ID: 133
TITLE: PREVENTION OF UNNECESSARY ANTIBIOTIC EXPOSURE IN TERM BABIES TREATED FOR SUSPECTED EARLY ONSET SEPSIS
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CONTENT:

Many babies treated for suspected early onset sepsis are well, but at risk of infection. A previous review of practice demonstrated that it took an average of 52 hours for blood culture reports to be available, but true positive blood cultures all signalled positive within 36 hrs of collection. Following this local guidance was introduced which aimed to prevent unnecessary exposure of antibiotics to babies treated for early onset sepsis. This recommended discontinuing antibiotics at 36 hours (prior to 2nd gentamicin dose) if the culture has not yet signalled positive (in the absence of the report) if babies were clinically well and had a static or falling CRP at 24 hours i.e. both ≤ 10.

We performed a retrospective audit of babies treated for suspected early onset sepsis from January 1st 2017 to December 31st 2017 from electronic records. Babies included were those with clinical indicators and/ or risk factors for sepsis, two CRPS ≤10, clinically well by 24 hours and blood cultures not signalling positive at 36 hours. Babies who were preterm or unwell at presentation or 24 hours were excluded. Of these, the number of babies who received a 2nd dose of gentamicin was documented. Positive blood cultures from all babies treated for suspected early onset sepsis were documented, and the time the culture was taken, first signalled positive and reported to the neonatal team, was recorded.

536 babies were treated for early onset sepsis; 277 (51.7%) fulfilled the inclusion criteria. Of the 277 babies, 33% received a 2nd dose of gentamicin. After excluding babies with any clinical indicators for sepsis, 24% received a 2nd dose of gentamicin. 14 (2.6%) had a positive blood culture, 6 (1.1%) of which were considered true positives. The average time from collection the culture first signalled positive was 16 hours 28 minutes (range 8 hours 7 mins – 30 hours 54 minutes) and the time taken by the microbiology team to communicate the results to the neonatal team was 21 hours 12 minutes (range 10 hrs 31 mins – 35 hours 22 minutes). All babies with a true positive culture had an elevated 2nd CRP (31 – 203).

The audit demonstrated that all positive blood cultures signalled positive within 36 hours, no babies had antibiotics unsafely discontinued and in 24-33%, the 2nd dose of gentamicin could have been safely avoided. This could facilitate early discharges, improve parent satisfaction, create capacity, reduce drug toxicity, nursing time and cost. A neonatal sepsis sticker has since been introduced, which prompts review of antibiotics at 36 hours.

COI: None declared
ID: 156
TITLE: INTRAVENOUS PARACETAMOL FOR PATENT DUCTUS ARTERIOSUS IN INDOMETHACIN-RESISTANT OR CONTRAINDICATED PRETERM INFANTS: A DOSE ESCALATION STUDY
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CONTENT:

Patent ductus arteriosus (PDA) is a significant cause of morbidity and mortality in preterm infants. Indomethacin is the standard treatment for hemodynamically significant patent ductus arteriosus (hsPDA) in Japan. However, this drug can be associated with potentially significant adverse effects, such as renal impairment and gastrointestinal complications. Paracetamol may be a promising alternative to indomethacin for the closure of PDA with possibly fewer adverse effects. Nonetheless, up to this point, there have been no reports of its use for hsPDA in Japan.

In this dose-escalation study, we assessed the safety and feasibility of intravenous paracetamol treatment in preterm infants with hsPDA, who were resistant to or contraindicated the use of indomethacin. The first 3 patients were given a low dose (7.5 mg/kg every 6 h for 3 days), and the next 15 patients were given a high dose (15 mg/kg every 6 h for 3 days).

A low dose intravenous paracetamol treatment was performed for 3 preterm infants, with a mean gestational age of 25.4 weeks and a mean birth weight of 880 g. Paracetamol was administered because of acute renal failure in 2 cases and because of the ineffectiveness of indomethacin in 1 case. Although PDAs were temporarily closed in 2 of 3 cases, surgical closure was eventually needed in all 3 cases. A high dose intravenous paracetamol treatment was performed for 15 preterm infants, with a mean gestational age of 27.1 weeks and a mean birth weight of 905 g. Paracetamol was administered because of acute renal failure in 9 cases and because of the ineffectiveness of indomethacin in 7 cases. PDAs were closed or narrowed in 14 cases, although surgical closure was eventually needed in 6 cases. The treatments were well tolerated without serious adverse effects.

