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Evidence-based primary care treatment guidelines for skin infections in Europe: A comparative analysis

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ABSTRACT

Background: In Europe, most antibiotics for human use are prescribed in primary care. Incorporating resistance data into treatment guidelines could improve appropriate prescribing, increase treatment effectiveness and control the development of resistance.

Objectives: This study reviews primary care treatment guidelines for bacterial skin infections across Europe and assesses to what extent they are based on antibiotic resistance data.

Methods: Thirteen primary care treatment guidelines were obtained from eight countries across Europe. Both the treatment recommendations and the underlying evidence were assessed. The class and dose of recommended antibiotics were investigated and compared using the World Health Organisation's standardized volume of Defined Daily Dose. Furthermore, analysis investigated whether guidelines included references to scientific publications about antibiotic resistance data, and whether these were of national origin.

Results: Guidelines were included regarding common skin infections in primary care: Impetigo, Cellulitis, Erysipelas, Folliculitis and Furuncle. Results showed a high agreement across Europe: all recommended antibiotics are of the beta-lactam class and mainly in the small spectrum. The advised treatment durations are consistent; the dosages, however, vary considerably, with the highest

dosages recommended in Sweden. Seven guidelines (54%) did not include scientific references related to resistance.

Conclusion: There may be a lack of relevant national data on resistance. This study highlights the need to collect more national resistance data (particularly regarding beta-lactams) to create stronger evidence-based treatment guidelines for skin infections in Europe.

1. European treatment guidelines for skin infections in primary care mostly recommend Beta-lactam antibiotics but vary considerably in the advised dosage.
2. Scientific references focusing on antibiotic resistance are presented in only six of the 13 guidelines.
3. National outpatient resistance data (particularly regarding beta-lactams) should be used to provide stronger guidelines.

INTRODUCTION

Recent studies have shown that over 90% of all antibiotics for human use in Europe are prescribed in primary care (1–3). In addition, emerging antibiotic resistance (e.g. methicillin-resistant *Staphylococcus aureus*) has become an important public health threat, since it frequently leads to a delay in the administration of effective therapy (4–6). The development of antibiotic resistance is correlated with antibiotic use (2,3) and next to cautious and limited prescribing a careful selection of effective antibiotics is needed to control the emergence of resistant bacteria and ensure the effective treatment of bacterial infections in the future (7).

Currently a wide range in antibiotic prescription behaviours exists in primary care in Europe (8). Highlighting the effects of antimicrobial use on resistance could reduce inappropriate prescribing by selecting those antibiotics to which the causal pathogen is less resistant. Several studies have recommended that existing evidence regarding national resistance data needs to be included in treatment guidelines for bacterial infections (7,9–11). The purpose of evidence-based guidelines is to bridge the gap between scientific research and practice (12); they can serve as a powerful step towards effective health care and a decrease in the development of antibiotic resistance (13–17).

Infections that underlie the majority of antibiotic prescriptions in primary care are respiratory tract infections, urinary tract infections and skin and soft tissue infections (18). The incidence of bacterial skin and soft tissue infections in general practice is relatively high, especially in children (19). In most cases, *Staphylococcus aureus* (*S. aureus*) or *Streptococcus Pyogenes* (*S. pyogenes*) is the pathogen involved in these infections. Methicillin-resistant *S. aureus* (MRSA) infections have emerged globally and are causing treatment problems because of resistance to beta-lactam antibiotics (20). Research groups have evaluated and graded guidelines on several clinical conditions, however, studies concerning the assessment of treatment guidelines for skin infections are lacking (21,22). The first aim of this study is, therefore, to provide an overview of the recommendations regarding antibiotic treatment of skin infections in European primary care guidelines. Second, we will assess to what extent European treatment guidelines are evidence based regarding antibiotic resistance data. This study is meant to increase awareness and the results will provide directions for

incorporating resistance data into treatment guidelines in order to increase treatment effectiveness and control the development of resistance.

