attempt to insure GRACE sustainability, we asked all our non-profit GRACE partners and similar partners outside GRACE if they would be willing to support TRACE. Meanwhile, we were hoping that more MOs would still commit themselves to fund TRACE. At present, we are delighted and very grateful that TRACE has reached the 80% threshold with support of eight ESF MOs and already 13 GRACE and other partners, representing 11 European countries and Australia (see Table). Hence, the Chief Executive of ESF has given her official approval for the launch of TRACE.

We will organise the kick-off meeting of TRACE in Antwerp together with the final GRACE meeting on Thursday morning June 16. Besides annual Steering Committee Meetings, these activities planned in TRACE include scientific conferences, workshops and postgraduate meetings, (exchange) visits, dissemination by means of a website and a newsletter, and maintenance of the GRACE database.

**Spreading Excellence in Respiratory Tract Infections**

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**Table Countries and organisations supporting TRACE**

<table>
<thead>
<tr>
<th>Country</th>
<th>Date of report</th>
<th>Number of swabs</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Netherlands</td>
<td>25/01</td>
<td>1609</td>
</tr>
<tr>
<td>Spain</td>
<td>21/01</td>
<td>1601</td>
</tr>
<tr>
<td>Hungary</td>
<td>20/01</td>
<td>1501</td>
</tr>
<tr>
<td>Austria</td>
<td>14/01</td>
<td>1326</td>
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<tr>
<td>Belgium</td>
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<td>1015</td>
</tr>
<tr>
<td>Sweden</td>
<td>20/01</td>
<td>957</td>
</tr>
<tr>
<td>Croatia</td>
<td>09/01</td>
<td>435</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>17/01</td>
<td>108</td>
</tr>
<tr>
<td>France</td>
<td>25/01</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>8563</strong></td>
</tr>
</tbody>
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Note: Table prepared 31 January 2011

**John Paget, Evelien van Bijnen and Francois Schellevis**

**APRES**  
The appropriateness of prescribing antibiotics in primary health care in Europe with respect to antibiotic resistance

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**Samuel Coenen**
In April 2011, a new and very ambitious project, RAPP-ID (“Development of Rapid Point-of-Care test Platforms for Infectious Diseases”) will be kicked-off in Cambridge. RAPP-ID is funded by the Innovative Medicines Initiative (IMI) (about 14 million EUR) and it is jointly coordinated and managed by an industrial (Jorge Villacian of Tibotec-Virco Virology/Johnson & Johnson, Belgium) and an academic (myself of the University of Antwerp) partner.

Twenty (11 industrial of which 6 SMEs and 9 academic) partners jointly aim to develop a Point-of-Care Test (POCT) for rapid (hospital <2h, primary care <30min) detection of bacteria, mycobacteria, fungi, as well as viruses and host biomarkers by combining novel specific probes, novel methods of sample preparation, and demonstrated ultra-high sensitive detection methods. The platforms will also determine resistance to antimicrobial drugs. The research will focus on the biomarkers and pathogens involved in 1) Sepsis, 2) Lower Respiratory Tract Infections (LRTI), including Community-Acquired Pneumonia (CAP) and Ventilator-Associated Pneumonia (VAP), and 3) Tuberculosis (TB). Detection of bacteria, fungi and antibiotic resistance will mainly involve Nucleic Acid (NA) tests, whereas viral and host biomarker detection will mainly involve selective immunobinding with a probe or with a sensor surface.

The diagnostic tests consist of four functional modules: 1) sample collection and interfacing, 2) upconcentration and extraction, 3) signal and/or sample amplification, and 4) detection. RAPP-ID will integrate the minimum number of modules required for each disease/syndrome in a microfluidic cartridge, for which a breadboard reader with Graphical User Interface (GUI) provides the necessary optical/ fluidic/electric/thermal interfaces. The integrated POCT will be validated on (spiked) reference samples and well characterised clinical samples and compared with the best reference standards and other standard available diagnostic tests.

