Tidsskriftet Tidsskrift for Den norske legeforening

Gentamicin serum concentration measurement in children

ORIGINAL ARTICLE

KAROLINA TERESA MAULEN GRODÅS

Faculty of Medicine and Health Sciences
Norwegian University of Science and Technology (NTNU)
Author contribution: data collection from electronic medical records, data analysis, preparation of the first draft of the manuscript and approval of the submitted version.
Karolina Teresa Maulen Grodås, medical student.
The author has completed the ICMJE form and declares no conflicts of interest.

HENRIK DØLLNER

Children's Clinic
St. Olav's Hospital, Trondheim University Hospital
and
Department of Clinical and Molecular Medicine
Faculty of Medicine and Health Sciences
Norwegian University of Science and Technology (NTNU)
Author contribution: study design, REC application, data analysis and interpretation, revision and finalisation of the manuscript and approval of the submitted version.
Henrik Døllner, senior consultant and specialist in paediatrics, and professor.
The author has completed the ICMJE form and declares no conflicts of interest.

CHRISTIAN MAGNUS THAULOW

Department of Clinical Science
University of Bergen
and
Children's Clinic

Haukeland University Hospital
Author contribution: collection and interpretation of data, revision and finalisation of the manuscript, and approval of the submitted version.
Christian Magnus Thaulow, specialist in paediatrics and senior consultant. He conducts research into antibiotic use in children.
The author has completed the ICMJE form and declares no conflicts of interest.

PER KRISTIAN KNUDSEN

Department of Paediatric and Adolescent Medicine
Oslo University Hospital, Ullevål
Author contribution: collection of gentamicin data, data interpretation, revision and finalisation of the manuscript, and approval of the submitted version.
Per Kristian Knudsen, PhD, senior consultant and specialist in paediatrics. He conducts research into paediatric infections.
The author has completed the ICMJE form and declares no conflicts of interest.

ANDERS TØNNESSEN

Faculty of Health Sciences
UiT The Arctic University of Norway
Author contribution: data collection from electronic medical records, data analysis, revision and finalisation of the manuscript, and approval of the submitted version.
Anders Tønnessen, medical student.
The author has completed the ICMJE form and declares no conflicts of interest.

MARI SKEIBROK

Faculty of Medicine and Health Sciences
Norwegian University of Science and Technology (NTNU)
Author contribution: data collection from electronic medical records, data analysis, revision and finalisation of the manuscript, and approval of the submitted version.
Mari Skeibrok, medical student.
The author has completed the ICMJE form and declares no conflicts of interest.

CLAUS KLINGENBERG

claus.klingenberg@unn.no
Department of Paediatrics University Hospital of North Norway
and
Department of Clinical Medicine

Faculty of Health Sciences
UiT The Arctic University of Norway
Author contribution: study design, data analysis and interpretation, revision and finalisation of the manuscript, and approval of the submitted version.
Claus Klingenberg, specialist in paediatrics, senior consultant/head of section, and professor.
The author has completed the ICMJE form and declares no conflicts of interest.

BACKGROUND
Gentamicin is often used to treat serious paediatric infections. It has been standard practice in Norway to measure the serum concentration of gentamicin immediately prior to the second or third dose (pre-dose [trough] concentration) to assess the risk of toxicity. The clinical significance of such measurements in children has not previously been evaluated in Norway.

MATERIAL AND METHOD
This is a retrospective study of routine pre-dose samples obtained for the measurement of serum gentamicin in paediatric patients aged 1 month to 17 years at four hospitals in Norway. Clinical data were extracted from electronic medical records from two of the hospitals. All children received treatment with intravenous gentamicin at a dose of 7 mg/kg once daily in accordance with Norwegian guidelines.

RESULTS
The most common indications for treatment were febrile urinary tract infection, febrile neutropenia, and suspected or confirmed sepsis. The median (interquartile range) duration of treatment in 353 episodes at two of the hospitals was 4 (3–5) days. Serum gentamicin pre-dose samples were analysed for 1,288 treatment episodes across four hospitals. In 1,223 episodes (95 %), the pre-dose sample showed a serum gentamicin concentration of less than 0.6 mg/L. In 7 episodes (0.5 %), the pre-dose sample showed an elevated gentamicin concentration, defined as greater than 1.0 mg/L.

