Antibiotic resistance in paediatric UTIs in Norway

ORIGINAL ARTICLE

CHRISTIAN MAGNUS THAULOW

E-mail: cmt85@hotmail.com
Department of Clinical Science
University of Bergen
and
Department of Paediatrics and Adolescent Medicine
Haukeland University Hospital
He contributed to the concept and protocol, and data collection,
processing and analysis, as well as to the design and drafting of the
manuscript.
Christian Magnus Thaulow, specialist in paediatrics, paediatrician and
researcher in antibiotic use in children.
The author has completed the ICMJE form and declares the following
conflict of interest: He has received a PhD stipend from the University of
Bergen.

PAUL CHRISTOFFER LINDEMANN

Department of Clinical Science
University of Bergen
and
Department of Microbiology
Haukeland University Hospital
Paul Christoffer Lindemann has contributed to the concept, data
processing and analysis, as well as the literature searches, data
interpretation and manuscript revision.
Paul Christoffer Lindemann, specialist in medical microbiology and
senior consultant/head of section.
The author has completed the ICMJE form and declares no conflicts of
interest.

CLAUS KLINGENBERG

Paediatric research group
Department of Clinical Medicine
UiT The Arctic University of Norway
and
Department of Paediatrics and Adolescent Medicine
University Hospital of North Norway
Claus Klingenberg has contributed to the concept, literature searches
and data interpretation, as well as to manuscript revision.
Claus Klingenberg, specialist in paediatrics, senior consultant/head of
section and professor.
The author has completed the ICMJE form and declares the following
conflict of interest: He is a member of the advisory board for the Nordic
Neonatal Meeting, which receives support from Chiesi.

BACKGROUND

Urinary tract infections are common in children. The purpose of this study was
to describe national resistance data from urinary isolates from children with a
view to informing antibiotic use.

METHOD

We conducted an observational study based on culture responses with
resistance determination in urine from the Norwegian Surveillance System for
Antimicrobial Drug Resistance (NORM). All urinary isolates from children (0–
17 years) in the period 2013–17 were included and compared with urinary
isolates from adults. For cephalexin resistance, we used data from two
Norwegian hospitals covering the period 2015–19.

RESULTS

Of 13 211 urinary isolates included in the NORM register, 589 (4.5 %) were
from children. Weighted by the number of data collection days, *Escherichia coli*
accounted for 85.2 % of the isolates from children. For *E. coli*, there was a
higher proportion of trimethoprim resistance in urine samples from children
(27.0 %) compared to adults (22.9 %), p = 0.02. For ciprofloxacin, we found a
lower resistance rate in *E. coli* in urine samples from children (5.7 %) compared
to adults (8.7 %), p = 0.03. For other selected antibiotics, we found the
following resistance rates in *E. coli* in children: nitrofurantoin (0.5 %),
mecillinam (4.0 %), cephalexin (4.3 %), amoxicillin-clavulanic acid (7.2 %) and
trimethoprim-sulfamethoxazole (24.1 %).

INTERPRETATION

Pivmecillinam, cephalexin and amoxicillin-clavulanic acid are relevant choices
in the empirical treatment of upper urinary tract infections. Nitrofurantoin and
pivmecillinam are relevant for lower urinary tract infections. Trimethoprim and

trimethoprim-sulfamethoxazole should only be used after resistance determination.

Main findings

Escherichia coli was confirmed in 85 % of urinary isolates from children in Norway.

We found a significantly higher proportion of trimethoprim resistance and a significantly lower proportion of ciprofloxacin resistance in urinary isolates of *E. coli* taken from children compared to adults.

For *E. coli* in urine samples in children with a urinary tract infection, there was a low incidence of resistance to nitrofurantoin (0.5 %), mecillinam (4.0 %), cephalexin (4.3 %) and amoxicillin-clavulanic acid (7.2 %).

