462. Appropriate use of antibiotics in respiratory infections in Europe (the GRACE project)

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Changing GPs' antibiotic prescribing behaviour in five European countries: A qualitative study within the GRACE project

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Background: In the last stage of the GRACE project a pragmatic trial was done to assess the effects of comuunication training and the use of a CRP test on antibiotic treatment of lower respiratory tract infections. The current study assessed the feasibility and acceptability of the intervention in this trial across 5 European countries (Belgium, Netherlands, Poland, Spain, UK). The aim was to elicit GP and patient attitudes before the intervention, in order to adapt the interventions as necessary.
Method: 30 GPs and 13 patients from the 5 countries were interviewed before the intervention using a "think aloud" approach. Data were coded following techniques taken from framework analysis.
Findings: GPs across all countries were supportive of the aims of the implementation trial, approved of the strong evidence base supporting the training and found the web-based format appealing. Country-specific differences often reflected differences in health systems, and highlighted where the intervention could be tailored. The patient data highlighted the importance of the When and How of using the booklet asvery important in the success of the use of the booklet. Analyses of patient data gathered during the intervention will also be presented if available.
Discussion: The findings provide valuable insights informing future development of behavioural interventions across Europe regarding antibiotic use.

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The effect of amoxicillin in lower respiratory tract infection (LRTI): A placebo controlled RCT in 16 primary care GRACE networks from 12 countries in Europe

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Introduction: LRTI is the commonest acute presentation managed in primary care and still a major driver of antibiotic prescribing. Systematic reviews of placebo controlled studies are small (<1000).
Aim: To determine the effectiveness of amoxicillin for lower respiratory tract infection.
Methods: 2054 patients presenting with uncomplicated acute cough (<4 weeks) as the main symptom were randomised to amoxicillin 1g three times a day or placebo for 7 days. Patients completed validated symptom diaries for symptom severity (7 point scale) and duration. Notes were reviewed for repeat consultations

Results: 593 of trial population (28%) were aged 60+, and symptom severity documented and duration were documented in 87% of patients. There was no significant difference in symptoms severity in the first 4 days after seeing the doctor (placebo mean 1.69, antibiotic 1.62; difference -0.07 (-0.18 to 0.06)), and no significant difference in the proportion with moderately bad or worse symptoms at 7 days (47% vs 40% respectively, p=0.07 NNT 14). Among the subgroup of patients aged 60 or over there was no evidence of selective benefit. 5% more patients in the antibiotic group compared with the placebo group developed nausea, rash or diarrhoea (NNH 20).
Conclusion: Antibiotics are very unlikely to provide meaningful symptomatic benefit in LRTI for most patients, and any benefit is likely to be similar to the magnitude of harm.

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Undetected chronic obstructive lung disorders in patients presenting with acute cough in primary care: Results from the European GRACE study
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Introduction: Cough is among the most frequently presented complaints, and a suitable opportunity to consider the presence of underlying asthma or COPD.
Aim: To determine the prevalence of undetected chronic obstructive lung disorders in patients consulting their general practitioner (GP) with acute cough.
Methods: For this cross sectional diagnostic study, 2532 adult patients without known asthma or chronic obstructive pulmonary disease (COPD), attending their GP with complaints of cough $\leq$ 28 days, were recruited from 12 European countries. All subjects underwent spirometry at day 28 after inclusion. Asthma was defined present if there were recurrent complaints of wheezing, cough or dyspnoea, AND an increase of the forced expiratory volume in one second (FEV1) $\geq$ 12% or $>$ 200 ml after bronchodilation. COPD was defined present according to two cut off values for the (post bronchodilator) ratio of the FEV1 to the forced expiratory volume (FEV1/FVC ratio): 1. below 0.7 ("fixed ratio"); 2. below the lower limit of normal (LLN) according to age, gender and height.
Results: 336 subjects had asthma (13%), and according to the used definitions of COPD 1 and 2, respectively 246 (10%) and 168 (7%) subjects had COPD. Spearman's Correlation between GOLD and LLN was 0.71. There was discrepancy between the GOLD and LLN definition for COPD in especially the elderly and the very young.
Conclusions: In patients presenting acute cough, undiagnosed asthma was more frequent than undiagnosed COPD. Different definitions for obstructive spirometry results led to large differences in the proportion of patients classified with COPD.

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Developing clinical definitions of LRTI for research and primary care practice in Europe: A consensus study using the GRACE Network of Excellence
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Introduction: Antibiotic prescriptions for LRTI accounts for a large proportion of antibiotic consumption and many of these prescriptions do not benefit patients and contribute to the growing problem of antibiotic resistance. Addressing the primary care research agenda to improve evidence-based management requires clear definitions of clinical entities.
Aim: We aimed to generate definitions for four LRTIs; community-acquired pneumonia, acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease, and acute infective exacerbations of asthma, that apply to clinical practice and low intensity investigation research settings in European primary care.
Methods: Candidate definitions elicited from a systematic review of literature and a nominal group meeting were the put to a Delphi panel of selected experts from Europe and the US over three rounds. The definitions achieving high consensus were then tested for usability by an expert panel.
Results: 253 papers met our search criteria. The nominal group meeting generated highly ranked definitions for two LRTIs. The Delphi panel considered five candidate definitions derived from the systematic review and nominal group meeting and agreed upon definitions and open comments for the expert panel to assess the "usability" of these emerging definitions.
Conclusion: We combined empirical evidence with expert opinion for the development of a set of clinically based definitions for the five most common LRTIs presenting in general practice.

