Empiric antibiotic prescribing guidelines in 84 European paediatric hospitals: wide variation in quality, drug choice and duration

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Empiric antibiotic prescribing guidelines in 84 European paediatric hospitals: wide variation in quality, drug choice and duration.

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**key words:** antibiotic guidelines, childhood infection, European paediatric hospitals

**Abstract**

Objective: To assess the availability and source of guidelines for common infections in European paediatric hospitals and determine their quality and content.

Design: Cross-sectional survey as part of the ARPEC study. Participating hospitals completed an online questionnaire on the availability and quality of antibiotic prescribing guidelines and on empiric antibiotic treatment including recommended duration of therapy for 5 common infection syndromes: respiratory tract, urinary tract, skin and soft tissue, osteoarticular and sepsis in neonates and children.

Results: 84 hospitals from 19 European countries participated in the survey of which 74 confirmed the existence of guidelines. Complete guidelines were reported by only 20% of hospitals and the majority (71%) used a range of different sources. Guidelines most commonly available were those for UTI (74%), neonatal sepsis (71%) and sepsis in children (65%). Penicillin and amoxicillin are the antibiotics most
commonly recommended for RTIs (up to 76%), cephalosporins for UTI (up to 50%) and for SSTI and bone infection (20% and 30% respectively). Antistaphylococcal penicillin recommendations for SSTIs and bone infections were 43% and 36% respectively. Recommendations for neonatal sepsis included 20 different antibiotic combinations. Duration of therapy guidelines was mostly available for RTI and UTI (82%) and only a third of hospitals with guidelines for sepsis provide recommendations for length of therapy.

Conclusion: Comprehensive antibiotic guideline recommendations are generally lacking from European paediatric hospitals. We documented multiple antibiotics and combinations for most infections. Considerable improvement in both the quality of guidelines and their evidence base of guidance is required, linking empiric therapy to resistance rates.

INTRODUCTION

In 2014, a World Health Organization (WHO) global report on antimicrobial resistance described the problem as so serious that it threatens the achievements of modern medicine.” The report encouraged nations to collaborate and identify targets for improvement (1). A key driver for the emergence of antibiotic resistance is over-prescribing for infections of presumed viral aetiology (2,3). The problem of AMR is further complicated by the reduction in the development of new antimicrobial agents and as a result treatment of patients infected by multi-drug resistant pathogens is becoming more challenging (4,5).

The single most important action needed to address the problem of antimicrobial resistance is to modify the way antibiotics are used. Antimicrobial stewardship programmes (ASPs) and interventions seek to promote judicious use of antimicrobials. More specifically, they aim to promote the use of antibiotics only when they are necessary and to choose the right drug, at the right dose for the right duration. The majority of data regarding ASPs is derived from adult populations but more recently data are emerging on the establishment and effectiveness of ASP in
paediatric departments (6,7,8). One of the key components of ASPs is the
development and implementation of evidence-based antibiotic prescribing guidelines
providing a standard approach to the optimal selection, dosage and duration of
antibiotic therapy. The development of ASP guidelines may be particularly useful in
middle and low resource settings where implementation of a full scale ASP is not
feasible (9,10).

The majority of published studies on prescribing guidelines have targeted decreasing
unnecessary antibiotic use (11,12) while optimal selection of drug and duration of
therapy remains less well examined (13). Data from the Antibiotic Resistance and
Prescribing in European Children Point Prevalence Survey (ARPEC-PPS) observed
marked variations of antibiotic use rates and it was unclear if this variation was due to
a lack of local guidance or patient, institutional and geographical characteristics. (14)
The aim of this study was to use a novel single web based method to assess the
availability of comprehensive guidelines for infections commonly encountered within
European paediatric hospitals and to determine their quality and content.

MATERIALS AND METHODS

A cross-sectional survey was conducted through the membership of the European
Society for Paediatric Infectious Diseases (ESPID) and the Global Research in
Paediatrics (GRiP) networks. Paediatricians participating in these networks were
invited to participate. Participation required registration on the official website of
ARPEC (www.arpecproject.eu) which also provided access to a Point Prevalence
Survey (PPS) on antibiotic use that was being conducted in parallel to this survey.
(14) Following registration participants were directed to a web-based standardized
questionnaire. There were no exclusion criteria for participating paediatric hospitals in
terms of population coverage, hospital size and academic characteristics. It was not
possible to determine a denominator of invited participants.