The GRACE experience, both in terms of management of large research projects and scientific know-how, will be instrumental for the success of RAPP-ID.

Herman Goossens
Spreading excellence in respiratory tract infections:

**CRP and the antibiotic prescribing decision**


Respiratory tract infections are the most common indication for antibiotic prescribing in primary care. The value of clinical findings in lower respiratory tract infection (LRTI) is known to be overrated. This prospective observational study of presentation and management of acute cough/LRTI in adults aimed to determine the independent influence of a point of care test (POCT) for C-reactive protein (CRP) on the prescription of antibiotics in patients with acute cough or symptoms suggestive of LRTI, and how symptoms and chest findings influence the decision to prescribe when the test is and is not used.

For this purpose, the GRACE WP8 data on adult patients contacting their GP with symptoms of acute cough/LRTI in the GRACE Primary Care Research Networks in Norway, Sweden, and Wales were analysed. Predictors of antibiotic prescribing were evaluated in those tested and those not tested with a POCT for CRP using logistic regression and receiver operating characteristic (ROC) curve analysis.

A total of 803 patients were recruited in the three networks. Among the 372 patients tested with a POCT for CRP, the CRP value was the strongest independent predictor of antibiotic prescribing, with an odds ratio (OR) of CRP 50 mg/L of 98.1 (22.7 – 424.6). Crackles on auscultation and a patient preference for antibiotics perceived by the GP were the strongest predictors of antibiotic prescribing when the CRP test was not used. In the subgroup tested for CRP, similar Area Under the ROC Curves (AUC) were found for a model including only clinical findings and a model including only the CRP value, whereas a significantly greater AUC was found for a model combining the clinical findings and the CRP value, called “clinical model plus CRP” (AUC = 0.95, 95% CI = 0.93 – 0.97) (see figure). Therefore, the CRP result appear to be a major influence in the decision whether or not to prescribe antibiotics for acute cough. Clinicians attach less weight to discoloured sputum and abnormal lung sounds when a CRP value is available. CRP testing could prevent undue reliance on clinical features that poorly predict benefit from antibiotic treatment.

Kristin Alise Jakobsen

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**Age, aging and susceptibility to infection**

Based on: a presentation at the 5th GRACE Workshop held in Budapest in November 2010 by David Dockrell. More information is freely available on the GRACE e-learning platform (www.grace-edut.org).

Steady increases in life-expectancy will mean that the proportion of older adults in the population will significantly increase over the next 50 years. The combination of medical co-morbidities, immunesenescence and environmental exposures in locations such as nursing homes put this group at increased risk of pulmonary infections. Older adults therefore have an increased incidence of pneumonia and a greater risk of complications and death as compared to younger adults. Infection with *Streptococcus pneumoniae* remains the most frequent cause of pneumonia in older adults and age is a significant risk factor for the acquisition of invasive pneumococcal disease. The basis of the increased susceptibility to pneumonia in elderly adults is incompletely understood. In addition to the effect of medical co-morbidities, altered lung physiology, changes in colonization of the upper airway and an increased risk of aspiration are likely contributing factors.

Age related changes in the immune system influence both innate and adaptive immune responses. In general Toll-like receptor responses are blunted in older adults. Rates of phagocytosis by macrophages and neutrophils are impaired and specific antimicrobial mechanisms such as macrophage-apoptosis and ROS-induced neutrophil killing may be
impaired. Conversely the inflammatory response may be dysregulated with enhanced pro-inflammatory cytokine and protease release. Adaptive immune responses are also altered with aging. Numbers of naïve B-cells are reduced with decreased response to vaccines and production of antibody of reduced avidity. Naïve T-cell numbers are also reduced but expansion of subsets of memory T-cells and the presence of many anergic memory T-cells reduces T-cell repertoire and compromises T-cell responses. Future challenges will include the need to selectively target specific immunological defects in older adults during the treatment of respiratory infection and the development of effective vaccines against common respiratory pathogens for older adults.