This is the first study in Japan demonstrating that intravenous paracetamol treatment in preterm infants with hsPDA who are resistant to or contraindicated the use of indomethacin is both safe and feasible, and a larger and controlled clinical trial is warranted for this approach.

COI: None declared
ID: 231

**TITLE:** CHANGES IN PRACTICE SUCCESSFULLY REDUCE ANTIBIOTICS USE IN A NEONATAL INTENSIVE CARE UNIT

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**CONTENT:**

Antibiotic therapy is a life-saving intervention in Neonatal Intensive Care Unit (NICU). Its use, however, needs to be rational and evidence-based. Worldwide, it has been encouraged to reduce unnecessary exposure of newborn to antibiotics, so we can avoid antibiotic-resistant infections, ototoxic and nephrotoxic effects, augmented risk of enterocolitis. Early antibiotic administration causes deleterious changes in microbiome, leading to long-term effects, like increased incidence of asthma, celiac disease and higher body mass index (BMI). However, translate evidence into practice is not always easy and requires a carefully designed program that targets changes in professional behavior and clinical practice. We aimed to improve antibiotic use in our unit by implementing a protocol that considers solely clinical symptoms to start antibiotics and positive cultures to determine its continuation. The purpose of this study is to compare the outcomes of newborns in the period before and after the implementation of this new protocol.

Study approved by local ethics committee. Design: prospective historical cohort. Participants: newborns admitted in the NICU in years 2011 (before the protocol) and 2016 (after the protocol). Newborns discharged with < 48h, birth weight < 500g, deceased due to malformations with < 48h and transferred to another hospital were excluded. Data collected from charts were gestational age, birth weight, gender, type of birth, Apgar score; maternal risk factors for infection; use of central venous access and mechanical ventilation; time to start enteral nutrition and duration of parenteral nutrition; use of antibiotic in first 48 hours of life or after this period and if treatment was suspended (ruled-out sepsis) or sustained and if there were positive blood cultures; time for discharge and death.

171 newborns were evaluated in 2011 and 142 in 2016. There was no difference in main characteristics between groups, except for a higher average birth weight in the group after the protocol (2133g versus 2443g; p = 0.002). When stratified by groups of birth weight < 2500g and < 1500g, there were no difference between groups. In 2011, 72 newborns (42%) started antibiotics for early neonatal sepsis, while only 24 (17%) in 2016 (p< 0.0001). Antibiotics were suspended more frequently in 2016: 46% versus 24% in 2011 (p = 0.04). Late neonatal sepsis treatment was more frequent in 2011: 28 newborns (16%) versus 11 (8%) in 2016 (p = 0.02). There was a non-statically significative difference between time to discharge, with a trend to an earlier discharge in 2016. There were 6 (4%) deaths in 2011 and 2 (1%) in 2016 (p = 0.2).

Implementing a protocol that guided antibiotic use by clinical symptoms and positive culture successfully reduced antibiotic use, without increasing mortality or time to discharge. Antibiotics were started less often and suspended more frequently after the implementation of the protocol, for both early and late suspected neonatal sepsis.

**COI:** None declared.
ID: 253

TITLE: EUROPEAN SURVEY ON PREMEDICATION USED FOR NON-EMERGENCY NEONATAL INTUBATION.

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CONTENT:

Despite existing recommendations, a wide variation in frequency and type of drugs used for premedication for neonatal intubation still exists. We sought to evaluate the use of premedication for non-emergency neonatal intubation in a group of international neonatal providers and identify attitudes and experience regarding safety, side effects and efficiency of neonatal intubation.

A survey was sent to physicians and neonatal nurse practitioners working within the neonatal intensive care setting in Europe. Respondents were recruited by email. Additionally, a link to the survey was provided on professional neonatal themed internet discussion groups.

718 completed questionnaires from 70 different countries (n=40 European and n=30 Non-European) were analysed. 69.6% responses were provided by neonatologists and 10.3% by paediatric/neonatal trainees.