INTERPRETATION
An in most cases mildly elevated serum gentamicin concentration was found in the pre-dose sample in 7 of 1,288 treatment episodes. Routine measurement of serum gentamicin via a pre-dose sample should in future be reserved for children receiving long-term gentamicin treatment, those with impaired kidney function, or those who are also receiving nephro- or ototoxic drugs.

Main findings

Pre-dose (trough) samples showed an elevated serum gentamicin concentration of more than 1.0 mg/L in 7 of 1,288 (0.5 %) treatment episodes.

In 95 % of treatment episodes, the serum gentamicin concentration in the pre-dose (trough) sample was less than 0.6 mg/L.

The majority of children in the study were treated with gentamicin for five days or less.

In Norway, gentamicin is the most common aminoglycoside used for the treatment of serious bacterial infections in children (1). Aminoglycosides have a concentration-dependent bactericidal effect, particularly on Gram-negative aerobic bacteria (2, 3), but also on staphylococci (4, 5). Gentamicin in combination with a beta-lactam antibiotic is recommended for empirical treatment in cases of sepsis, febrile neutropenia and pyelonephritis (6, 7).

Aminoglycosides are eliminated via the kidneys. They have little effect on anaerobic intestinal flora and are ecologically beneficial antibiotics that do not promote the development of resistance (5). Resistance to aminoglycosides is not currently widespread in Norway, except among enterococci (8, 9). However, there are concerns over nephrotoxicity and ototoxicity, as aminoglycosides accumulate in the renal tubules as well as in the inner ear (10, 11). Caution should therefore be exercised regarding the use of aminoglycosides in children with significant renal impairment or known hearing loss, and in children receiving concurrent treatment with other nephro- or ototoxic drugs (12). In children, once-daily dosing of aminoglycosides is thought to be more efficacious and less nephrotoxic than multiple daily doses (13, 14). Aminoglycosides are considered safe and effective antibiotics provided they are not used long-term, administered repeatedly, or given to children with clearly impaired renal function (15, 16). In Norway, it is recommended that the serum concentration of gentamicin (s-gentamicin) is measured in paediatric patients immediately prior to the second or third dose, a so-called pre-dose (or 'trough') sample, in view of the potential risk of accumulation and toxicity (17). Such measurements entail additional blood draws and pain for the children concerned, but their clinical significance has never been evaluated in Norway. In this study, we have evaluated the s-gentamicin pre-dose sample in children treated for various infections in paediatric and adolescent medicine departments at four Norwegian hospitals.

Material and method

Study design, participants and approvals

This is a retrospective study in paediatric patients aged 1 month to 17 years admitted to St. Olav's Hospital, Trondheim University Hospital, between 2014 and 2018; to the University Hospital of North Norway between 2014 and 2019; or to Oslo University Hospital, Ullevål, between 2014 and 2019, as well as children aged 1 month to 15 years admitted to Haukeland University Hospital between 2014 and 2019. We included children who were treated with intravenous gentamicin at the recommended dose of 7 mg/kg once daily, and in whom the concentration of s-gentamicin was measured in one or more pre-dose samples. Participants were identified by obtaining lists of all s-gentamicin measurements for the relevant age groups from the medical biochemistry departments of St. Olav's Hospital, the University Hospital of North Norway and Haukeland University Hospital, and from the Section for Clinical Pharmacology at Oslo University Hospital, Ullevål.