David Dockrell

**Improving the Patient Care Pathway in the Management of LRTI - A Hospital Specialist View**

Based on a presentation at the 5th GRACE Workshop held in Budapest in November 2010 by Mark Woodhead. More information is freely available on the GRACE e-learning platform (www.grace-edut.org).

Hospital care for adults with LRTI is very heterogeneous. The same condition may be managed with different investigations, different antibiotics and with different outcomes not only between countries, but also between hospitals in the same country. The evidence base for most practices is weak, but despite this the variations in management cannot be explained by what is known about the different LRTIs.

A number of strategies may improve management and outcomes. Accurate diagnosis is an important first step. A clear distinction between pneumonia and COPD exacerbations is easy to make on chest radiograph, but is often not put into practice. This means that antibiotics are overused in COPD patients who may have a viral cause for their illness. Biomarkers may help this distinction from pneumonia and between bacterial and non-bacterial exacerbations in the future.

For pneumonia illness severity assessment is the key to place of management, type of investigation and type of antibiotic therapy. Various methods have been proposed, but the CURB-65 score is the simplest of those with adequate operating characteristics to apply in practice. A similarly simple tool for prediction of intensive care requirement has not so far been developed.

Early antibiotic therapy results in better outcome. Aggressive drives to give early antibiotics have the perverse effect of reducing the accuracy of diagnosis as the antibiotic target becomes more important than the disease. Strategies are required to safely speed antibiotic delivery.

Appropriate antibiotic choice has for long been hampered by poor quality clinical trials. In COPD exacerbation the first decision has been to whom to give antibiotics. Historically the Anthonisen score has been the best guide, but biomarker, particularly procalcitonin, guided therapy may be the way for the future. Such biomarkers may also be useful for shortening duration of therapy in COPD and pneumonia. Dual β-lactam and macrolide therapy has become the norm for CAP therapy although monotherapy is probably just as good for non-severe (CURB-65 0 – 1) disease. Indeed the evidence to support dual therapy even for more severe disease is weak.

Biomarkers may also be useful for monitoring therapy. In pneumonia, failure to halve the admission CRP level by day 4 is associated with significantly worse outcomes. Routine use of this may guide further investigation and management. Use of stability markers are associated with better outcome following discharge and should also be used routinely.

Finally much research is still required to answer even many of the most basic management questions in LRTI care.

Mark Andrew Woodhead
WP12 News

5th GRACE Workshop: Hot Topics in Lower Respiratory Tract Infection

The workshop venue was the Semmelweis University, Budapest, hosting us in their newly built education centre, which was buzzing with students. With a total of 50 participants, lively discussion and interaction were the hallmark of this meeting.

The workshop began with an excellent series of presentations on genetic susceptibility, aging and smoking as determinants of infection. There followed excellent reviews of the recent literature on LRTI from a laboratory and clinical viewpoint. The recently published ERS/ESCMID guidelines on LRTI were critically appraised and followed by two valuable presentations on care pathways for the management of LRTI in primary care and in hospital. A lively and enjoyable evening pro/con debate discussed the topic of ‘Empirical antibiotic management – an approach that is unsustainable’. The second day commenced with an excellent overview of the approach to difficult Gram-negative infections and was followed by a series of presentations on the recent H1N1 pandemic covering its epidemiology, the adoption of healthcare worker immunisation and the impact of the pandemic on the GRACE project. The final session discussed current and future education and training requirements in primary care and hospital-based specialties dealing with LRTI. The standard of presentations at the workshop was excellent and the delegates proved appreciative and enthusiastic.

All educational material, slides and handouts are available on the GRACE e-learning platform www.grace-edut.org.

Roger Finch
WP12 co-leader

10th GRACE Postgraduate Course at 2011 ECCMID/ICC

The 10th GRACE Postgraduate Course will be held at 2011 ECCMID/ICC in Milan on 7 May. It will be held in collaboration with the ESCMID Fungal Infection Study Group (EFISG) as Educational Workshop 02 with the theme of ‘Fungi in the respiratory tract & antifungal stewardship’.

