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Background Paper

Infectious diseases in primary care; managing the interface between the person and the community

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KEY MESSAGE(S):

- The persistence of resistant bacteria in individuals might differ by antibiotic class
- Quality Indicators for outpatient antibiotic prescribing are available
- Public awareness campaigns and professional interventions—point-of-care tests, communication skills training, interactive patient booklets—can safely reduce antibiotic prescribing
- Interventions should also aim at prescribing of ‘first-choice’ antibiotics

ABSTRACT

Respiratory infections are still among the most common new diagnoses in primary care. The most frequent reason for encounter is acute cough. General practitioners have to make antibiotic prescribing decisions in a context of diagnostic uncertainty, patient preferences and antimicrobial resistance. There is a causal link between antimicrobial resistance and antibiotic prescribing in primary care. GRACE observational studies (www.grace-lrti.org), show that variation in clinical presentation does not explain the considerable variation in antibiotic prescribing in Europe for adults presenting in primary care with acute cough and that recovery is similar between those treated with any antibiotic, a particular antibiotic class, or no antibiotic. A GRACE randomized controlled trial (RCT) of the effect of antibiotics for acute cough has recruited more patients than all RCTs combined in the current Cochrane Review and will have the power to identify subgroups of patients who will (not) benefit from amoxicillin. Another multi-country GRACE RCT assessing the effect on antibiotic prescribing of largely web-based versions of successful interventions including a C-reactive protein point-of-care test, a communication skill training and an interactive patient booklet is awaited. Given potential long-term cost-effectiveness, the GRACE suite of observational and interventional studies are enhancing the evidence base for reducing diagnostic uncertainty and managing patient expectations in a patient-centred way to achieve greater evidence-based antibiotic prescribing that is likely to help containing antimicrobial resistance.

Key words: Infectious diseases, quality of care, antibiotics, antimicrobial resistance, primary care

Infectious diseases are still among the most common new diagnoses in primary care and respiratory tract infections account for most of these presentations. The most frequent reason for encounter is acute cough. Primary care physicians have to make antibiotic prescribing decisions in a context characterized by diagnostic uncertainty, often strong patient preferences and expectations, while taking into account the global problem of antimicrobial resistance. Therefore, the topic of the EGPRN (European General Practice Research Network; www.egprn.org) meeting held in Krakow, Poland, 13–16 October 2011, ‘Infectious diseases in primary care; managing the interface between

the person and the community,’ was simply about the antibiotic prescribing decision for acute cough; or was there more to it?

ANTIBIOTIC USE AND RESISTANCE

A causal link between antimicrobial resistance and antibiotic prescribing in primary care cannot be derived from albeit strong associations between outpatient antibiotic use data collected within the ESAC (European Surveillance of Antimicrobial Consumption; currently ESAC-Net) project and EARSS (European Antimicrobial Resistance

Surveillance System; currently EARS-Net) antimicrobial resistance data at country level (1). Causality has, however, been shown at the individual patient level by randomized controlled trials (RCTs) (2), including the most convincing RCT to date by Malhotra-Kumar et al., who assessed the effect of macrolide use on resistance selection in healthy volunteers (3). This study also described resistance selection by macrolides (azithromycin and clarithromycin) persisted for more than six months. A non-randomized study by Chung et al., suggests shorter persistence after amoxicillin treatment (4), but these findings require confirmation by an RCT.

VARIATION IN ANTIBIOTIC USE

The most recent ESAC data, confirm persistent variation in outpatient antibiotic use in Europe expressed in defined daily doses per 1 000 inhabitants per day (DID) (5). This variation is mainly driven by the use of penicillin, but is striking for any antibiotic class, even when use is expressed in packages—a proxy for prescriptions—per 1 000 inhabitants per day (PID) (6–10). Mixed-effects models, allowing statistical assessment of the trend over time (11), have shown that over the last decade use and seasonal variation of use of both macrolides and quinolones significantly increased, suggesting higher volumes of use and increasing use for influenza-like illnesses (8,9). These trends suggest decreasing quality of outpatient antibiotic use in Europe (12), but the ESAC-Net data are not linked to diagnoses.