METHODS

Data collection

Nine countries across Europe were enrolled in this study: Austria, Belgium, Croatia, France, Hungary, the Netherlands, Spain, Sweden, and the UK. Selection was based on participation in a collaborative EC-funded primary care research project (APRES ‘The appropriateness of prescribing antibiotics in primary care in Europe with respect to antibiotic resistance’) due to their variation in prescription behaviour (23). In each country, a coordinator of a national General Practitioner Network was asked to supply nationally issued and authorized treatment guidelines according to the following inclusion criteria:

- Used in primary care
- Treatment of (bacterial) skin and soft tissue infections
- Issued and available nationally

Three countries had multiple organizations issuing guidelines; in this study, only the most frequently used primary care guidelines per country were included, based on the expertise of our local partner. With the exception of Croatia, all countries have issued national treatment guidelines for bacterial skin infections. The inventory resulted in 13 guidelines from eight European countries (Table 1, web-only). The guidelines are all freely available online and can be downloaded. For the purpose of this study, they were accessed in June 2013. The guidelines are published in the respective national languages, and for this study, relevant sections of the guidelines were translated and checked with the national experts.

[TABLE 1]

Review of guidelines

Guidelines were reviewed and compared with respect to: (1) recommendations for the prescription of antibiotics, i.e. type of antibiotic and dose; and (2) evidence provided for these recommendations, i.e. the number of references to peer-reviewed literature on antibiotic resistance and their content.

Comparison of recommendations for antibiotic treatment

A common way of treating a bacterial skin infection is prescribing an antibiotic, often a systemic antibiotic. For more superficial skin infections or for accelerating the healing process, a topical antibiotic can also be used (24–26). The following aspects of the treatment paragraph of each guideline were analysed:

- Is a topical antibiotic recommended?
- If systemic antibiotics are indicated, which class of antibiotics is recommended?
- What is the recommended dosage and treatment duration?

If more than one antibiotic was mentioned, only the first recommendation was included. Treatment duration and dosage of the recommended systemic antibiotics were compared using the standardized defined daily dose (DDD) introduced by the World Health Organisation (WHO) (27). The DDD is the assumed average maintenance dose per day for a systemic or parenteral drug used for its main indication in adults. If guidelines indicated a range regarding dosage or duration, the average value was used for calculation (e.g. if the guideline recommended a duration of five to nine days, seven days was used). By applying the DDD to each recommendation, different guidelines could be compared using a standardized measure. Since the DDD value is only valid for adults, these results will only be presented for adults.

Comparison of evidence

Evidence was defined as one or more references to scientific, peer reviewed sources. The following aspects of the guideline were assessed:

- Are scientific references included?
If applicable:
- Do these references refer to publications based on antibiotic resistance data?
- Is the resistance data from national or international origin?

EvB extracted and analysed the data from the 13 treatment guidelines and the national experts validated the results for their country.

RESULTS

Thirteen treatment guidelines were evaluated, with the year of publication ranging from 2004 to 2012. The structure of the documents varied: some countries issued separate documents for recommendations and argumentation for the guidelines.

Treatment recommendations

Guidelines varied in scope as some countries issued one overall guideline for bacterial skin and soft tissue infections, whilst others issued guidelines per separate infection. Also, the range of clinical conditions included in the guidelines varied. Only recommendations for the most common skin diseases were taken into account: Impetigo, Cellulitis, Erysipelas, Folliculitis and Furuncle. Since Cellulitis and Erysipelas, and Folliculitis and Furuncle are related infections, they are often discussed together in the guidelines and the same recommendations apply. If a guideline provides separate recommendations for children, this information is also presented.