31.6% (n=227) practitioners reported that their unit does not have a protocol for neonatal intubation. In units without a protocol 60.4% of the practitioners would choose premedication according to personal preference, 37% do not use any drugs for non-emergency intubation. The most frequently reported combination for premedication was fentanyl, atropine and succinylcholine [6,8%]. Majority of the practitioners (78.5%) use the same drugs for term and preterm infants. Only 24.8% of physicians were fully satisfied with their premedication practice.

Despite international recommendations, a significant percent of practitioners continue not to use premedication. Education about potential harms and complications of intubation without analgesia and sedation should be enforced world-wide. A well planned, controlled trial is required in order to overthrow existing false convictions regarding drugs used for neonatal intubation.

COI: none declared
ID: 392

**TITLE:** PENTOXIFYLLINE AS RESCUE THERAPY IN SEVERE NEONATAL SEPSIS: AN OBSERVATIONAL STUDY

**AUTHORS:** Serife Kurul 1; Rob Taal 1; Robert Flint1,2; Karel Allegaert 1; Irwin Reiss 1; Sinno Simons1.

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**CONTENT:**

Neonatal sepsis is one of the main causes of death and morbidity in preterm neonates. Neonatal sepsis is associated with an excessive neonatal inflammatory response that is strongly correlated with mortality and morbidity. By modulating the hyper inflammatory response, pentoxifylline (PTX) is a high potential candidate for treatment in neonatal sepsis. PTX is not registered for this indication and is only used in a few neonatal intensive care units. Here we present our experience with pentoxifylline.

In this observational study we describe the use of intravenous PTX in the last year at our level III NICU. PTX was started as a last resort for critically ill neonates with sepsis as a 3-day course with 30 mg/kg/day infusion over 6 hours, according to local protocol. The Dutch Inspection of Health Care gave permission to administer PTX therapy next to antibiotic treatment in refractory sepsis in premature neonates.

PTX was started 14 times at our center, with one patient receiving PTX treatment twice (table 1). All patients had clinical symptoms of severe sepsis and associated inflammatory response, with exception of one case. The sepsis-mortality rate was 50%. The patients who survived received PTX therapy for 3 days. PTX therapy was often started much later than antibiotic treatment. The median time between the onset of infection and the start of PTX therapy was 21.1 hours (2.4 - 94.6).

Tachycardia in one patient was speculated to be related to PTX. However, this could also have been context specific, considering that tachycardia is very common in sepsis. No other adverse events attributed to PTX administration were observed.

Our study indicates that PTX therapy may be effective and safe as an additional treatment for sepsis. To be effective PTX must probably be started as soon as possible and ideally concomitant with antibiotic treatment. If PTX therapy is delayed, the devastating effects of the hyper inflammatory response might be irreversible. This might have occurred in part of our population because PTX was used as a last resort in the majority of the patients.

**IMAGES:**
https://www.eiseverywhere.com/eselectv3/v3/events/351149/submission/files/download?fileID=755bd6295d446fc8ed56d5adb3d0c9b-MjAxOS0wNSM1Y2UyNjY2YzQ4YTY0

Table 1: Characteristics of the patients

**COI:** None declared
ID: 408  
TITLE: PAIN SCALES IN CLINICAL TRIALS IN NEWBORN INFANTS – A MAPPING OF THE EVIDENCE  
AUTHORS: Mats Eriksson 1, Hanna Ahl 2, Kevin Bengtsson 3, Matteo Bruschettini 4, 5, Elisabeth Norman 2, 4, Emma Olsson 1, 6, Dhashini Naidu Vejayaram 4  
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CONTENT:

Numerous clinical studies have aimed at finding a strategy to reduce the pain newborn infants are subjected to by their medical conditions and also by medical and caring procedures. Little is however known about whether the outcome measures in these trials are valid for the specific type of pain or group of infants included in the studies. There are today over 40 published scales, consisting of behavioral or physiological signals or a combination of both. The aim of this study was to evaluate the reporting of pain scales assessments that were most commonly used in all the published trials examining interventions related to neonatal pain.

