In addition to DDD and inpatient days, alternative parameters such as number of patient-admittances and number of used vials were included in the calculation.

Result Pediatric-specific pitfalls affecting the quantification and comparability were identified:

- Hospital guidelines concerning the multiple usage of dissolved and diluted antibiotics.
- Regional composition of the pediatric patient population in terms of pathology.
- Intramural allocations of wards sharing the drug deposit.

Conclusion Unexpected factors have severe impact on the reliability of annual antibiotic quantification and interpretation. Those factors need to be taken into account when comparing pediatric hospitals.

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P41 PRENATAL EXPOSURE TO ANTIBIOTICS AND DEVELOPMENT OF EPILEPSY IN CHILDREN

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Background Studies reported that prenatal exposure to antibiotics in general represents a risk factor for development of epilepsy and/or cerebral palsy in children. A pathophysiological relationship seemed improbable and required adjustment to possible confounders.

Methods In a retrospective cohort investigation, we enrolled children aged 3 to 18 years born between 1998 and 2012 at the single regional hospital, and their mothers, members of 'Clalit' (the largest Health Service Organization in the region). Computerized medications database was linked with hospital records of mothers and their children. The exposed group included all children whose mothers purchased one or more antibiotic medications during their pregnancy. Epilepsy was defined by Epilepsy diagnosis and/or by chronic dispensing of antiepileptic drugs. After applying inclusion and exclusion criteria for mothers and children, 88,899 children and their 74,416 mothers were selected for the study.

Results The group exposed prenatally to antibiotics comprised 36,622 (or 41.2%) children. Of them, 326 (0.9%) developed epilepsy compared to 370 (0.7%) in the unexposed group ($p=0.002$); Number Needed to Harm 500. Exposure during the first, second and third trimester was characterized by incidence of epilepsy in 0.8% ($p=0.928$), 0.9% ($p=0.270$) and 0.9% ($p=0.094$) of exposed children, respectively, compared to unexposed group. Based on Poisson regression analysis, epilepsy was associated with male sex, maternal smoking and delivery by cesarean section. The

possibility of confounding by indication was refuted by sensitivity analysis.

Conclusion We found an association of intrauterine exposure to antibiotics (particularly in late pregnancy) and development of epilepsy in children. Possible pathophysiological mechanisms are discussed. The effect of some undetermined confounder(s) cannot be ruled out.

Disclosure(s) Nothing to disclose

P42 EXTERNAL VALIDATION OF MODEL-BASED DOSING GUIDELINES FOR VANCOMYCIN, GENTAMICIN AND TOBRAMYCIN IN CRITICALLY ILL CHILDREN

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Background Pharmacokinetic models are frequently used to simulate dosing strategies for special populations, including critically ill children. The Dutch Pediatric Formulary (DPF) partially bases its guidelines on these models. However, prospective validation of updated dosing regimens is rare. We aimed to identify target attainment and safety of vancomycin, gentamicin and tobramycin after a dose update in the DPF for critically ill neonates and children.

Methods Retrospective cohort study in PICU and NICU patients receiving vancomycin, gentamicin or tobramycin between January 2015 and March 2017 in 2 university hospitals. Demographic clinical laboratory and TDM-data were collected. Target (steady state) trough concentrations for vancomycin, gentamicin and tobramycin used were 10–15, ≤ 1 and ≤ 1 mg/l, respectively. Target gentamicin peak concentrations used were 8–12 mg/l.

Results 486 patients were included in total (165 vancomycin, 97 gentamicin and 224 tobramycin). Trough concentrations of vancomycin, gentamicin and tobramycin were within the target range in 37.5%, 85.3% and 77.2% of patients, respectively. Target attainment of gentamicin peak concentrations in NICU patients was 31%. Non-target trough concentrations were most prevalent in term NICU patients (vancomycin 70%, gentamicin 26% and tobramycin 36.8%). Gentamicin peak concentrations were subtherapeutic in 91% and 45.5% for term and preterm NICU patients, respectively. Creatinine concentrations correlated positively with antibiotic concentrations (correlation coefficient range 0.46–0.54, $p \leq 0.01$ in all cohorts).

Conclusion Despite recent model-based dosing alterations, sub- and supratherapeutic concentrations of vancomycin, gentamicin and tobramycin are still frequent in critically ill children. Linear dose alterations did offer improvements in target attainment, but did not fully address all relevant covariates that contribute to the large interindividual variation in clearance and/or volume of distribution in these patients. Creatinine clearance was consistently correlated with concentrations of all 3 drugs, but future research is needed to identify whether including this parameter in dosing can improve target attainment and safety.

Disclosure(s) Nothing to disclose