Impetigo

Table 2 presents the assessment of the seven guidelines for Impetigo. Guidelines often start with a recommendation to improve hygiene; when treatment does not lead to recovery, all guidelines recommend that the General Practitioner (GP) first prescribes a topical antibiotic (often Fusidic acid). When complaints are more severe, or the affected area is large, a systemic antibiotic is advised in all guidelines. The

systemic antibiotic recommendations belong to the same Penicillin class, except for the Swedish Cephalosporin recommendation for children. The treatment guideline in France does not explicitly advise a specific antibiotic; it recommends the choice of an antibiotic to which Staphylococci and Streptococci are susceptible.

[TABLE 2]

Four of seven guidelines mention specific dosage and treatment duration for Impetigo. The daily- recommended dose does not exceed the DDD advised by the WHO, except for the Swedish guideline. Three recommendations are the same (5.25 DDDs); the Swedish recommendation equals nine DDDs.

Cellulitis and erysipelas

In Table 3, the same results are shown for Cellulitis and Erysipelas. For these infections, all guidelines recommend immediate systemic drugs from the Penicillin class, except for the Dutch Macrolide recommendation for children. The recommended dosages are higher than for Impetigo, and often exceed the DDD defined by the WHO. This could be explained by the deeper nature of Cellulitis and Erysipelas infections. The range in total DDDs is smaller than for Impetigo, with the UK guidelines recommending the smallest total dosage and the Swedish guideline recommending the highest dosage.

[TABLE 3]

Folliculitis and furuncle infections. Folliculitis and Furuncle infections were less often included in the treatment guidelines (Table 4). Drainage of the wound, if applicable, is the advised intervention, together with the prescription of a systemic antibiotic (usually penicillin derivatives). The recommended antibiotic dosages resemble those for the treatment of Impetigo. Again, the total dosage recommended in Sweden is twice as high as in the other countries.

[TABLE 4]

Evidence about resistance

The range in the number of scientific references in the treatment guidelines is considerable: from zero in Spain and Hungary to 185 in Sweden. We assessed whether references focussing on antibiotic resistance were included in the treatment guidelines. Seven of 13 guidelines (54%) did not include scientific references related to resistance data. Of the included references on antibiotic resistance (26 in total), three in four involved international data.

DISCUSSION

Treatment recommendations

This comparative study shows that European treatment guidelines for skin and soft tissue infections in primary care are consistent regarding the choice of antibiotic: most recommended antibiotics are of the same small-spectrum Penicillin class, excluding the Cephalosporins and one Macrolide. In most cases, the recommended antibiotic for children is the same as is used for adults. These findings are consistent with the validated regimen for common bacterial skin infections (24). In addition, the duration of therapy is quite homogeneous. However, the recommended dosages are often lower than the WHO DDD and a range in daily dosages was found, with Sweden recommending the highest dosages. The debate regarding the optimal dosage-duration regime for antibiotic treatments is still ongoing. In the context of antibiotic resistance, it is unclear whether short courses with high dosages will lead to different and/or lower resistance than long courses with lower dosages (28). Recommendations in the Swedish guideline are based on expert opinion and advise a much higher dosage than in guidelines issued in the other European countries, combined with a slightly longer duration of the antibiotic course. This difference could possibly be explained by varying interpretations of evidence, the influence of professional bodies, cultural and socioeconomic factors or characteristics of the health care systems (12,29).

Guidelines only are not sufficient for enhancing appropriate prescribing; the actual adherence to the guidelines is the proof. Several factors (e.g. the implementation process of the guidelines) affect evidence-based practice (30). Evidence-based guidelines are, however, a first step to control the development of antibiotic resistance.

Evidence regarding resistance

This study also provides an overview of the extent to which antibiotic treatment guidelines are related to evidence regarding resistance to antibiotics. Scientific references focusing on antibiotic resistance are used in six of the 13 guidelines (46%). Of all references in this study, 5% are related to antibiotic resistance data. This is comparable to the American treatment guidelines issued by the Infectious Diseases Society of America (IDSA) (31), where there are 236 citations, of which 7% concern antibiotic resistance data.

