Variation in paediatric hospital antibiotic guidelines in Europe

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ABSTRACT

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

Design Participating hospitals completed an online questionnaire on the availability and characteristics of antibiotic prescribing guidelines and on empirical antibiotic treatment including 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 (existing guidelines for all requested infection syndromes) were reported by 20% of hospitals and the majority (71%) used a range of different sources. Guidelines most commonly available were those for urinary tract infection (UTI) (74%), neonatal sepsis (71%) and sepsis in children (65%). Penicillin and amoxicillin were the antibiotics most commonly recommended for respiratory tract infections (RTIs) (up to 76%), cephalosporin for UTI (up to 50%) and for skin and soft tissue infection (SSTI) and bone infection (20% and 30%, respectively). Antistaphylococcal penicillins were recommended for SSTIs and bone infections in 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%). A third of hospitals with guidelines for sepsis provided recommendations for length of therapy.

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

What is already known on this topic

Antibiotic prescribing guidelines are a key tool in appropriate drug selection and duration of therapy.

What this study adds

- Comprehensive antibiotic prescribing guidelines are lacking in many European paediatric hospitals.
- Antibiotic guidelines vary significantly in terms of antibiotic choice, bacterial coverage and recommended duration of therapy.

INTRODUCTION

In 2014, a WHO global report on antimicrobial resistance described the problem as so serious that it 'threatens the achievements of modern medicine'.[1] A key driver for the emergence of resistance is overprescribing of antibiotics for infections of presumed viral aetiology,[2 3] which is further complicated by limited development of novel classes of antimicrobial agents.[4]

An 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. 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.[5–7] 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 in different healthcare settings.[8–10]

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 the types of antibiotics used across Europe 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

This cross-sectional survey was part of the broader ARPEC study. Paediatricians, members of the European Society for Paediatric Infectious Diseases (ESPID) and the Global Research in Paediatrics networks were invited to participate in this cross-

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sectional survey. Following the initial call, a single registration per hospital was accepted in order to avoid duplications. Participation required registration on the official website of ARPEC (http://www.arpecproject.eu) which also provided access to a PPS on antibiotic use that was being conducted in parallel to this survey.[14] Following registration participants were directed to a web-based standardised 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 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 empirical (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 months–5 years old children and >5 years old children, (2) urinary tract infections (UTI) in children >3 months old, (3) skin and soft tissue infections (SSTIs), (4) osteoarticular infections and (5) community acquired sepsis in neonates and children. The Anatomical Therapeutic Chemical classification system of medicines (WHO, V.2011) was used in all fields of suggested antimicrobials.[15] The survey was made accessible simultaneously with the antibiotic use PPSs in 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 ensure the accuracy of their data entry by extracting the corresponding excel file. This study was funded by the European Commission DG SANCO through the Executive Agency for Health and Consumers and was part of the context of the broader ARPEC 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 representing a response rate of 60%, when compared with the hospitals that participated in the antibiotic PPS.[14] The UK was the country with the highest participation (20 hospitals). Eighty-nine per cent (74/84 hospitals) confirmed the existence of guidance for at least one infection syndrome but only 15/74 (20%) had complete guidelines, that is, submitted data for all infections listed in the questionnaire. Out of 74 hospitals that reported having guidelines, 53 (71%) used guidelines that were derived from a range of different published sources (international, national, local guidelines). Guidelines most widely available were those for UTI (54/74, 74%), neonatal sepsis (52/74, 71%) and sepsis in children (48/74, 65%). More than half of participating institutions (43/74, 58%) submitted guideline data for upper RTIs (URTIs tonsillitis, sinusitis, AOM, rhinitis) of which 26/43 (60%) included tonsillitis and otitis media. Forty-four hospitals (60%) reported having guidelines for lower RTI (LRTI: bronchitis and pneumonia) followed by 43 (59%) for osteoarticular infection, and 35 (48%) for SSTI.