Urinary tract infections (UTIs) are common in children. Approximately 2 % of boys and 8 % of girls will have had a UTI before the age of eight (1). In paediatrics, there is a tradition of distinguishing between upper (febrile) and lower (afebrile) UTIs (1–3). The incidence is highest among infants, who mainly contract upper UTIs (1, 3, 4). A meta-analysis found that the incidence of upper UTIs among febrile children < 2 years was 7 % (4). In older children, the incidence of upper and lower UTIs is relatively similar (1). Most children can be treated with peroral antibiotics, but choosing the right antibiotic is crucial for preventing severe symptoms (3). However, unnecessary use of broad-spectrum antibiotics also needs to be avoided in order to curb the development of antibiotic resistance (5).

Escherichia coli is reported to cause at least 70 % of UTIs in children (1, 3). Globally, there is concern about the high rates of resistance to a number of antibiotics in *E. coli* urinary isolates from children (6–8). Norway has seen a slow but gradual increase in antibiotic resistance among *E. coli* in urine over the last 10–20 years (9).

Both the Norwegian Directorate of Health and the Norwegian Society of Pediatricians issue recommendations for the treatment of UTIs in children in Norway (2, 10), but these are partly based on microbiological resistance data that have been collated for all age groups (9). Reports from other countries show clear differences in resistance patterns in *E. coli* isolates from children compared with isolates from adults (11–13). One study showed that access to data specifically relating to resistance among *E. coli* in urine from children could potentially improve the quality of treatment for UTIs (13).

We wanted to strengthen the evidence base for choosing antibiotics to treat paediatric UTIs in Norway by using national data to describe the presence of bacteria and resistance patterns in urinary isolates.

Material and method

Data collection and bacterial isolates

This is a national observational study based on register data from the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM) covering the period 2013–2017. The register collects resistance data from bacterial isolates at all clinical microbiological laboratories in Norway (9). A urine sample must be provided if bacteria are detected in significant numbers in a patient with symptoms of a UTI. In urine aspiration sampling, $\geq 10^2$ colony-forming units (CFU)/mL is regarded as significant, while a midstream sample or disposable catheter requires $\geq 10^3$ CFU/mL. For mixed flora, $\geq 10^4$ CFU/mL is required, while $\geq 10^5$ CFU/mL is required from urine collection bags and permanent catheters. Only one isolate per patient is included during the collection period. Resistance data are interpreted according to clinical breakpoints set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), based on minimum inhibitory concentration (MIC) levels or zone diameter (14). In order to assess whether the bacterium is sensitive (S), sensitive to increased exposure (I) or resistant (R), each bacterium has a fixed limit for the breakpoint of different antibiotics. Increased exposure (I) means that a higher than standard dosage is needed for the bacterium to be sensitive.

We included all urine samples among the entire Norwegian population that met the NORM criteria, both from the primary and specialist health services, in defined periods in 2013–2017 (Table 1). In total, 13 211 urine samples were included, each representing one patient. Data from urine samples in children (0–17 years) were extracted from the NORM database and included the following: the patient's month of birth, sample date and antibiotic sensitivity with MIC levels/zone diameter. We divided the children into three age groups: infants (< 1 year, up to and including the month they turned one year old); preschool children (1–5 years, from the month following their first birthday up to and including the month of their sixth birthday); school children (6–17 years, from the month following their sixth birthday up to and including the month they turned 18). Urine samples from adults were separated from the year-specific NORM data by subtracting paediatric isolates from the total number of isolates presented in the report. This was done for each combination of bacteria and antibiotics, so that all paediatric isolates were eliminated.