As part of their Master's degree in medicine, three of the authors (KTMG, AT and MS) extracted clinical and microbiological data from electronic medical records at St. Olav's Hospital and the University Hospital of North Norway. De-identified data were stored in secure directories. Data collection was approved by the Regional Committee for Medical and Health Research Ethics, Central Norway (REK Central, no. 125804). All participants aged 16 or over, plus the parents/guardians of all subjects identified at St. Olav's Hospital and the University Hospital of North Norway, received written information about the study and were given the opportunity to opt out. We wished to validate our findings from St. Olav's Hospital and the University Hospital of North Norway in material from two further Norwegian hospitals. We therefore obtained anonymised data from Haukeland University Hospital and Oslo University Hospital, Ullevål, regarding the first s-gentamicin pre-dose sample – plus creatinine measured at the same time – in patients whose pre-dose samples showed elevated s-gentamicin. The data were obtained from the paediatric wards of both hospitals and from the paediatric intensive care unit at Ullevål Hospital. No data from electronic medical records were obtained from Haukeland University Hospital or Ullevål Hospital. Any infants younger than 1 month or who were treated in neonatal wards at the four hospitals were excluded as the recommended doses and dosing intervals for gentamicin in newborns differ from those in older children.

Registered variables

From St. Olav's Hospital and the University Hospital of North Norway we recorded age, sex, indication for gentamicin treatment, creatinine levels, highest C-reactive protein (CRP) level measured during the treatment episode, blood culture results, number of doses of gentamicin per treatment episode, and s-gentamicin concentration measured immediately prior to the second or third dose (pre-dose sample). The highest s-creatinine level measured in the

period from seven days before to seven days after the treatment episode was compared with age-specific reference values (18). We had not sought ethical approval to obtain clinical data from Haukeland University Hospital or Oslo University Hospital, Ullevål, but assessed s-creatinine levels, where available, in children with elevated pre-dose s-gentamicin levels.

Analysis of s-gentamicin concentration

Since 2016, St. Olav's Hospital has used the Siemens ADVIA Chemistry XPT System to analyse s-gentamicin concentrations, having previously used the Roche COBAS Integra 400 plus. The University Hospital of North Norway and Oslo University Hospital, Ullevål, have both been using the CEDIA Gentamicin II Assay since 2016, and prior to that the Roche GENT2. Haukeland University Hospital used the CEDIA Gentamicin II Assay until August 2014, and then switched to the Roche COBAS Integra 400 plus, before switching back to the CEDIA assay in June 2016. At the Department of Laboratory Medicine at the University Hospital of North Norway, the analysis of s-gentamicin costs NOK 176 per test, although the total cost is higher due to personnel costs and the use of disposable equipment for sample collection. The lowest s-gentamicin concentrations reported by the laboratories were <0.3 mg/L, <0.5 mg/L or <0.6 mg/L, depending on the assay and manufacturer. In this article, we have chosen to present all values <0.6 mg/L in a single category.

Statistical analysis

All data were entered into the programme IBM SPSS Statistics Version 26. We have presented descriptive statistics in the form of proportions and percentages with median and interquartile range or mean and standard deviation.

Results

A total of 292 children – 129 girls and 163 boys – were included in the study from St. Olav's Hospital and the University Hospital of North Norway. Four sets of parents at St. Olav's Hospital declined to participate, but all agreed to take part at the University Hospital of North Norway. Some children were treated more than once, such that the total number of treatment episodes evaluated in the two hospitals was 353 (Table 1). The indications for gentamicin treatment comprised urinary tract infections, febrile neutropenia, sepsis and other suspected or confirmed serious infections. Positive blood cultures were found in 26 out of 353 (7.4 %) treatment episodes; 9 of these 26 were in children with cancer. The median duration of treatment across all episodes was 4 days (interquartile range 3–5) (Figure 1). A total of 556 children with s-gentamicin pre-dose samples were identified at Haukeland University Hospital. Two children, both of whom had normal creatinine levels but whose pre-dose samples showed s-gentamicin levels of 5.0 mg/L and 32.2 mg/L, respectively, were excluded. This was because these values were considered unrealistic 24 hours after a dose of 7 mg/kg and were attributed to measurement error. A further 381 children with s-gentamicin pre-dose samples were identified from Oslo University Hospital, Ullevål.

Table 1

Age, type of infection, and renal function for 292 children who received gentamicin in 353 treatment episodes at St. Olav's Hospital and the University Hospital of North Norway. Number (%) unless otherwise stated. IQR = interquartile range.

