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ID 76. Nosocomial infections in neonatal care: a scoping review of the surveillance case definitions that are used for pneumonia in newborns admitted in the hospital

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Background: Neonatal nosocomial infections (NNI) may lead to increased risk of morbidity, mortality and increased hospital stay. Therefore it is critical to monitor and prevent NNI. Surveillance of NNI is an indispensable tool in this process. The objective of this review is to provide an overview of surveillance case definitions, surveillance methods and outcome measures for NNI.

Methods: A scoping review was performed according to the guidelines of the Briggs institute. Only results for the subtypes hospital acquired pneumonia* (HAP) en *ventilator acquired pneumonia* (VAP) are presented here.

Results: Full text screening was performed on n = 294 of 16.067 articles of which n = 86 were included.

HAP: Surveillance case definitions were provided in 17 studies: 5 were according to CDC, 3 according to NEO-KISS, 4 used other sources and 5 were formulated by researchers (Table1). Manual surveillance was used in six; semi-automatic in two studies. Surveillance method was not reported in 53%. Outcome measures were: number of episodes (1x); number of neonates with HAP (11x); days with HAP/per 1000 in hospital days (3x).

VAP: Surveillance case definitions were provided in 74 studies: 49 were according to CDC, 2 according to NEO-KISS, 18 used other sources and 5 were formulated by researchers. Manual surveillance was used in 28; semi-automatic in 17 studies. Surveillance method was not reported in 39%. Outcome measures were: days with VAP/per 1000 ventilation days (33x); number of neonates with VAP (23x); % neonates with VAP (8x); number of episodes (2x); cases of VAP/per 1000 mechanically ventilated neonates (1x).

Conclusion: There is a serious lack of reporting and an extensive variation in surveillance case definitions, surveillance methods and outcome measures for neonatal HAP and VAP. This makes it impossible to compare results from different studies. A possible solution for this is a core outcome and minimum reporting set developed through consensus. By using a consistent, pragmatic surveillance method for neonatal HAP and VAP, as well as other subtypes of NNI, we will be able to study the true burden in terms of neonatal outcome and costs, as well as the effects of preventive measures.

HAP/Article	Chest X-ray changes	Worsening gas exchange	Clinical criteria	Laboratory findings	Antibiotic therapy	At least 48h of hospitalization
Abdel-Wahab, F. et al	x	x		x		
Asanathong, N. W. et al	x	x	x			x
Bartels, D. B. et al	x		x	x		
Gadallah, M. A. H. et al	x		x	x		
Geffers, C. et al	x		x	x		
Gulcan, H. et al	x		x	x		
Hibbard, J. U. et al	x		x			
Keene, S et al	x	x	x		x	
Kordek, A. et al	x	x		x		
Pessoa-Silva, C. L. et al	x		x	x		

Su, B. H. et al	x	x		x	
Tavora, A. C. V. C. F. et al	x	x	x	x	
Touati, A. et al	x		x		
van der Zwet, W. C. et al	x		x	x	x
Walter, J. et al	x	x	x	x	
Wang, Y. et al	x	x	x		
Wojkowska-Mach, J. et al	x	x	x	x	

(ID 76) - Table 1. Frequency of the elements used in the surveillance case definitions for HAP as an illustration of the variation

None declared.

ID 99. SARS-CoV-2 status and immune profiling of breastmilk in pregnant women: a case-control study

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Background: Transmission of SARS-CoV-2 through human milk has not been documented. However, more data are needed on its safety and efficacy in providing immune compounds in infected woman. This research aims to address questions related on the safety and the efficacy of breastmilk feeding of neonates born to mothers with non-severe SARS-CoV-2 infection: the prevalence of viral RNA in breastmilk according to SARS-CoV-2 status, the impact of SARS-CoV-2 infection on the milk profile of cytokines, chemokines and growth factors, and the evolution of the concentrations of such immune compounds during the first 5 weeks of lactation.