Empirical recommendations by clinical infection syndromes

Figure 2 presents data on the antibiotic therapy recommended according to type of infection. Penicillin and amoxicillin were the most common antibiotics suggested for the treatment of tonsillitis (41/56, 73%), AOM (44/57, 77%) and sinusitis (27/48, 56%) as well as for pneumonia in infants and children up to 5 years of age (44/59, 75%). In older children with pneumonia, penicillin or amoxicillin was recommended by 28/59 (48%) while a macrolide was recommended by 18/59 (30%) of institutions. Significant variation in recommended antibiotic therapy for UTI, SSTI, and bone and joint infections was reported. In children with suspected UTI up to 28/56 (50%) of hospitals recommended a cephalosporin (all classes combined, of which 30% were of a third generation). For SSTI and bone infections, antistaphylococcal penicillins were recommended by 17/39 (43%) and 17/47 (36%) of hospitals, respectively. Cephalosporin

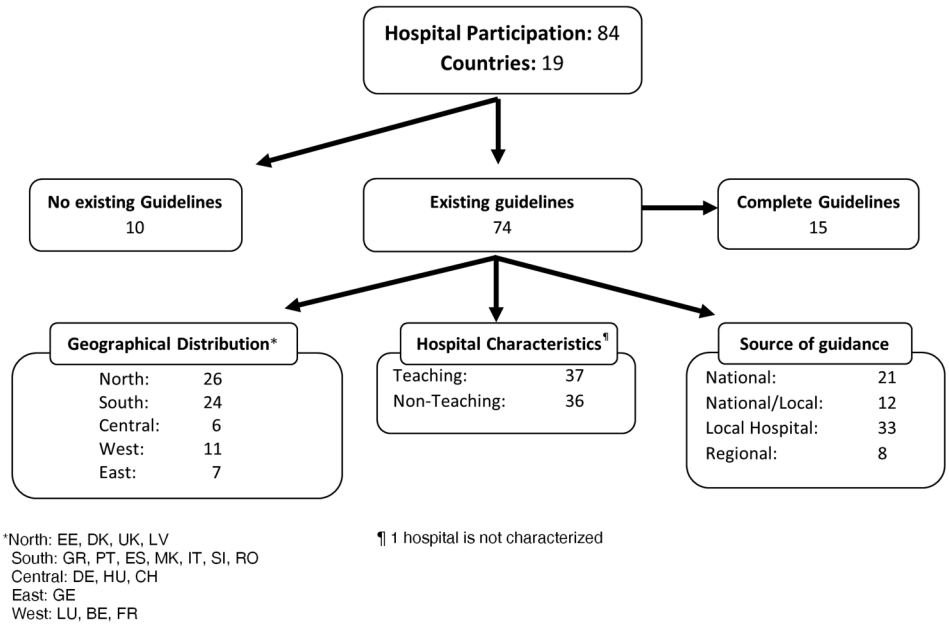

Figure 1 Availability and characteristics of antibiotic prescribing guidelines in participating European paediatric hospitals.