A systematic and broad search up to January 2019 was performed in Embase, PubMed, PsycInfo, Cinahl, Cochrane Library, Scopus and Luxid. Randomized and quasi-randomized clinical trials on neonatal pain were included. Title and abstract screening followed by full text screening were performed by two independent researchers using an online tool for the preparation of systematic reviews (Covidence). Disagreements were resolved by a third researcher or in discussions within the group, as recommended in the Cochrane handbook. Data extraction and quality assessment were also performed by two researchers independently.

The systematic search retrieved 3715 scientific articles. Following screening, 342 studies with a total of 16210 infants were included, reporting data from the use of at least one neonatal pain assessment scale. Ninety per cent of the studies concerned procedural pain where the most frequently used pain scales were PIPP or PIPP-R (43%), followed by NIPS (17%). For ongoing or post-operative pain there was a more unclear pattern with COMFORT (24%) and NFCS (10%) as the most reported. We observed a wide variation of pain scales (Fig 1) and found numerous studies where pain scales were used that were not validated for the studied population or type of pain. In 11 papers self-constructed study-specific scales were used. The most frequent sources of procedural pain were heel lance (28% of the studies) followed by venipuncture (10%) and ROP-screening (5%).

This is the first scoping review reporting systematically how neonatal pain scales are used in clinical trials. There are a few validated pain assessment scales used in most clinical studies. It is crucial to choose an appropriate scale, validated for the type of pain and population of infants included in the study. The inappropriate use of pain scales raises serious concerns on ethical conduct of research and waste of resources.

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Fig 1. Pain scales reported in the 342 included studies. Example of “other” are different sedation scales and neurological assessment scales.

COI: None declared
ID: 496

TITLE: GENTAMICIN TROUGH LEVELS IN PATIENTS WITH HYPOXIC ISCHAEMIC ENCEPHALOPATHY RECEIVING THERAPEUTIC HYPOTHERMIA

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CONTENT:

National Institute for Health and Clinical Excellence (NICE) guidance recommends benzylpenicillin and gentamicin as first line antibiotics for early onset sepsis in neonates. Gentamicin is generally well tolerated but can cause renal and ototoxicity. Babies with hypoxic ischaemic encephalopathy (HIE) are particularly vulnerable to toxicity due to potential poor clearance. Trough gentamicin levels before second dose are routinely measured before administering second dose. We aimed to review all cases of HIE treated with therapeutic hypothermia within our tertiary neonatal service to determine the incidence of high trough gentamicin levels and their correlation with peak creatinine levels.

Retrospective review of neonatal database to identify all patients that received therapeutic hypothermia over a 24 month period (January 2017 – December 2018) within Nottingham University Hospitals neonatal units. We reviewed individual patient notes, discharge summaries and laboratory databases of babies receiving therapeutic hypothermia (TH) to collect information about clinical details, renal function, sepsis work-up and trough gentamicin levels. Assumptions made:-

- a) Gentamicin prescribed at correct dose
- b) Gentamicin levels taken immediately prior to time 2nd dose due

63 patients identified; 5/63 died. 3 patients although qualified for TH, did not have a final diagnosis of HIE (encephalopathy – not HIE, subdural haemorrhage and stroke). 60 patients included for analysis. 59/60 babies that had HIE and received therapeutic hypothermia were above 36 weeks’ gestation; all babies >2kg in weight. Minimum peak creatinine level 69 with associated high trough gentamicin level. 25 (41.7%) patients receiving therapeutic hypothermia had high trough levels. Table 1 contains additional information about the grades of HIE, patients with creatinine >/= 75, evidence of neonatal sepsis and high gentamicin levels.

High (41.7%) proportion of babies with HIE receiving TH had high trough levels indicating susceptibility to toxicity. We need to consider alternative antibiotic choice for babies with HIE who qualify for TH.

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Table 1. Characteristics of patients with HIE that received TH

COI: None declared
ID: 612
TITLE: ANTIBIOTIC EXPOSURE IN PATIENTS OF NEONATAL INTENSIVE CARE UNITS IN FRANCE
AUTHORS: Séverine Martin-Mons 1,2,3; Béatrice Gouyon 2,3; Elodie Garnier 2; Silvia Iacobelli 2; Simon Lorrain 1,2; Jean-Bernard Gouyon 1,2
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CONTENT:

In France, antibiotics protocols vary widely from one neonatal intensive care unit (NICU) to another (S. Leroux 2014), which is consistent with findings in other countries. This led to a multicenter and retrospective analysis of electronic prescriptions prospectively collected as part of a neonatal prescription benchmarking program (B-PEN).