When cited, antibiotic resistance data mostly come from international sources (75%). This may be due to the limited amount of national data. Since all recommendations involved Beta-lactams, we recommend that persons involved in the development and update of guidelines take the susceptibility of *S. aureus* and *S. pyogenes* into account for this class of antibiotics. We encourage stakeholders to use national or local resistance data if available.

Strengths and limitations

Strength of this study is the broad scope of countries included in this inventory; nine countries were covered from all regions in Europe with varying levels of antibiotic use. The treatment guidelines have also been supplied by coordinators of national GP networks, who are aware of the most frequently-used guidelines in their countries. Research in this area is very sparse; this study is the first to assess primary care treatment guidelines for skin infections. A limitation of this study is that interpretation of recommendations regarding children was not possible since the

outcome measure DDD is only applicable to adults. In addition, as the focus was on content and evidence for recommendations, other aspects of the guidelines (e.g. the development process or clarity of presentation) were not taken into account.

Implications

This study found that national resistance data is rarely incorporated into treatment guidelines for skin infections (< 10%) in Europe. Resistance to Beta-lactams is especially important information to be included in the development of these guidelines. Some of the studied guidelines have not recently been updated; it is advised that in the next revision, national outpatient resistance data (particularly regarding beta-lactams) is used to a larger extent. Incorporating national outpatient resistance data will provide stronger evidence-based treatment guidelines, and this will help control the emergence of antibiotic resistance in Europe.

Conclusion

There may be a lack of relevant national data on antimicrobial resistance, since only six of the 13 treatment guidelines (46%) incorporated scientific references focussing on antibiotic resistance, mostly from international sources. This study highlights the need to collect more national antimicrobial resistance data in the community, particularly regarding beta-lactams. This data can be used in the process of developing or updating guidelines to create stronger evidence-based primary care treatment guidelines for skin infections in Europe.

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Table 1. Overview of analysed guidelines.

Issuing country	Issuing organization	Title of guideline in English (link)	Year of publication	Number of guidelines
Austria	Verlagshaus der Ärzte	Evidence based medicine for use in clinical and practice environment (http://www.ebm-guidelines.at/index.php)	2009–2012	3
Belgium	Belgian Antibiotic Policy Coordination Committee (BAPCOC)	Belgian guide for anti-infectious treatment in primary care (http://www.bcfi.be/userfiles/File/antibioticagids-NL.pdf)	2012	2
Croatia	No national guidelines for skin infections available			0
France	French Society for General Medicine (SFMG)	Prescription of topical antibiotics in primary and secondary skin infections (http://www.infectiologie.com/site/medias/_documents/consensus/2005-atb-locale-dermato-argu-afssaps.pdf)	2004	1
Hungary	Ministry of Health	The Ministry of Health protocol for Erysipelas (http://www.eum.hu/egeszsegpolitika/minosegfejlesztes/borgyogyaszat)	2008	1
Netherlands	Dutch College of General Practitioners (NHG)	Standards of the Dutch college of General Practitioners—Bacterial skin infections—M68 (http://www.nhg.artsennet.nl/standaarden/) Currently under revision	2007	1
Spain	Medical College/ Ministry of Health and Consumption	Guide to good clinical practice for antimicrobial treatment in the community (http://www.comsegovia.com/pdf/guias/GBPC%20TTO%20ANTIMICROBIANO.pdf)	2006	1
Sweden	Swedish Medical Products Agency and Strama (Swedish strategic programme against antibiotic resistance)	Pharmacological treatment of skin and soft tissue infections (http://www.strama.se/dyn//,244,60,77.html)	2008	1
UK	National Health Service (NHS)	Clinical knowledge summaries (http://www.cks.nhs.uk/clinical_topics)	2007–2012	3

TABLES

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Table 2. First-choice recommendations for the antibiotic treatment of Impetigo: Comparison of guidelines.