Species

Table 1

Demographic overview of bacterial isolates from urine samples in children up to age 17 and adults, collected periodically from the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM) in the period 2013–2017. Spp. = (several unspecified species within a genus)

	Children aged 0–17 (crude rate/100 000 inhabitants[1])	Adults ≥ 18 years (crude rate/100 000 inhabitants)
Total number of isolates[2]	589 (49)	12 622 (311)
Age groups		
< 1 year	94 (158)	-
1–5 years	139 (45)	-
6–17 years	356 (43)	-
Bacteria		
Escherichia coli	403 (34)	6 105 (150)
Klebsiella spp.	101 (8)	4 751 (117)
K. pneumoniae	74 (6)	2 811 (69)
K. oxytoca	14 (1)	1 227 (30)
Other *Klebsiella spp.*	13 (1)	713 (18)
Enterococcus spp.	59 (5)	1 201 (30)
E. faecalis	59 (5)	1 117 (27)
E. faecium	0 (0)	82 (2)
Other *Enterococcus spp.*	0 (0)	2 (0)
Proteus spp.	22 (2)	411 (10)
Enterobacter spp.	4 (0)	154 (4)

[1]Number of inhabitants in the specific age groups in 2017, based on data from Statistics Norway.

[2]Number of days vary where data have been collected for NORM in the period 2013–17: E. coli 14 days (2013–17), Klebsiella spp. 105 days (2013–17), Enterococcus spp. 21 days (2015), Proteus spp. 21 days (2017), Enterobacter spp. 21 days (2016)

Cephalexin resistance is not reported to the NORM register, but cephalexin is recommended as an alternative antibiotic for upper UTIs in children (2). Since 2015, however, Haukeland University Hospital and the University Hospital of North Norway have routinely tested for cephalexin resistance in *E. coli* urinary isolates from children. We therefore chose to include resistance data for cephalexin in the period 2015–19 for samples taken from children aged 0–15 (from birth to 15 years) and analysed at the two hospitals. Only one isolate per child was included.

Data processing and statistics

We categorised antibiotic sensitivity as either S and I (sensitive isolate) or R (resistant isolate), according to the breakpoint defined by EUCAST that corresponded to the year of the NORM analysis.

Demographic data were presented as absolute numbers and as the crude rate per 100 000 inhabitants based on population data from Statistics Norway (15). The crude rates were calculated for adults and for children in different age groups. The population was based on the total number of inhabitants for the respective age groups in 2017. The length of the data collection period varied for the different bacteria. In order to estimate the relative distribution of the different bacteria, we therefore weighted the number of days that data were collected for each microbe.

Resistance data were presented as percentages with a corresponding 95 % confidence interval (95 % CI) based on the standard deviations of the percentages. All isolates from children were analysed for sensitivity to clinically relevant antibiotics. Bacteria that included ≥ 50 isolates were compared with adults as a percentage of resistant isolates. The resistance rate for *Enterococcus faecalis* was calculated separately, while for *Klebsiella species (spp.)*, we included all the species in the comparison.

We used the chi-squared test to compare percentages and Fisher's exact test in cases where the expected frequency was ≤ 5. Stata SE version 16.1 was used for the analysis. A p-value < 0.05 was considered significant.

Ethics

The data were collected in accordance with the Resistance Register Regulations, and the study was approved by the Data Protection Officer at Haukeland University Hospital (ID 1075).