Data collection

The questionnaire was designed and supported by the University of Antwerp,
Belgium, and it was based on a simple, user-friendly drop-down list questionnaire.
The questionnaire was divided into two major sections. The first section requested
information on the availability of antibiotic prescribing guidelines, source of guidance
(national, regional, local hospital), availability of hard copies or electronic reference for these guidelines and time of most recent update. The second main section requested information on empiric (first line) antibiotic treatment and recommended duration of therapy for the following infection syndromes: 1/ Respiratory tract infection (RTI): rhinitis, tonsillitis, acute otitis media, sinusitis, bronchitis, pneumonia in 3 mo-5 yrs old and > 5yrs old children, 2/ urinary tract infections (UTI) in children> 3 months old, 3/ skin and soft tissue infections (SSTI), 4/ osteoarticular infections, and 5/ community acquired sepsis in neonates and children. The Anatomical Therapeutic Chemical (ATC) classification system of medicines (WHO, version 2011) was used in all fields of suggested antimicrobials (15). The survey was made accessible simultaneously with the antibiotic use PPS’s in both September 2011 and in November 2012 in order to encourage participation. Hospitals were able to register their responses once during the two survey periods and they were asked to validate their responses by extracting the corresponding excel file. This study was funded by the European Commission DG SANCO through the Executive Agency for Health and Consumers (EAHC) and was part of the context of the broader ARPEC (Antibiotic Resistance and Prescribing in European Children) project. (16)

RESULTS

Characteristics of submitted guidelines

Figure 1 presents data on survey participation and source of guidelines. Eighty-four hospitals from 19 European countries participated in the survey. The United Kingdom was the country with the highest participation (20 hospitals). Eighty nine percent (74/84 hospitals) confirmed the existence of guidance for at least one infection syndrome but only 20% (15/74) submitted data for all infections listed in the questionnaire. Out of 74 hospitals that reported having guidelines, 71% (53/74) used guidelines that were derived from a range of different published sources (international, national, local guidelines). Guidelines most widely available were those for UTI (74%), neonatal sepsis (71%) and sepsis in children (65%). More than half of participating institutions (58%) submitted guideline data for URTIs (tonsillitis, sinusitis, AOM, rhinitis) of which 60% included tonsillitis and otitis media. Sixty percent of hospitals reported having guidelines for LRTI (bronchitis and pneumonia)
followed by 59% for osteoarticular infection, and 48% for skin and soft tissue infection (SSTI).

(Figure 1)

Empiric recommendations by clinical infection syndromes

Figure 2 presents data on recommended antibiotic therapy according to type of infection. Penicillin and amoxicillin were the most common antibiotics suggested for the treatment of tonsillitis, AOM and sinusitis (73%, 77% and 56% respectively) as well as for pneumonia in infants and children up to 5 years of age (75%). In older children with pneumonia, penicillin or amoxicillin is recommended by 48% while a macrolide is recommended by 30% of institutions. Significant variation in recommended antibiotic therapy for UTI, SSTI, bone and joint infections was reported. In children with suspected UTI up to 50% of hospitals recommended a cephalosporin (all classes combined, of which 30% were of a 3rd generation). For SSTI and bone infections, anti-staphylococcal penicillins were recommended by 43% and 36% respectively. Cephalosporin use for these indications (all classes) was up to 20% for skin infections and 30% for bone.

(Figure 2)

Table 1 presents data on antibiotic recommendations for infants and children with suspected sepsis. Fifty-seven European hospitals (57/74, 77%) provided information on suggested antibiotic management of early (EOS) and late onset neonatal sepsis (LOS). Eighty five percent recommended a combination of antibiotics of which 88% included a beta-lactam (penicillin or ampicillin) along with an aminoglycoside for either EOS or LOS.

Antibiotic guidelines for community acquired sepsis in young infants and children were submitted by 45 participating hospitals (45/74, 60%). A third generation cephalosporin was recommended by 78% of institutions and always combined with a second antibiotic in infants 1-3 months old. Ceftriaxone was recommended as a single agent by 27 institutions for the treatment of sepsis in older children (27/45 hospitals,
60%). Seven institutions (7/45, 15%) recommended the use of a carbapenem (meropenem) as first line therapy for children with suspected sepsis.

(Table 1)

**Treatment duration**

Duration of therapy guidance was most widely available for RTI and UTI (82%) and 67% and 63% for neonatal EOS and LOS. Only a third of hospitals (34% and 36%) with guidelines for sepsis in older infants and children reported providing recommendations for duration of therapy. Median duration of therapy for AOM was 7 (IQR 5-10) days, for pneumonia 8 days (IQR 7-10) (all ages), UTI 10 (IQR 7-10) days, arthritis and osteomyelitis, 21 (IQR 14-28) and 28 (IQR 21-28) days respectively. For sepsis the median duration of therapy for suspected sepsis in neonates was 7 (IQR 3-10) days, while for older infants and children 10 (IQR 10-14) days.

**Discussion**

To our knowledge, this cross sectional survey is the first to use a standard method to document the presence and quality, mostly in terms of completeness, of antibiotic guidelines in European paediatric hospitals. Our findings indicate that few European hospitals participating in this survey have comprehensive antibiotic prescribing guidelines for common paediatric infections and the majority use a wide mixture of reference sources. National antibiotic recommendations were reported as being used only by a third of participating hospitals. Guidelines most commonly available were those for URTI, UTI and neonatal sepsis.