Cornelia Lass-Flörl (Austria) and Roger Finch (UK) are the co-convenors for a programme that comprises:

- Detection of Candida: a marker of chronic disease?
- Sensitisation to fungi: allergic broncho-pulmonary aspergillosis (ABPA)
- Invasive pulmonary aspergillosis - therapeutic options
- Antifungal stewardship for Candida
- Antifungal stewardship for Aspergillus
- Antifungal stewardship for other fungal pathogens

With expert speakers and a topical programme, we are looking forward to an exciting workshop. Registration is open at www.eccmid-icc2011.org. We warmly welcome you to Milan.

Murat Akova
ESCMID Education Officer and GRACE Representative in WP12
Final GRACE Meeting
“Where did we make the difference?”

The final GRACE Meeting will be hosted by the GRACE MT, and held in Antwerp 16-18 June 2011. Thursday June 16 a closed meeting will be held by the Governing Council (GC) in the afternoon. The Work Package (WP) leaders will for the last time report on their activities in the fifth year and part of the six month extension. The scientific part of the final GRACE Meeting starts on Friday June 17, is open to all GRACE participants and other stakeholders, and presents a very comprehensive programme answering the question: “Where did we make the difference?”

Friday June 17

08.30 Welcome - Rector University of Antwerp
08.45 GRACE Online System - Frank Leus
09.00 Establishing a pan European Primary care Research Network: what are the magic ingredients for success? - Chris Butler
09.15 Discussion - All
09.30 Unhelpful variation in the commonest prescribing decision, green sputum, and bodies that get used to antibiotics: practice changing research from the first GRACE clinical studies - Chris Butler
10.30 Coffee break
11.00 Detecting pneumonia in primary care patients: intuition or technology? - Saskia van Vugt
11.20 Can we differentiate between viral and bacterial infections in patients with acute cough? - Theo Verheij
11.40 Prediction of poor outcome in lower respiratory tract infections in outpatients: old and new rules - Samuel Coenen
12.00 Hidden chronic lung disorders in patients with acute cough - Lidewij Broekhuizen
12.20 Does bacterial resistance matter in the severity and clinical outcome of lower respiratory infections outside hospital? - Greet leven
12.40 Cost-effectiveness of additional diagnostic tests in patients with acute cough - Jo Coast/Richard Smith
13.00 Lunch
14.00 What is the effectiveness of antibiotics for patients with acute uncomplicated LRTI? - Paul Little
14.40 What is the effectiveness of an internet supported communication package or a near patient CRP test for LRTI in six European countries? - Paul Little
15.30 Coffee break
16.00 LRTI: bacterial causes or do viruses also matter? - Greet leven
16.20 Does quantitative PCR testing predict for clinical relevance? - Frank Coenjaerts
16.40 Are all rhinoviruses equally harmful? - Eric Claas
17.00 A novel respiratory virus in GRACE? - Lia van der Hoeck
17.20 Epidemiology of pneumococci in GRA CE - Birgitta Henriques-Normark
17.40 Haemophilus spp: different resistances in different centers? - Derrick Crook
18.00 End of day 1 scientific meeting

Saturday June 18

08.30 Human genetics introduction - Adrian Hill
08.40 Genome wide searches for susceptibility loci - Anna Rautanen
08.55 Human genetic association results in GRACE - Tara Mills
09.10 Questions
09.15 How should we maximise benefit from the resources available to treat lower respiratory tract infection? - Jo Coast, Richard Smith
10.15 GRACE WP12 – building an Education, e-Learning and European Society supported platform - Roger Finch, Francesco Blasi
10.45 Coffee break
11.15 News from the EU: FP8 - European Commission representative?
11.45 Round table: Did we reach our goals? - All
12.30 Concluding remarks: Was GRACE really the flagship European network on Community-acquired LRTI? - Herman Goossens
13.00 End of day 2 scientific meeting