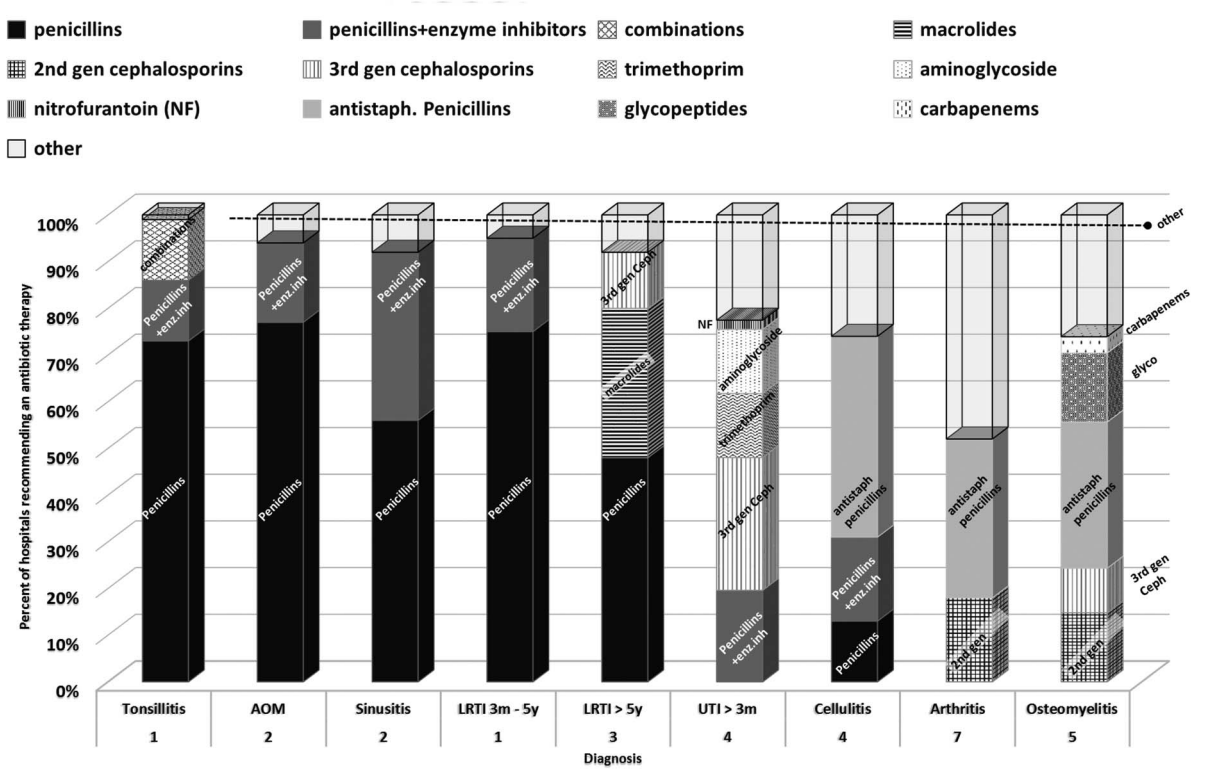

Figure 2 Recommended antibiotic therapy for children with suspected respiratory tract infection (RTI), urinary tract infection (UTI), skin and soft tissue infection (SSTI), bone and joint infection in European paediatric hospitals. For illustration purposes, up to four categories per diagnosis were graphed provided they represented >10% of antibiotic recommendations. 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'.

use for these indications (all classes) was 8/39 (20%) for skin infections and 14/47 (30%) for bone. An anti-MRSA antibiotic (vancomycin) was recommended by 4/50 (8%) and 8/47 (17%) of institutions for joint and bone infections.

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 onset neonatal sepsis (EOS) and late onset neonatal sepsis (LOS). Forty-eight institutions (85%) recommended a combination of antibiotics of which 40 (88%) included a β-lactam (penicillin or ampicillin/amoxicillin) together 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 35 institutions (78%) 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.

Treatment duration

Duration of therapy guidance was most widely available for RTI (60/74, 82%), UTI (49/74 67%) and neonatal EOS and LOS (46/74 63%). Only a third of hospitals (27/74, 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 days and IQR was 5–10 days, for pneumonia 8 days (IQR 7–10) (all ages), UTI 10 (IQR 7–10) days, septic arthritis and osteomyelitis, 21 (IQR 14–28) days 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

Our findings indicate that few European hospitals participating in this survey have comprehensive antibiotic prescribing guidelines for common paediatric infections and the majority uses 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 two of three of the participating hospitals for the treatment of URTI and LRTI. Guidelines for UTI, SSTI, bone and joint 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 LOS rather than EOS.

Most published guidelines from professional organisations, encourage the use of amoxicillin for the treatment of non-complicated bacterial URTI and community acquired pneumonia in children <5 years old[17–20] especially in the developed world where high vaccination rates against *H. influenzae* type b 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

Table 1 Recommended antibiotic therapy for neonatal and infantile sepsis in European paediatric hospitals