Country	Topical antibiotic advised	Advised antibiotic	Advised daily dose (grams)	Defined daily dose (DDD) by WHO (grams)	Advised dose % of DDD	Advised duration (days)	Total use (in DDDs) ^a
Austria—adults	Yes—Fusidic acid	Cephalosporin 1st	No specific advice				
Austria—children	Yes—Fusidic acid	Cephalosporin 1st	50 mg/kg				
Belgium—adults	Yes—Fusidic acid	Flucloxacillin	1–2 g	2g	75%	7d	5.25
Belgium—children	Yes—Fusidic acid	Flucloxacillin	25–50 mg/kg				
France—adults	Yes—Fusidic acid	No specific advice					
Hungary	No guideline available						
Netherlands—adults	Yes—Fusidic acid	Flucloxacillin	1.5g	2g	75%	7d	5.25
Netherlands—children	Yes—Fusidic acid	Flucloxacillin	40–50 mg/kg				
Spain—adults	Not advised—Mupirocin	Penicillin (IM) Bullous Impetigo: Cloxacillin	No specific advice				
Sweden—adults	Yes—Retapamilin	Flucloxacillin	2.25–3 g	2 g	131%	7d	9.2
Sweden—children	Yes—Retapamilin	Cefadroximix	25–30 mg/kg				
UK—adults	Yes—Fusidic acid	Flucloxacillin	1–2 g	2 g	75%	7d	5.25
UK—children	Yes—Fusidic acid	Flucloxacillin	50–100 mg/kg				

^aTotal use is calculated using the advised duration and the advised daily dose.

Table 3. First-choice recommendations for the antibiotic treatment of Cellulitis and Erysipelas: comparison of guidelines.

Country	Advised antibiotic	Advised daily dose (grams)	Defined daily dose (DDD) by WHO (grams)	Advised dose % of DDD	Advised duration (days)	Total use (in DDDs) ^a
Austria—adults	Penicillin	Parenteral				
Belgium—adults	Flucloxacillin	2 g	2 g	100%	10 d	10
Belgium—children	Flucloxacillin	25–50 mg/kg				
France	No guideline available					
Hungary (Erysipelas)—adults	Amoxicillin + Clavulanic acid	1.875 g	1 g	188%	No information	Cannot be calculated
Netherlands—adults	Flucloxacillin	2 g	2 g	100%	10 d	10
Netherlands—children	Clarithromycin	15 mg/kg				
Spain (Cellulitis)—adults	Cloxacillin	1.5–4g	2 g	137%	No information	Cannot be calculated
Sweden—adults	Penicillin V	3 g	2 g	150%	10–14 d	18
Sweden—children	Penicillin V	50–75 mg/kg				
UK—adults	Flucloxacillin	2 g	2 g	100%	7 d	7
UK—children	Flucloxacillin	0.5–2 g				

^aTotal use is calculated using the advised duration and the advised daily dose.

Table 4. First-choice recommendations for the antibiotic treatment of Folliculitis and Furuncle: comparison of guidelines.

Country	Advised antibiotic	Advised daily dose (grams)	Defined daily dose (DDD) by WHO (grams)	Advised dose % of DDD	Advised duration (days)	Total use (in DDDs) ^a
Austria—adults	Cephalosporin 1 st	1.5 g	2 g	75%	No specific information	
Austria—children	Cephalosporins	50 mg/kg				
Belgium	No guideline available					
France	No specific advice					
Hungary	No guideline available					
Netherlands—adults	Flucloxacillin	1.5–2 g	2 g	88%	7 d	6.125
Spain—adults	Cloxacillin	2–4 g	2 g	150%	No information	Cannot be calculated
Sweden—adults	Flucloxacillin	2.25–3 g	2 g	131%	7–10d	11.2
UK—adults	Flucloxacillin	1–2 g	2 g	75%	7d	5.25
UK—children	Flucloxacillin	0.25–2 g				

^aTotal use is calculated using the advised duration and the advised daily dose.