Results

We included a total of 589 urinary isolates from children. These accounted for 4.5 % of all isolates reported to the NORM register in 2013–17. A comparison to the background population showed approximately three times as many isolates from infants as from older children, and compared with adults, we found more *E. coli* and less *Klebsiella spp.* in children (Table 1). We found the following distribution of bacterial species among children: *E. coli* 85.2 % (95 % CI 84.0–86.3), *Enterococcus spp.* 8.3 % (7.4–9.3), *Proteus spp.* 3.1 % (2.6–3.7), *Klebsiella spp.* 2.8 % (2.3–3.4) and *Enterobacter spp.* 0.6 % (95 % CI 0.3–0.9). Figure 1 shows the distribution by æ.
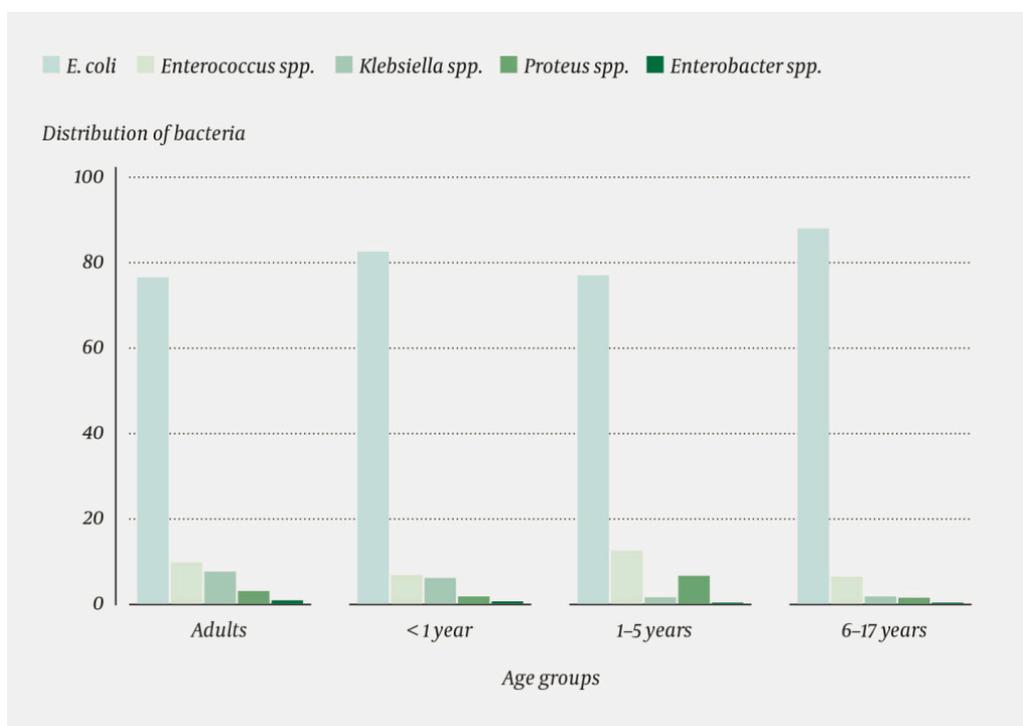
Figure 1 Estimated distribution of different microbes in urine based on periodic collection from the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM) in the period 2013–17. Spp. = Species (several unspecified species within a genus).

Table 2 shows resistance rates in isolates from children compared with isolates from adults. Among the 16 *E. coli* urinary isolates from children that were resistant to mecillinam, 12 (75.0 %) were also resistant to amoxicillin-clavulanic acid. Of the 22 *Proteus spp.* collected from children, all were sensitive to gentamicin and amoxicillin-clavulanic acid, while one isolate was resistant to mecillinam. Of four *Enterobacter spp.* collected from children, all were sensitive to gentamicin, cefotaxime and trimethoprim-sulfamethoxazole, while three (75.0 %) were resistant to amoxicillin-clavulanic acid.

Table 2

Resistance rates in urinary isolates from children up to and including 17 years of age compared with adults, based on data from the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM) in the period 2013–17.

Bacteria	Age 0–17 years		Age ≥ 18 years		Difference, %
	No.	Per cent (95 % CI)	No.	Per cent (95 % CI)	
Escherichia coli	403	–	6 105	–	–
Ampicillin	142	35.2 (30.6–40.1)	2 139	35.0 (33.8–36.2)	0.2
Mecillinam	16	4.0 (2.3–6.4)	351	5.7 (5.2–6.4)	1.7
Amoxicillin-clavulanic acid	29	7.2 (4.9–10.2)	441	7.2 (6.6–7.9)	0.0