Variable	Result
Age	
1–11 months	87 (24.6)
1–9 years	204 (57.8)
10–17 years	62 (17.6)
Diagnosis/indication and CRP[1]	
Urinary tract infection	137 (38.8)
CRP (mg/L), median (IQR)	180 (85–260)
Febrile neutropenia[2]	50 (14.2)
CRP (mg/L), median (IQR)	60 (29–107)
Sepsis	63 (17.8)
CRP (mg/L), median (IQR)	117 (80–225)
Other conditions, infections or suspected infections	103 (29.2)
CRP (mg/L), median (IQR)	109 (59–218)
Elevated peak s-creatinine level	
No	286 (81.0)
Yes	28 (7.9)
S-creatinine not measured	39 (11.0)

[1]Highest CRP level measured during treatment period.

[2]Children who were treated for malignant disease and who had low white blood cell counts in association with infection.

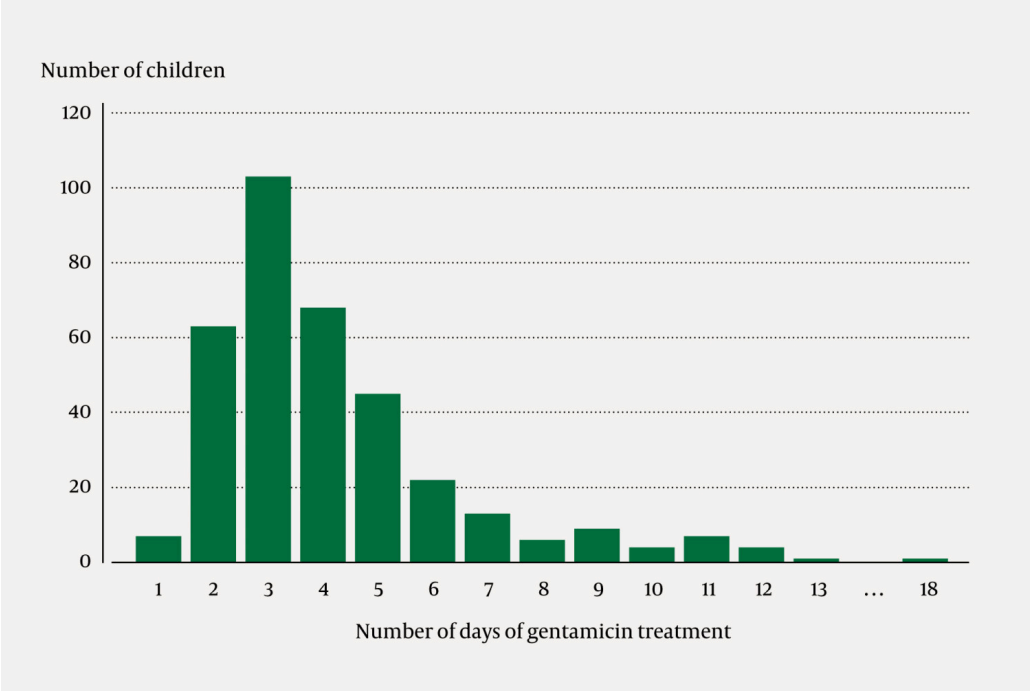

Figure 1 Treatment duration for 353 episodes of gentamicin treatment at St. Olav's Hospital and the University Hospital of North Norway in which an s-gentamicin pre-dose sample was also obtained. Children aged 1 month to 17 years.

The distribution of s-gentamicin concentrations is shown for each of the four hospitals in Table 2. There were no pre-dose samples with values above 1.0 mg/L among 353 treatment episodes at St. Olav's Hospital and the University Hospital of North Norway. The pre-dose sample had a value above 1.0 mg/L in 4 out of 554 (0.7 %) treatment episodes at Haukeland University Hospital, and in 3 out of 381 (0.8 %) treatment episodes at Oslo University Hospital, Ullevål.

Table 2

S-gentamicin concentration (pre-dose sample) in 1,288 treatment episodes in children (aged ≥ 1 month) treated at four university hospitals in the period 2014–2019. Number (%).