	EOS N (%)	LOS N (%)	1–3 months N(%)	>3 months N(%)
	57	51	45	45
Ampicillin/penicillin based	41 (72%)	22 (43%)	8 (17%)	3 (6%)
Ampicillin+aminoglycoside	22 (38%)	12 (23%)		1 (2%)
Ampicillin+aminoglycoside+benzylpenicillin	1 (1.5%)			
Benzylpenicillin+aminoglycoside	15 (26%)			
Antistaph pen+aminoglycoside	1 (1.5%)	6 (11%)	1 (2%)	
Co-amoxiclav+aminoglycoside	1 (1.5%)	3 (6%)	7 (15%)	1 (2%)
Co-amoxiclav	1 (1.5%)			1 (2%)
Penicillin+Antistaph penicillin		1 (2%)		
Cephalosporin based	9 (16%)	14 (27%)	34 (75%)	32 (71%)
2nd gen+aminoglycoside		1 (2%)	1 (2%)	1 (2%)
2nd gen				2 (4%)
3rd gen		1 (2%)	8 (18%)	27 (60%)
3rd gen cephalosporin+ampicillin	5 (9%)	9 (17%)	15 (33%)	
3rd gen cephalosporin+ampicillin+aminoglycoside	4 (7%)	2 (4%)		
3rd gen+aminoglycoside		1 (2%)	9 (20%)	2 (4%)
3rd gen+penicillin+aminoglycoside			1 (2%)	
Vancomycin based	7 (12%)	8 (15%)	3 (6%)	3 (6%)
+Carbapenem+aminoglycoside	7 (12%)			
+Ampicillin		1 (2%)		
+Antistaph penicillin		1 (2%)		
+Antistaph penicillin+aminoglycioside		1 (2%)		
+3rd gen cephalosporin		1 (2%)	2 (4%)	2 (4%)
+3rd gen cephalosporin+aminoglycoside				1 (2%)
+Aminoglycoside		3 (6%)	1 (2%)	
+Meropenem		1 (2%)		
Meropenem based		7 (14%)		7 (15%)
Aminoglycoside+meropenem		7 (14%)		
Meropenem				7 (15%)

Absolute numbers represent number of hospitals with existing guidelines.
antistaph, antistaphylococcal; EOS, early onset sepsis; gen, generation; LOS, late onset sepsis; pen, penicillin.

antistaphylococcal penicillin or a cephalosporin for a suspected skin or bone infection targeting *Strep. pyogenes* and methicillin susceptible *S. aureus*.[21] Only a small number of institutions would recommend the use of either glycopeptides (eg, vancomycin) or lincosamides (eg, clindamycin) as empirical therapy for bone and joint infections despite recent recommendation for their use if MRSA rates exceed 10%.[22 23]

The wide variation in the empirical guidance for UTI and neonatal sepsis emphasises the need for improving the use of local microbiology data. No data on urine resistance were available in this study, so we cannot comment on the appropriateness of the recommended high percentage of broad-spectrum antibiotics. In neonatal sepsis we recorded 20 different antibiotic combinations. Similar variability in antibiotic recommendations in NICU patients was shown by Leroux *et al*[24] in a French national survey and by Lutsar *et al*[25] in a survey of neonatal units from five European hospitals. This large variability could explain why most published guidelines on UTI and neonatal sepsis focus mostly on prompt diagnosis rather than antibiotic recommendations, suggesting that clinicians should work closely with local microbiology labs before they decide on the most appropriate antibiotic regimen.[26–30]

In terms of recommended duration of therapy we documented; (A) limited availability of guidance for certain infection syndromes and (B) long courses for infants and children with sepsis, bone and joint infection. In general randomised 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.[31–34]

Limitations

This study has several weaknesses. Even though the antimicrobial PPS and the guideline questionnaire were distributed simultaneously, 60% of those who took part in the PPS submitted information about guidelines as well. It is possible 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 likely risk that we overestimated the overall availability of antibiotic guidance. Second, submitted information was not externally validated as participants were only asked to submit and validate the accuracy of their own responses. We did not use quality assessment tools such as the Appraisal of Guidelines Research and Evaluation score[35] 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 also involves 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 underlying medical conditions.

Future actions

The Manual of Childhood Infection from the ESPID 'Blue Book'[36] and the US 'Red Book'[37] already provide detailed guidance on the management of common infections. Guideline panels formed by professional organisations can lead by educating clinicians how to write evidence-based guidelines.[38 39] International collaboration on harmonisation of the management of paediatric HIV infection including the use of antiretrovirals has led the way in this area.[40] It is equally challenging to provide good quality evidence integrating routine surveillance data on current rates of antimicrobial resistance into local guidelines development. Improved methods to link surveillance data most effectively into local or national guidance are required.

Antibiotic guidelines for common infection syndromes vary significantly in European paediatric hospitals especially in terms of completeness and choice of antibiotics. Harmonisation is feasible for certain infections (RTI, SSTI, bone and joint) where good quality evidence already exists while further clinical trial data are required to improve the evidence base for other infections such as UTI and sepsis in infants.

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Contributors NS, MT and MS were study leaders. HG, AV and ND prepared the online data tool. JK, TZ and GK analysed the data. NS, JK and GS prepared the initial draft of the manuscript. All authors reviewed and commented on the draft.

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