Bacteria	Age 0–17 years		Age ≥ 18 years		Difference, %
	No.	Per cent (95 % CI)	No.	Per cent (95 % CI)	
Meropenem	0	0.0 (0.0–0.9)	0	0.0 (0.0–0.1)	0.0
Gentamicin	11	2.7 (1.4–4.8)	241	3.9 (3.5–4.5)	1.2
Ciprofloxacin	23	5.7 (3.7–8.4)	533	8.7 (8.0–9.5)	3.0[1]
Nitrofurantoin	2	0.5 (0.1–1.8)	81	1.3 (1.1–1.6)	0.8
Trimethoprim	109	27.0 (22.8–31.7)	1 396	22.9 (21.8–23.9)	4.1[1]
Trimethoprim-sulfamethoxazole	97	24.1 (20.0–28.5)	1 264	20.7 (19.7–21.7)	3.4
Extended spectrum beta-lactamases (positive = resistant)[2]	8	2.0 (0.9–3.9)	190	3.1 (2.7–3.6)	1.1
Cephalexin (N = 2 064)[3]	88	4.3 (3.4–5.2)	–	–	–
Klebsiella spp.	101	–	4 751	–	–
Mecillinam	5	5.0 (1.6–11.2)	479	10.1 (9.2–11.0)	5.1
Amoxicillin-clavulanic acid	12	11.9 (6.3–19.8)	344	7.2 (6.5–8.0)	4.7
Meropenem	0	0.0 (0.0–3.6)	2	0.0 (0.0–0.2)	0.0
Gentamicin	2	2.0 (0.2–7.0)	89	1.9 (1.5–2.3)	0.1
Ciprofloxacin	2	2.0 (0.2–7.0)	256	5.4 (4.8–6.1)	3.4
Trimethoprim-sulfamethoxazole	14	13.9 (7.8–22.2)	592	12.5 (11.5–13.4)	1.4
Extended spectrum beta-lactamases (positive = resistant)	4	4.0 (1.1–9.8)	142	3.0 (2.5–3.5)	1.0
Enterococcus faecalis	59	–	1 117	–	–
Ampicillin	0	0.0 (0.0–6.1)	0	0.0 (0.0–0.3)	0.0
Gentamicin (high-level resistance)	5	8.5 (2.8–18.7)	160	14.3 (12.3–16.5)	5.8
Vancomycin (screening)	0	0.0 (0.0–6.1)	0	0.0 (0.0–0.3)	0.0

[1]P-value < 0.05. For ciprofloxacin: 0.03. For trimethoprim: 0.02. Chi-squared test was used.

[2]Bacteria that produce extended spectrum beta-lactamases will generally also be resistant to third-generation cephalosporins such as cefotaxime.

[3]Based on 2064 urinary isolates from children up to and including 15-year-olds at the University Hospital of North Norway and Haukeland University Hospital in the period 2015–19.

Discussion

We have described national epidemiology and resistance rates in paediatric UTIs in Norway and used corresponding data from adults as a reference. *E. coli* was the predominant microbe in urine samples from children, with low resistance rates (< 10 %) for nitrofurantoin, mecillinam, cephalexin and amoxicillin-clavulanic acid.

The higher proportion of urinary isolates from infants compared to older children reflects the higher incidence of upper UTIs in this age group [1]. The predominance of *E. coli* in urinary isolates from children is well known [1, 3], but a high incidence of other bacteria is also reported internationally [16]. The higher proportion of *Enterococcus spp.* and *Proteus spp.* among preschool children in our study has also been observed in the United States [8].

Use of ciprofloxacin in children in Norway is very low [17, 18], but overuse among adults is viewed as problematic [19]. Lower ciprofloxacin resistance rates in *E. coli* in children compared to adults have also been observed internationally [11–13] and are likely to be linked to the lower usage in children [9].

We found greater resistance of *E. coli* to both trimethoprim and trimethoprim-sulfamethoxazole in children compared to adults, which also corresponds with the findings in a US study [13]. In the Norwegian Directorate of Health's guidelines for antibiotic use, trimethoprim and trimethoprim-sulfamethoxazole are among the empirical first choices for children with lower and upper UTIs respectively [10]. Consumer statistics from the Norwegian Prescription Database show that trimethoprim and trimethoprim-sulfamethoxazole have been frequently used among children ≤ 5 years in recent years [17]. We can assume that a significant proportion of the prescriptions were for treatment of a UTI. We can also assume that a significant proportion were prescribed empirically on the basis of the guidelines. In general, however, empirical antibiotics are not recommended for the treatment of UTIs if the *E. coli* resistance rate exceeds 20 % [6].