S-gentamicin, Pre-dose sample	St. Olav's Hospital (*n* = 222)	University Hospital of North Norway (*n* = 131)	Haukeland University Hospital (*n* = 554)	Oslo University Hospital, Ullevål (*n* = 381)	Total (*n* = 1288)
< 0.6 mg/L	218 (98.2)	130 (99.2)	517 (93.3)	358 (94.0)	1 223 (95.0)
0.6–0.7 mg/L	3 (1.4)	1 (0.8)	23 (4.2)	16 (3.9)	43 (3.3)
0.8–1.0 mg/L	1 (0.4)	0 (0)	10 (1.8)	4 (1.3)	15 (1.2)
> 1.0 mg/L	0 (0)	0 (0)	41 (0.7)	32 (0.8)	7 (0.5)

[1]1.4, 1.5, 2.6 and 2.9 mg/L, respectively. Three of the four children had creatinine levels within the reference range for their age. During treatment, one child with an s-gentamicin level of 1.5 mg/L was found to have a highly elevated creatinine level (206 µmol/L). Treatment was discontinued in this child.

[2]1.1, 1.2 and 1.3 mg/L. Two of the three children had creatinine levels within the reference range for their age. One child with an s-gentamicin level of 1.1 mg/L had a slightly elevated creatinine level, but this was decreasing the day after the gentamicin serum concentration measurement.

Discussion

We studied s-gentamicin pre-dose samples in all children who received treatment with gentamicin following admission to four paediatric departments covering the paediatric population in large parts of Northern Norway, Central Norway, Western Norway and Oslo. Among 1,288 treatment episodes, we found a pre-dose s-gentamicin concentration of more than 1.0 mg/L in seven children (0.5 %). In five of the seven children with elevated values, the pre-dose concentration was 1.1–1.5 mg/L. Norwegian paediatric guidelines and international publications recommend extending the dose interval in children with a pre-dose s-gentamicin concentration that is above 1.0 mg/L (6, 12, 17). A small percentage of the children had creatinine levels above the reference range for their age, but none of the children at St. Olav's Hospital or the University Hospital of North Norway developed gentamicin-induced renal failure. Of the patients with an elevated s-gentamicin level in the pre-dose sample, one had a significantly elevated creatinine level, and another had a slightly elevated creatinine level that decreased during treatment. Creatinine levels after treatment initiation were normal in the other children with elevated pre-dose s-gentamicin levels. The majority of children at St. Olav's Hospital and the University Hospital of North Norway were treated with gentamicin for five days or less.

Norwegian guidelines state that for adults with a presumed normal volume of distribution and normal renal function, a pre-dose sample is not indicated for gentamicin treatment of less than three days' duration if no other nephrotoxic drugs are used (19). Children usually have normal renal function that has not yet been affected by degenerative ageing processes. The evidence base for routine measurement of s-gentamicin in children is limited. Nevertheless, standard practice in Norway has been to take a pre-dose sample for the measurement of s-gentamicin immediately before either the second or third dose.

Gentamicin is considered to have a low risk of toxicity in children with no underlying chronic health conditions. However, few studies have examined s-gentamicin concentrations and toxicity in children treated with a once-daily dose of 7 mg/kg. A prospective cohort study from the United States included 79 children aged 1 month to 16 years who underwent a total of 106 episodes of gentamicin treatment (15). Two children (1.9 %) were subsequently diagnosed with hearing impairment in the high-frequency range, and one child (0.9 %) had transient nephrotoxicity. Both children with hearing impairment had also received cisplatin, which is associated with hearing loss, and the child with transient renal impairment had been treated with cyclophosphamide. All three children with reported toxicity had normal s-gentamicin levels according to the

Hartford nomogram (20). A study from England included 59 children aged 6 months to 16 years who underwent 113 episodes of gentamicin treatment (21). None of the children had abnormal s-gentamicin levels according to the Hartford nomogram, and thus no dose adjustment was necessary in any of the treatment episodes. No significant nephro- or ototoxicity was observed, and the authors concluded that s-gentamicin measurement is unnecessary for the short-term treatment (less than five days) of children with normal s-creatinine levels who are not receiving other nephrotoxic medications (21). A study from the United States examined s-gentamicin concentrations in 54 children with cancer aged 2–12 years, who were treated for a total of 73 febrile episodes. All received gentamicin 7 mg/kg, which resulted in a mean peak s-gentamicin concentration of 17 mg/L at 30 minutes post-infusion, and a mean s-gentamicin concentration of 0.9 mg/L at 12 hours post-infusion (22). The authors concluded that 7 mg/kg gives rise to an adequate peak concentration, consistent with international guidelines for gentamicin dosage in children (23).