With respect to antibiotic recommendations, narrow spectrum guidance using penicillin or amoxicillin were recommended by only 2/3 of participating hospitals for the treatment of URTI and LRTI. Guidelines for UTI, SSTI, musculoskeletal infections and neonatal sepsis varied considerably between European hospitals with a mixture of antibiotics in terms of spectrum and combinations. Interestingly we documented 20 different antibiotic combinations for the treatment of neonatal sepsis, mostly reflecting late onset rather than early onset sepsis.
Published guidelines from professional organizations, encourage the use of amoxicillin for the treatment of non-complicated bacterial URTI and CAP in children <5 years old. (17,18,19,20). Strong evidence supports the superiority of amoxicillin over other antibiotics, including β- lactams, in the treatment of uncomplicated RTIs (21,22) especially in the developed world where high vaccination rates against *H. influenzae* have been documented.

Antibiotic therapy for skin and bone infections is usually empirical as pathogen isolation is rare in children. Most institutions in this study recommend either an anti-staphylococcal penicillin or a cephalosporin for a suspected skin or bone infection targeting *Strept. pyogenes* and methicillin sensitive *S. aureus*. (23). Only a small number of institutions would recommend the use of either glycopeptides (e.g. vancomycin) or lincosamides (e.g clindamycin) as empiric therapy for bone and joint infections despite recent recommendation for their use if MRSA rates exceed 10%. (24, 25)

The wide variation in the empirical guidance for UTI and neonatal sepsis emphasizes the need for improving the use of local microbiology data. No data on urine resistance was available in this study, so we cannot comment on the appropriateness of therapy although the number of centres recommending routine use of broad-spectrum antibiotics such as 3rd generation cephalosporins (30%) appears high. Similarly, in neonatal sepsis we recorded 20 different antibiotic combinations, which is similar to the results shown by Lutsar et al in a survey of neonatal units from 5 European countries. (26) That could explain why most published guidelines on UTI and neonatal sepsis focus mostly on prompt diagnosis rather than antibiotic recommendations, encouraging clinicians to work closely with local microbiology labs before they decide on the most appropriate antibiotic regimen. (27,28,29,30,31)

In terms of recommended duration of therapy we documented (a) presence of guidance for RTI with course duration reflecting established practices, (b) limited availability of guidance for infants and children with sepsis with prolonged antibiotic courses used when guidelines did include duration recommendations (c) a wide range of treatment durations for bone and joint infections. In general, large scale randomized trials to guide the appropriate duration of antibiotic therapy are lacking and practice is based mostly on retrospective case series and expert opinions. This study indicates that clinicians are not yet confident that ‘shorter is better’ despite the existence of clinical indications with established shorter courses. (32,33,34,35)
Limitations

This study has several weaknesses. First, the response rate among those invited to take part and completing the antimicrobial PPS was around 60%. It is likely that clinicians submitting data only to the PPS, but not completing the guidelines survey more frequently work at hospitals without antibiotic guidelines in place. There is therefore a risk that we overestimated the overall availability of antibiotic guidance. Second, submitted information was not externally validated as participants were only asked to submit reference and validate the accuracy of their responses. We did not use quality assessment tools such as the Appraisal of Guidelines Research and Evaluation (AGREE) score (36) that should be able to provide valuable feedback since the submitted information was not adequate in order to proceed to this analysis. Third, the questionnaire explored hospital guidelines but the responses reflect mostly acute management in the emergency department setting that involves also patients returning to the community. Finally, although participants were asked to submit information on first line antibiotic therapy for the “previously healthy child”, we were not able to document antibiotic recommendations according to severity of the infection.

Conclusions

The Manual of Childhood Infection from the European Society of Paediatric Infectious Diseases (ESPID) “Blue Book” (37) and USA “Red Book” (38) already provide detailed guidance on the management of common infections. Guideline panels formed by professional organizations can lead by educating clinicians how to write evidence-based guidelines (39,40). There is currently reasonable quality evidence on certain infection syndromes, such as RTI, SSTI, bone and joint infections. International collaboration on harmonisation of the management of paediatric HIV infection including the use of antiretrovirals has led the way in this area (41). It is equally challenging to provide good quality evidence integrating routine surveillance data on current rates of antimicrobial resistance into local guidelines development. A more structured approach to link surveillance data most effectively into local or national guidance is required. Further clinical trial data are required to improve the evidence base for the optimal management of clinical infection syndromes in children.
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Figure 1. Availability and characteristics of antibiotic prescribing guidelines in participating European paediatric hospitals