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Detecting pneumonia in patients with acute cough in primary: Results from the European GRACE study
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Introduction: It is still unclear what the best strategy to detect pneumonia in primary care patients should be.
Aim: To quantify the diagnostic value of history, physical examination and the added value of inflammation markers in detecting pneumonia in patients presenting with acute cough in primary care.
Methods: 2820 adult patients attending their general practioner with complaints of cough $\leq$28 days, were recruited from 12 European countries. Patient's history and physical examination were recorded on the day of presentation. C-reactive protein (CRP) and pro-calcitonin (PCT) were drawn from venous blood samples and chest radiographs were taken within the next three days. Pneumonia was diagnosed by chest X-ray. With multivariable logistic regression a diagnostic model was developed for diagnosing or ruling out pneumonia.
Results: 140 patients had radiographic pneumonia (5%). Symptoms and signs with independent diagnostic value were; absence of runny nose, presence of breathlessness, diminished vesicular breathing and crackles on auscultation, tachycardia (pulse $>$100/min), and temperature $>$37.8°C. Combined these items showed an area under the ROC curve of 0.70 (95% confidence interval 0.65-0.75). A combination of the 2 strongest predictors (crackles and temperature $>$37.8, n=30) had a positive predictive value for pneumonia of 37%. Analysis of the added value of CRP and PCT is in progress; results will be available in the presentation.
Conclusions: Radiographic pneumonia is uncommon in adults presenting in primary care with acute cough. Brief history and physical examination can help discriminate between those at high and low risk for pneumonia.

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GRACE Network of Excellence: Genetic susceptibility to lower respiratory tract infections in Europe
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Introduction: Lower Respiratory Tract Infection (LRTI) is one of the leading reasons for seeking medical care in Europe. However, not everyone is equally susceptible to LRTI.
Aims and objectives: To identify host genetic factors that may play an important role in explaining this inter-individual variation in susceptibility to LRTI.
Methods: DNA was extracted from blood samples of 3000 cases and 3000 matched controls recruited within the GRACE study. Single nucleotide polymorphisms (SNPs) in 19 genes, selected based on our earlier studies on severe LRTI (invasive pneumococcal disease (IPD)), were genotyped with Sequenom's iPLEX technology.
Results: SNPs in the genes PTPN22 (Arg620Trp: p=0.037, OR 2.0) and NFKBIZ (rs616597: p=0.022, OR 0.87; rs600718: p=0.028, OR 0.87) associated with LRTI in the initial analysis which included half of the cases and controls. PTPN22 is a lymphoid specific protein tyrosine phosphatase that regulates the immune response through T-cell signalling. NFKBIZ is one of the NFκB inhibitors and thereby affects the transcription of pro-inflammatory genes. Genotyping of the rest of the samples is ongoing. In addition, more candidate genes possibly involved in the host immune response to viral infections will be genotyped. In the further analyses, cases will be subdivided based on the microbiological cause of their LRTI, namely between bacterial and viral infection, and further to specific pathogens.
Conclusions: Host genetic factors involved in the pathogenesis of IPD might also be important in defence against milder LRTIs. Identification of these factors may potentially lead to more individualised detection, treatment, and prevention of LRTIs.

4514
Lower respiratory tract infections in the European GRACE primary care network: Bacterial causes or do viruses also matter?
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Especially the role of the newly recognised viruses is not well known in adult

lower respiratory tract infections in the community (LRTI). We investigated the role of *S. pneumoniae* (*S.pn*), *Haemophilus* spp (*H.*spp) and viruses in LRTI in the GRACE primary care network (PCN) using culture and real-time nucleic acid amplification tests (RT-NAATs) From 10/2007-04/2010 3102 patients with LRTI were enrolled in a prospective study in 16 PCNs in 12 EU countries. Nasopharyngeal swabs (NPS) and sputa for culture of *S.pn* and *H.*spp were collected and frozen until transport to the central lab for nucleic acid (NA) extraction. Aliquots of NA extracts were sent to the LUMC and UMC-U for detection of influenzaviruses (INF) A/B, parainfluenzavirus (PIV)1-4, human rhinoviruses (HRV), human metapneumovirus (hMPV), respiratory syncytial virus (RSV), adenovirus (HAdV), Bocavirus (BOCA), coronaviruses (HCoV) OC43, NL-63, 229E, polyomaviruses KI and WU by in-house RT-PCR.

In 3082/3102 patients a NPS was collected. An aetiologic agent was detected in 77% of patients: *S.pn* and *H.*spp in 9.1% and 14.9% respectively; a respiratory virus in 53.1%: HRV 18.6%, INF 11.1%, HCoV 7.4%, hMPV 4.4%, RSV 4.4%, polyomaviruses 2.8%, PIV 2.5%, HAdV 1.4%, BOCA 0.5%. For most viruses no significant differences were observed in prevalence between the 3 winters. In <5% of patients persistence of respiratory virus was seen in the follow up visit.

This is the largest aetiologic study on LRTI in PCNs: in ±80% of the patients a microbial aetiology was found, over 50% were viral infections: HRV's account for the majority. Use of RT-NAATs results in a significant improvement of the aetiologic diagnosis LRTI.