A systematic review from 2021 reported that children with impaired renal function, children with cystic fibrosis who often receive repeated courses of aminoglycosides, and children with cancer who are treated with other ototoxic drugs (especially platinum derivatives) are at risk of developing aminoglycoside-induced hearing loss (16). An extended treatment duration, usually defined as more than a week, and chronic kidney disease are also significant risk factors associated with aminoglycoside-induced nephrotoxicity (10, 24). However, the risk of gentamicin toxicity in other children is very low. A study in adults showed that an initial dose of gentamicin in patients with severe sepsis posed no threat to renal function (25). We have previously shown in a large cohort of neonates treated with gentamicin at a dose of 6 mg/kg that there was no association between s-gentamicin concentration or cumulative gentamicin dose and risk of hearing loss or subclinical kidney damage at school age (26, 27). In our current study, gentamicin was usually administered for three to five days, often with a switch to oral dosing of other antibiotics, particularly in the case of urinary tract infections. We therefore consider the risk of toxicity to be very low.

This study has both strengths and weaknesses. The study population consists of all children treated with gentamicin over a five-year period following admission to four primary hospital departments covering the paediatric population in large areas of Northern Norway, Central Norway, Western Norway and Oslo. Gentamicin treatment and s-gentamicin measurements were performed in accordance with Norwegian paediatric guidelines (17), and the sample is considered representative of Norwegian children requiring treatment with gentamicin. A weakness of the study is that data were collected retrospectively. We cannot rule out the possibility of dosing errors, or of some pre-dose samples not having been taken 24 hours after the first dose and just before the second or third dose. We also lack clinical data from Haukeland University Hospital and Oslo University Hospital, Ullevål, including for the seven children who had elevated gentamicin levels in the pre-dose sample. It is important to be aware that gentamicin is distributed into body water. Overweight is common in Norwegian children (28), and in individuals with significant obesity, dosing by weight may result in too high a dose of gentamicin being administered.

However, body weight was not recorded in the present study. A strength of the study is that we have a complete set of gentamicin pre-dose samples from almost 1,300 treatment episodes. No structured follow-up was performed with respect to hearing, but the short treatment durations and low s-gentamicin concentrations indicate that the cumulative gentamicin exposure was low in our cohort. For the majority of children in the study, s-gentamicin levels were below a detection limit of 0.3–0.6 mg/L. While we do not know the exact s-gentamicin levels for these children, other studies have reported that s-gentamicin concentrations are typically below 0.5–1 mg/L after 10–15 hours (15, 22). Gentamicin has a post-antibiotic effect (15, 21, 29), and we found no evidence of therapeutic failure at the two hospitals for which clinical data were available.

Conclusion

In our study of almost 1,300 episodes of gentamicin treatment at the recommended dose of 7 mg/kg once daily, we found elevated s-gentamicin levels in the pre-dose samples of seven children (0.5 %). The duration of gentamicin treatment was five days or less in more than 80 % of patients at the two hospitals in which this was examined. Based on our findings, and those of others (21), we recommend a more restrained use of s-gentamicin monitoring in children (Box 1). This would save many children from unnecessary blood tests and avoid the costs associated with blood sampling and laboratory analyses, without compromising safety.

Box 1 Proposed recommendations for measuring serum gentamicin concentration in children treated with intravenous gentamicin at a dose of 7 mg/kg once daily, based on earlier literature (15, 21–23) and the current dataset.

S-creatinine should be measured when other blood tests are performed, or within 48 hours after initiation of gentamicin treatment.

• In children with normal s-creatinine levels, s-gentamicin should be measured before the 5th dose.
If s-gentamicin is > 1.0 mg/L, consider discontinuing gentamicin or extending the dose interval by 12 hours.