The study focuses on antibiotic prescriptions in 25 NICUs (23 level 3) that use the same prescription software powered by a common reference formulary adaptable to local prescription protocols. All prescription data were collected in 2017 and were deidentified before export to a common data warehouse (regulatory compliance). The study only includes newborns admitted in the first 28 days of life.

A- Overall population
- 12,212 neonates
- Distribution by gestational age:
  4.0 % at 22-26 wks; 13.8% at 27-31wks; 18.4% at 32-34 wks, 15.0% at 35-36 wks; 48.9% at ≥ 37 wks.
- Antibiotic exposure rate: 45.5% (95% CI: 44.6-46.4).
  of which 74.0% on D0-D1, 12.6% on D2-D6, 13.4% after D6
- Antibiotics on D0-D1: aminoglycosides (97.0%), cefotaxime (57.3%), other β-lactams (63.2%), glycopeptides (1.2%), carbapenems (0.3%), another antibiotic (1.6%).
- Simultaneously given antibiotics on D0-D1: one: 2.5%; two: 75.4%; three: 22.1%.

B - Very preterm neonates (GA < 32 wks)
- 2168 neonates
- Overall exposure rate: 77.2% (95% CI: 75.4 - 79.0). of which 75.9% on D0-D1.
- Antibiotics on D0-D1: aminoglycosides (97.7%), cefotaxime (84.0%), other β-lactam (42.1%), a glycopeptide (1.3%), a carbapenem (0.7%), another antibiotic (0.9%).

The variability of exposure according to NICUs is confirmed. Compared with other GAs, very preterm infants (GA <32 wks) are overexposed to antibiotics, particularly cephalosporins 3G (cefotaxime). Simultaneous administration of 3 antibiotics was observed in more than 1 in 5 children while this practice is not recommended.

COI: None declared.
ID: 649

**TITLE:** MEDICATION PRESCRIPTION IN 29 NICUs OVER A 2-YEAR PERIOD

**AUTHORS:** Jean-Bernard Gouyon 1,2; Severine Martin-Mons 1,3; Béatrice Gouyon 3; Elodie Garnier 1; Simon Lorrain 1,2; Anaëlle Pignolet 1; Evelyne Jacqz-Aigrain 4; Silvia Iacobelli 1,2

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**CONTENT:**

Patients in neonatal intensive care units (NICUs) have the highest rate of off-label and unlicensed medication prescription compared to other hospitalized patients. This study aims to identify precisely the International Nonproprietary Names (INNs) of medications prescribed to patients in NICUs with special focus on exposure in the most immature preterm infants and on INNs pharmaceutical substances given without any approval by the Summaries of Product Characteristics (SmPC) for the first month of life.

The research is an observational cohort study with retrospective analysis of medications prescribed in 29 Level 3 French NICUs (11 academic) over a 2-year period (2017-2018). Medications were prescribed with the same Computerized Prescriber Ordering Entry/Clinical Decision System. All prescriptions data were deidentified before storage in a common data warehouse. The primary objective of the study is to determine the current medication exposure rate of patients. Secondary objectives included assessment of medication exposure in preterm infants and rate of medication prescription not approved by the Summaries of Product Characteristics (SmPC).

The study population included 27,382 neonates. Two hundred and sixty one different medication INNs were prescribed. Twelve INNs (including paracetamol) were prescribed to at least 10% of the patients, 55 to less than 10% but at least 1%, and 194 to less than 1%. The lowest the gestational ages (GA) were exposed to the highest medications number (18 at GA < 27 wks vs 3 at GA > 34 wks). According to the French SmPCs, 69.2% of the 351 combinations of medication INNs and routes of administration, were not allowed in the neonatal period. Ninety five percent of preterm infants with GA below 32 weeks were administered at least one not-allowed medication.

Neonates remain therapeutic orphans. Consequences of polypharmacy should be rapidly assessed particularly in the most immature infants.