VARIATION IN ANTIBIOTIC PRESCRIBING

Data on antibiotic prescribing for adults presenting in primary care with acute cough, were collected within the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe; www.grace-lrti.org) project, a Seventh Framework Programme Network of Excellence. Multivariable analysis showed that variation in clinical presentation did not explain the considerable variation in antibiotic prescribing between 14 primary care networks in Europe for adults presenting with acute cough (13). Moreover, less than half of those who were prescribed antibiotics received a first choice antibiotic (i.e. tetracycline or amoxicillin) (14). Work from Gjelstad et al., also presented at the EGPRN meeting, found that higher consultation rates were associated with higher antibiotic prescribing rates (of not recommended antibiotics) (15,16).

BENEFITS OF ANTIBIOTIC PRESCRIBING

Observational study evidence

Using data from the observational GRACE study, no clinically meaningful differences in recovery were found

between those treated with any antibiotic, a particular antibiotic class or no antibiotic (13,17). Patients with discoloured sputum were prescribed antibiotics more often, but sputum colour, alone or together with feeling generally unwell, was not associated with recovery or benefit from antibiotic treatment either (18). Likewise, smokers were prescribed antibiotics more frequently, and in this subgroup too being prescribed antibiotics were not associated with recovery (19).

Randomized controlled trial evidence

Nested within a subsequent GRACE observational study on the aetiology, diagnosis and prognosis of adult patients with acute cough, a first randomized double-blind placebo-controlled trial was conducted, which has recruited more patients than in all trials combined in the current Cochrane Review (20). If the results from this GRACE RCT confirm the results from the observational GRACE study and the Cochrane review, antibiotics are very unlikely to provide meaningful symptomatic benefit for most patients with acute cough, and any benefit will be very likely to be similar to the magnitude of harm. This new GRACE RCT, will also have sufficient power to identify any relevant treatment benefit in subgroups of patients, for example, the elderly.

While establishing the aetiology, diagnosis and prognosis in these patients remains a challenge, work by Michiels et al., also presented at the EGPRN meeting, found that influenza can be ruled out in primary care patients with influenza-like illness by the absence of cough and fever ($> 37.8^{\circ}\text{C}$), especially outside an influenza epidemic (21,22). This body of work and associated calls for further research to establish the additional diagnostic value of rapid point of care tests as well as the GRACE work, resonate with the Primary Care Research Agenda on diagnostic strategies and reasoning (23).

CHANGING PRESCRIBING BEHAVIOUR

Reducing antibiotic prescribing

A further randomized controlled trial from the GRACE Network is assessing the effect on antibiotic prescribing of two interventions based on the positive results of earlier work by Cals et al. (24); Francis et al. (25); and Butler et al. (26); as well as on the available results from GRACE and a linked European project, CHAMP (Changing behaviour of Health care professionals And the general public towards a more prudent use of antimicrobial agents; www.champ-antibiotics.org). One intervention consists of an online training on the use of a C-reactive protein point-of-care test supplemented with the provision of such a device, the other of an online communication skill training supplemented with the provision of an interactive patient booklet endorsed by the European Antibiotic

Awareness Day of the European Centre for Disease Prevention and Control (ECDC; <http://antibiotic.ecdc.europa.eu>) (see Figure 1). This RCT of largely web-based interventions may confirm the positive effects of these successful, previous interventions and their combination on reducing antibiotic prescribing, and, moreover, that the effect is lasting and cost-effective.

Improving antibiotic prescribing

In conditions where antibiotic treatment is justified, we also need to take into account the degree of prescribing the guideline-recommended antibiotics, when assessing prescribing quality. Recently, ESAC published a set of disease-specific quality indicators for assessing the quality of antibiotic prescribing in primary care (27). This consists of three quality indicators for the six main indications for antibiotic prescribing (acute otitis media, acute upper respiratory infection, acute/chronic sinusitis, acute tonsillitis, acute bronchitis/bronchiolitis, cystitis/other urinary infection) and for pneumonia, the percentage prescribed (a) antibiotics; (b) recommended antibiotics; (c) quinolones. At the EGPRN Meeting, Ryckebosch et al., showed that the quality of antibiotic prescribing in a Flemish out-of-hours service centre was

suboptimal according to these indicators. In particular, improving the proportion of 'first choice' antibiotics offers a huge opportunity for quality improvement for both respiratory (RTI) and urinary tract infections (UTI) (28). These indicators have also been applied to data from another Flemish project (www.intego.be), their validity outside Europe is being assessed, and their integration in primary care physicians' electronic medical health records is being recommended.