• In children with elevated s-creatinine, consider a) discontinuing gentamicin or b) extending the dose interval by 12 hours and measuring s-gentamicin before the next gentamicin dose.

In children receiving treatment with other nephro- or ototoxic drugs, or with significantly impaired renal function or high creatinine levels, the indication for gentamicin treatment and the dose interval must be evaluated on an individual basis.

• If gentamicin is administered, the pre-dose sample may be taken prior to the 2nd or 3rd treatment dose.

Assessment of creatinine levels in relation to age should be based on the age-dependent reference range published in the National User Manual in Medical Biochemistry (30).

The authors are grateful to the following individuals for supplying the data on s-gentamicin concentrations used in this study: Gustav Mikkelsen, senior consultant and associate professor, Department of Medical Biochemistry, St. Olav's Hospital; Jorunn Norberg, consultant, Administrative Centre for Laboratory Systems, University Hospital of North Norway; Tom Atle Jermstad, specialist bioengineer, Department of Medical Biochemistry, Haukeland University Hospital; Ingebjørg Gustavsen, senior consultant and head of section, Section for Clinical Pharmacology, Department of Pharmacology, Oslo University Hospital, Ullevål.

The article has been peer-reviewed.

REFERENCES

1. Helsebiblioteket. 3.1 Valg av antibiotika – generelle betraktninger. https://www.helsebiblioteket.no/innhold/retningslinjer/pediatri/akuttveileder-i-pediatri/3.infeksjoner/valg-av-antibiotika-generelle-betraktninger Accessed 10.6.2022.

2. Begg EJ, Peddie BA, Chambers ST et al. Comparison of gentamicin dosing regimens using an in-vitro model. J Antimicrob Chemother 1992; 29: 427–33. [PubMed][CrossRef]

3. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 1987; 155: 93–9. [PubMed][CrossRef]

4. Legemiddelhåndboka. L1.2.9 Aminoglykosider 2016. https://www.legemiddelhandboka.no/L1.2.9/Aminoglykosider Accessed 10.6.2022.

5. Krause KM, Serio AW, Kane TR et al. Aminoglycosides: An Overview. Cold Spring Harb Perspect Med 2016; 6: a027029. [PubMed][CrossRef]

6. Germovsek E, Barker CI, Sharland M. What do I need to know about aminoglycoside antibiotics? Arch Dis Child Educ Pract Ed 2017; 102: 89–93. [PubMed][CrossRef]

7. Hanberger H, Edlund C, Furebring M et al. Rational use of aminoglycosides–review and recommendations by the Swedish Reference Group for Antibiotics (SRGA). Scand J Infect Dis 2013; 45: 161–75. [PubMed][CrossRef]

8. Simonsen GS, Blix HS, Grave K et al. NORM/NORM-VET 2020. Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway.

https://www.fhi.no/publ/2021/norm-og-norm-vetusage-of-antimicrobial--agents-and-occurrence-of-ant/ Accessed 10.6.2022.

9. Thaulow CM, Lindemann PC, Klingenberg C et al. Epidemiology and Antimicrobial Susceptibility of Invasive Bacterial Infections in Children-A Population-Based Study From Norway. Pediatr Infect Dis J 2021; 40: 403–10. [PubMed][CrossRef]

10. McWilliam SJ, Antoine DJ, Smyth RL et al. Aminoglycoside-induced nephrotoxicity in children. Pediatr Nephrol 2017; 32: 2015–25. [PubMed][CrossRef]

11. Jiang M, Karasawa T, Steyger PS. Aminoglycoside-Induced Cochleotoxicity: A Review. Front Cell Neurosci 2017; 11: 308. [PubMed][CrossRef]

12. Wang H, Sherwin C, Gobburu JVS et al. Population Pharmacokinetic Modeling of Gentamicin in Pediatrics. J Clin Pharmacol 2019; 59: 1584–96. [PubMed][CrossRef]

13. Miron D. Once daily dosing of gentamicin in infants and children. Pediatr Infect Dis J 2001; 20: 1169–73. [PubMed][CrossRef]

14. Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV et al. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics 2004; 114: e111–8. [PubMed][CrossRef]