*North: EE, DK, UK, LV
South: GR, PT, ES, MK, IT, SI, RO
Central: DE, HU, CH
East: GE
West: LU, BE, FR

¶ 1 hospital is not characterized
Figure 2: Recommended antibiotic therapy for children with suspected RTI, UTI, SSTI, bone and joint infection in European paediatric hospitals. For illustration purposes, up to 4 categories per diagnosis were graphed provided they represented >10%. The rest were grouped under “other”. The number under the diagnosis on the X axis signifies the number of suggested antibiotic therapies included in “other”.
**Table 1:** Recommended antibiotic therapy for neonatal and infantile sepsis in European paediatric hospitals. Absolute numbers represent number of hospitals with existing guidelines.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>EOS N(%)</th>
<th>LOS N(%)</th>
<th>1m-3m N(%)</th>
<th>&gt;3m N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ampicillin/Penicillin Based</strong></td>
<td>57 (87.72%)</td>
<td>51</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Ampicillin &amp; 3rd gen cephalosporin</td>
<td>57 (87.72%)</td>
<td>9 (17.65%)</td>
<td>15 (33.33%)</td>
<td>3 (6.67%)</td>
</tr>
<tr>
<td>Ampicillin &amp; 3rd gen cephalosporin &amp; Aminoglycoside</td>
<td>5 (8.77%)</td>
<td>4 (7.02%)</td>
<td>2 (3.92%)</td>
<td></td>
</tr>
<tr>
<td>Ampicillin &amp; Aminoglycoside</td>
<td>22 (38.60%)</td>
<td>12 (23.53%)</td>
<td>1 (2.22%)</td>
<td></td>
</tr>
<tr>
<td>Ampicillin &amp; Aminoglycoside &amp; Benzylpenicillin</td>
<td>1 (1.75%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzylpenicillin &amp; Aminoglycoside</td>
<td>15 (26.32%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antistaph pen &amp; Aminoglycoside</td>
<td>1 (1.75%)</td>
<td>6 (11.76%)</td>
<td>1 (2.22%)</td>
<td></td>
</tr>
<tr>
<td>Ampicillin &amp; Enzyme inhibitor &amp; Aminoglycoside</td>
<td>1 (1.75%)</td>
<td>3 (5.88%)</td>
<td>7 (15.56%)</td>
<td>1 (2.22%)</td>
</tr>
<tr>
<td>Penicillin &amp; Antistaph penicillin</td>
<td>1 (1.96%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cephalosporin based</strong></td>
<td>7 (12.28%)</td>
<td>19 (42.22%)</td>
<td>32 (71.11%)</td>
<td></td>
</tr>
<tr>
<td>2nd gen &amp; Aminoglycoside</td>
<td>1 (1.96%)</td>
<td>1 (2.22%)</td>
<td>1 (2.22%)</td>
<td></td>
</tr>
<tr>
<td>2nd gen</td>
<td></td>
<td>2 (4.44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd gen &amp; Aminoglycoside</td>
<td>1 (1.96%)</td>
<td>8 (17.78%)</td>
<td>27 (60.00%)</td>
<td></td>
</tr>
<tr>
<td>3rd gen &amp; Penicillin &amp; Aminoglycoside</td>
<td>1 (1.96%)</td>
<td>9 (20.00%)</td>
<td>2 (4.44%)</td>
<td></td>
</tr>
<tr>
<td><strong>Vancomycin based</strong></td>
<td>7 (12.28%)</td>
<td>8 (15.69%)</td>
<td>3 (6.67%)</td>
<td>3 (6.67%)</td>
</tr>
<tr>
<td>&amp; Carbapenem &amp; Aminoglycoside</td>
<td>7 (12.28%)</td>
<td></td>
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<tr>
<td>&amp; Ampicillin</td>
<td>1 (1.96%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; Antistaph penicillin</td>
<td>1 (1.96%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; Antistaph penicillin &amp; Aminoglycoside</td>
<td>1 (1.96%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&amp; 3rd gen cephalosporin &amp; Aminoglycoside</td>
<td>1 (1.96%)</td>
<td>2 (4.44%)</td>
<td>2 (4.44%)</td>
<td></td>
</tr>
<tr>
<td>&amp; 3rd gen cephalosporin</td>
<td>1 (1.96%)</td>
<td>1 (2.22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; Aminoglycoside</td>
<td>3 (5.88%)</td>
<td>1 (2.22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; Meropenem</td>
<td>1 (1.96%)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Meropenem based</strong></td>
<td>7 (13.73%)</td>
<td>7 (15.56%)</td>
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<tr>
<td>Aminoglycoside+Meropenem</td>
<td>7 (13.73%)</td>
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<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>7 (13.73%)</td>
<td></td>
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</tr>
</tbody>
</table>

EOS: Early Onset Sepsis, LOS: Late Onset Sepsis