Our data support current recommendations that pivmecillinam and amoxicillin-clavulanic acid should be among the first choices for empirical treatment of upper UTIs in children [2, 10]. We found lower resistance rates among both *E. coli* and *Klebsiella spp.* to pivmecillinam than to amoxicillin-clavulanic acid. Furthermore, *E. faecalis* is sensitive to amoxicillin-clavulanic acid, and has inherent resistance to pivmecillinam. Despite the lack of good

clinical evidence for the use of pivmecillinam in upper UTIs, it is our view that the available literature, low resistance rates, favourable ecological profile and good clinical experience provide an adequate foundation for recommending this in Norway (20–22). Pivmecillinam is not available as an oral solution. The tablets can be crushed and mixed with food such as jam etc., but crushed tablets have an unpleasant taste. Permission was granted to market amoxicillin-clavulanic acid as an oral solution in Norway in 2019, and this is well established as a treatment for upper UTIs in children (23). However, there are concerns about high resistance rates in several countries (6, 7), and increasing use could also lead to a further development of resistance in Norway (24).

At Haukeland University Hospital and the University Hospital of North Norway, we found low cephalexin resistance rates in *E. coli* urinary isolates from children. These are not national data, but they nevertheless provide a good indication of the likely level of resistance nationally. Cephalexin is available as an oral solution and is recommended in other high-income countries as the first choice for upper UTIs in children (25, 26). A large observational study showed good clinical efficacy in UTIs in children (27). However, consideration should also be given to the possible selection of extended spectrum beta-lactamases in cases of excessive use (28). Overall, it is our view that cephalexin should be considered on an equal footing with amoxicillin-clavulanic acid in the empirical guidelines for upper UTIs, also to avoid excessive use of amoxicillin-clavulanic acid.

Nitrofurantoin is not for use in upper UTIs due to poor tissue penetration, but is a good first choice for lower UTIs. In 2009, a Norwegian literature review called for approval of nitrofurantoin in drop form (22), but it is still only available as an unpleasant-tasting water-soluble tablet.

Intravenous gentamicin and ampicillin are recommended for clinically weak patients, and there should be a liberal threshold for their use in children younger than 3–6 months (2). The gentamicin resistance rate was < 3 % for all bacteria included except enterococci. This confirms that gentamicin and ampicillin represent a potent empirical regimen for Norwegian children.

One of the strengths of this study is that using national data from a reliable register gave us a basis for assessing the level of resistance in children in relation to the current guidelines for choosing antibiotics in the treatment of UTIs in children in Norway.

The lack of clinical data is a weakness of the study. Randomised controlled clinical trials investigating the efficacy of relevant peroral antibiotics for the treatment of upper UTIs would be useful. Different data registration periods meant that we had to estimate the distribution of the microbes, but we consider this to be sufficiently precise for our purposes. Some UTIs are likely to have been treated without a urine culture sample. Our data are therefore probably not representative of all clinical UTIs during the registration periods.

Some of the urine samples in the NORM register are likely to be collection bag samples. This increases the risk of contamination, but the register's strict inclusion criteria mean that the isolates in our material are most likely

uropathogenic. Resistance data for cephalexin are only available from two hospitals, but data on cephalexin and *E. coli* in urine samples will be included in future NORM reporting.

Conclusion

Our description of resistance data from urinary isolates from children in Norway strengthens the knowledge base for recommendations for empirical treatment of UTIs among this group. In the oral treatment of upper UTIs, pivmecillinam and amoxicillin-clavulanic acid should still be among the first choices, but consideration should also be given to whether cephalexin should be included as an equivalent first choice. Pivmecillinam and nitrofurantoin should be the first choice for lower UTIs. Trimethoprim-sulfamethoxazole and trimethoprim should preferably only be used following resistance determination.

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