15. Best EJ, Gazarian M, Cohn R et al. Once-daily gentamicin in infants and children: a prospective cohort study evaluating safety and the role of therapeutic drug monitoring in minimizing toxicity. Pediatr Infect Dis J 2011; 30: 827–32. [PubMed][CrossRef]

16. Diepstraten FA, Hoetink AE, van Grotel M et al. Aminoglycoside- and glycopeptide-induced ototoxicity in children: a systematic review. JAC Antimicrob Resist 2021; 3: dlab184. [PubMed][CrossRef]

17. Helsebiblioteket. 3.2 Dosering og serumspeilmåling av aminoglykosider og vancomycin. https://www.helsebiblioteket.no/innhold/retningslinjer/pediatri/akuttveileder-i-pediatri/3.infeksjoner/3.2-dosering-og-serumspeilmaling-av-aminoglykosider-og-vankomycin Accessed 10.6.2022.

18. Helsebiblioteket. 1.6 Pediatriske referanseverdier. https://www.helsebiblioteket.no/innhold/retningslinjer/pediatri/generell-veileder-i-pediatri/1.prosedyrer-og-undersokelser/1.6-pediatriske-referanseverdier Accessed 10.6.2022.

19. Helsedirektoratet. 20. Dosering og konsentrasjonsbestemmelse av antibiotika. https://www.helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus/dosering-og-konsentrasjonsbestemmelse-av-antibiotika Accessed 10.6.2022.

20. Nicolau DP, Freeman CD, Belliveau PP et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995; 39: 650–5. [PubMed][CrossRef]

21. Tomlinson RJ, Ronghe M, Goodbourne C et al. Once daily ceftriaxone and gentamicin for the treatment of febrile neutropenia. Arch Dis Child 1999; 80: 125–31. [PubMed][CrossRef]

22. Shankar SM, Jew RK, Bickert BM et al. Pharmacokinetics of single daily dose gentamicin in children with cancer. J Pediatr Hematol Oncol 1999; 21: 284–8. [PubMed][CrossRef]

23. Kinderformularium. Gentamicine 2021 https://www.kinderformularium.nl/geneesmiddel/23/gentamicine Accessed 10.6.2022.

24. Menon S, Kirkendall ES, Nguyen H et al. Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months. J Pediatr 2014; 165: 522–7.e2. [PubMed][CrossRef]

25. Cobussen M, Haeseker MB, Savelkoul PHM et al. Re: 'The renal safety of a single dose of gentamicin in patients with sepsis in the emergency department' - Author's reply. Clin Microbiol Infect 2021; 27: 301–2. [PubMed][CrossRef]

26. Rypdal V, Jørandli S, Hemmingsen D et al. Exposure to an Extended-Interval, High-Dose Gentamicin Regimen in the Neonatal Period Is Not Associated With Long-Term Nephrotoxicity. Front Pediatr 2021; 9: 779827. [PubMed][CrossRef]

27. Hemmingsen D, Mikalsen C, Hansen AR et al. Hearing in Schoolchildren After Neonatal Exposure to a High-Dose Gentamicin Regimen. Pediatrics 2020; 145: e20192373. [PubMed][CrossRef]

28. Øvrebø B, Bergh IH, Stea TH et al. Overweight, obesity, and thinness among a nationally representative sample of Norwegian adolescents and changes from childhood: Associations with sex, region, and population density. PLoS One 2021; 16: e0255699. [PubMed][CrossRef]

29. Stubbings W, Bostock J, Ingham E et al. Mechanisms of the post-antibiotic effects induced by rifampicin and gentamicin in Escherichia coli. J Antimicrob Chemother 2006; 58: 444–8. [PubMed][CrossRef]

30. Nasjonal brukerhåndbok i Medisinsk Biokjemi. Kreatinin, P. https://www.brukerhandboken.no/index.php?action=showtopic&book=biokjemi&topic=3a8ea3b21c9df1acf399 Accessed 14.11.2022.

Publisert: 16 January 2023. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.22.0238
Received 21.3.2022, first revision submitted 10.6.2022, accepted 16.11.2022.