At the EGPRN meeting, also Vellinga et al., presented antibiotic prescribing quality problems for UTI by showing low antibiotic prescribing rates for UTI (56%), and low rates of prescribing recommended antibiotics, e.g. nitrofurantoin, trimethoprim (37%), in general practice in Ireland (29). Den Heijer et al., showed increased prescribing of broad spectrum antibiotic for UTI in men in general practice in the Netherlands, a low antibiotic prescribing country (30). The work that Heytens et al., presented, showed other similarities between RTI and UTI than the antibiotic prescribing quality problem. Women with suspected uncomplicated infections also had symptoms associated with upper infections, the symptom duration exceeded antibiotic treatment duration, and women with a positive culture did not necessarily have more severe symptoms (31,32).

Implications for practice and research

Taking all these findings into account one could argue that the scope of primary care infection research interest groups should include both RTI and UTI. Moreover, why not also include skin and soft-tissue infections? The latter is to some extent achieved by the APRES (Appropriateness of prescribing antibiotics in primary health care in Europe; www.nivel.eu/apres) study, presented by van Bijnen et al. (33). The former might result in broadening the scope of the GRACE intervention (GRACE INTRO). Its scope could also be expanded from aiming to reduce antibiotic prescribing in primary care to also supporting the choice of recommended antibiotics in those conditions where antibiotic treatment is justified.

However, to disseminate, exploit and build upon the results of the work presented at the EGPRN meeting, especially that of the European research projects, support is needed both at the national level and the European level (34). Although ESAC-Net is currently coordinated by ECDC, and the sustainability of GRACE and CHAMP is temporarily achieved through the European Science Foundation (www.esf.org/TRACE), more needs to be done. After all, given potential long-term cost-effectiveness, the GRACE INTRO intervention evaluated in four languages in six European countries will provide a great opportunity for large-scale and much needed support of primary care physicians all over Europe in managing respiratory infections, particularly the antibiotic prescribing decision (35). If the study turns out to

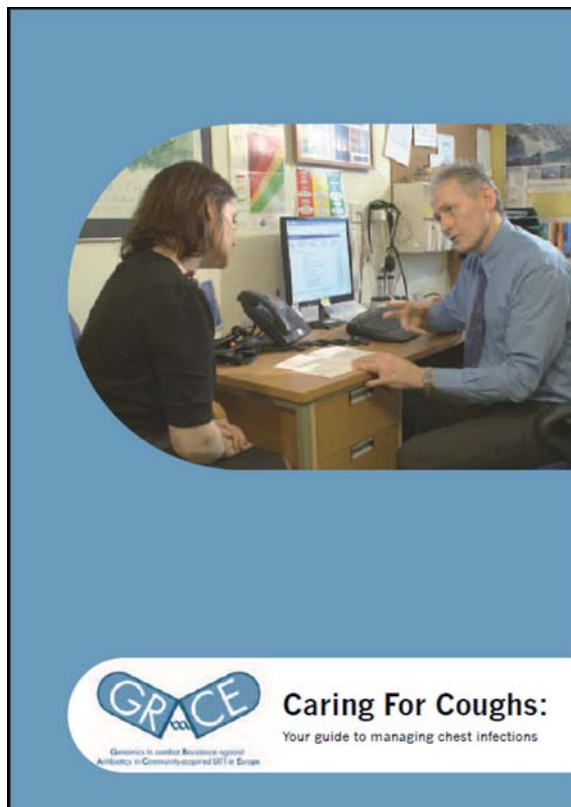


Figure 1. The cover of the English version of the interactive patient booklet supplementing the online communication skills training of the GRACE INTRO intervention. *Note:* The training and the booklet are available in Dutch-Flemish, English, Polish and Spanish.

be negative, GRACE INTRO can be further developed in accordance with the findings of a process analysis performed alongside the RCT (36). Moreover, strong synergy is to be expected between such professional interventions and public awareness campaigns (35,37). In addition, compelling evidence for the shorter temporal persistence of resistance selection after amoxicillin compared to macrolide treatment would have important therapeutic and public health implications, and should be taken into account in any strategy promoting appropriate antibiotic use and targeting prescribers, including GRACE INTRO. Finally, the additional diagnostic (or prognostic) value in primary care of the (newly) marketed point of care tests should be established.

In conclusion, it is hoped that the European primary care physicians and European policy makers read the European Journal of General Practice and/or attend future EGPRN meetings.

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