**COI:** None declared
ID: 722

TITLE: ‘COSTLY COFFEE’ FOR PREMATURE INFANTS: COULD REGULATION MAKE IT CHEAPER?

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3 University Maternity Hospital Limerick (UMHL), Limerick, Ireland

CONTENT:

Caffeine is one of the most widely used medicines in neonatal care. There is near universal use of caffeine citrate (CC) among extremely low birth weight (ELBW) cohort and among a significant proportion of very low birth weight (VLBW) infants. Perception of relative safety of CC results in the prolonged neonatal use over many weeks. Even though patient-level cost per unit dose may not be considered high, cumulative expenditure is often under recognised by clinical community. European Medicines Agency facilitates the authorisation of medicines for ‘rare diseases’ which are termed ‘orphan medicines’. Caffeine citrate was designated ‘orphan medicine’ status by the European Commission in 2003.

We aimed to analyse the purchase cost of CC for a regional neonatal unit in Ireland over a decade and highlight the importance cumulative cost curve (CCC) for caffeine. Annual purchase cost of CC by the hospital pharmacy was retrieved from the computerised pharmacy management system of UL Group of hospitals in the Mid-West of Ireland from 1st January 2009 to 31st December 2018. Based on annual number of ELBW and VLBW infants, cost per regional premature birth cohort was determined and was extrapolated to reach the national figures. We did not evaluate costs associated with product wastage, vial sharing, non-usage after expiry or variations at the patient-level dosage due to changes in clinical guidelines. Hospital audit committee approved the study as part of quality improvement project.

Mean yearly purchase cost of CC from 2014 to 2018 was €17,421 in order to care for our annual birth cohort of 35-45 infants of <1,500 gm. birth weight. Nationally the cost, if assumed without significant variation in unit cost or variation in dosage or duration of treatment, could be €265,102 annually with approximately 625 infants born <1,500 gm. birth weight. Actual figure could be higher allowing for the potential variations. During 2009 to 2013 when a CC preparation without an exclusive EU orphan drug license was used, our annual cost was €4,225 and if projected nationally would be €73,932. Cumulative cost curve for caffeine demonstrates (graphically) the under perceived financial burden from repetitive dosing.

One CC product holds market exclusivity in EU until July 2019. When period of market exclusivity for an indication ends, orphan designation could be removed from the EC register. In many non-EU countries, with non-exclusivity of market access, cost of CC has come down. Clinical communities, pharmaceuticals and EU regulatory bodies should work together towards sustainable availability of commonly used neonatal medicines at relatively low cost.

COI: None declared
ID: 941

TITLE: THE POSTNATAL DEVELOPMENT OF DESCENDING SEROTONERGIC MODULATION OF THE NOCICEPTIVE NETWORK

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CONTENT:

Pain in early life affects the postnatal development of the nociceptive system, including descending pain modulation. In order to understand the effect of neonatal procedural pain on descending serotonergic modulation, it is important to understand the normal physiological development of these projections. Developmental changes in expression of serotonin receptor subtypes may underlie and affect the functional postnatal maturation of the serotonergic modulation. However, knowledge in this field remains fragmentary. This review aims to summarize how descending serotonergic modulation of nociception changes with postnatal age in the rat.

Literature search was conducted in PubMed. Articles were included if they reported postnatal development of the serotonergic system or its receptors (1A, 1B, 2A, 3 and 7) in the brainstem or spinal cord of rats related to nociception. Thirty-nine articles were eligible for inclusion.

Throughout the first postnatal weeks, descending serotonergic inhibition is functionally immature, where modulation changes from facilitatory before postnatal day 21 to a bimodal modulation in adulthood. Sprouting of descending serotonergic tracts, projecting from the rostroventral medulla to the spinal cord, as well as changes in receptor expression and function take place in the first postnatal weeks. The developmental stage of the descending serotonergic system should be taken into account when providing analgesia in the postnatal period as it may influence the mechanism of action for pharmacological agents acting on the descending serotonergic system.

A comprehensive understanding of the development of the descending serotonergic system based on preclinical data could help optimize treatment of pain through postnatal development in a clinical setting as for instance with neonatal procedural pain in the NICU.

COI: None declared