Methods: This multicenter prospective case-control study was conducted in 37 clinically stable, SARS-CoV-2 positive term pregnant women (study group), and in 45 SARS-CoV-2 negative women in identical conditions (control group), using consecutive sample. Participants collected and stored breastmilk every 72 h during the first month postpartum. Reverse transcription polymerase chain reaction (RT-PCR) was used for viral detection. Thirty soluble immune factors in colostrum and mature breastmilk were measured by magnetic bead-based multiplex immunoassays.

Results: Demographics and relevant clinical data of mother-infant dyads were comparable between groups. Symptomatic infection was present in 56.8% of mothers in the study group. All breastmilk samples were negative for SARS-CoV-2 RNA. Colostrum-transition breastmilk of the study group showed higher concentrations of most factors (interferon-γ, interleukins-1ra, 4, 6, 7, 9, 13, tumor necrosis factor-α, Eotaxin, interferon produced protein-10, macrophage inflammatory protein-1a, regulated on activation normal T-cells expressed and secreted, fibroblast growth factor, granulocyte-macrophage colony stimulating factor, and platelet-derived growth factor BB) compared to controls. These compounds tended to decreased in mature milk, particularly in the control group. Time of nasopharyngeal RT-PCR to become negative but not disease severity, influenced the immune compound milk profile.

Conclusion: This study confirms no viral RNA and a distinct immunological profile in breastmilk according to mother's SARS-CoV-2 status indicating efficient reaction, being especially suitable to protect the recipient children.

None declared.

ID 285. Body weight measurements support machine-learning algorithms in neonatal sepsis prediction

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Background: The initially subtle clinical signs in combination with its high mortality makes neonatal sepsis a challenging diagnosis. Clinical decision support systems (CDSS), continuously evaluating the risk of sepsis from vital signs time series can assist in the diagnosis of neonatal sepsis. However, it is currently unknown how body weight affects development of vital signs, and its potential influence on the predictive ability of CDSS in neonates.

Method: This was a longitudinal cohort study including 342 infants admitted to the neonatal intensive care unit at Karolinska University Hospital, Sweden. We prospectively collected high frequency monitor data with manually annotated event timelines. We then studied the influence of body weight on sample entropy measures of inter-beat interval time-series. Repetitive weight measurements were then added to a novel machine-learning-based algorithm, partly based on sample entropy measures of inter-beat intervals for sepsis prediction.

Results: Median birth weight for the study cohort was 2609 g and median gestational age was 36 weeks. A total of 4262 weight measurements were used. Sample entropy increased with gain of body weight, suggesting augmented heart rate variability during postnatal development in the subgroup of very low birth weight (VLBW) infants ($n = 91$) ($p < 0.05$, Fig. 1). Further, the group of VLBW infants did not fully catch up in entropy, even when reaching a comparable weight to their non-VLBW peers ($p < 0.05$). Our CDSS algorithm achieved a predictive ability with an area under receiving operating characteristics (AUROC) of 0.8 up to 24 h before clinical suspicion of sepsis, with a trend towards higher predictive ability when adding repetitive weight measures to the model.

Conclusion: We provide insight into how weight development correlates with heart rate variability, described as sample entropy from inter-beat interval time-domain analysis. Entropy increase could be explained by the maturation of the autonomic nerve system. Premature infants have a lower heart rate variability, likely explaining the lower entropy in the VLBW subgroup. Repetitive weight measurements might have an additive predictive value in CDSS for sepsis detection in neonates. Thus, there might be possibilities to calibrate CDSS with weight measurements, increasing their predictive ability and enabling earlier therapeutic interventions to save lives.

(ID 285) - * $p < 0.05$ change of median SampEn for VLBW infants. † $p < 0.05$ difference between VLBW/Non-VLBW median SampEn. * $p < 0.05$ change of median SampEn for Non-VLBW. Abbreviations: VLBW: very low birth weight. SampEn: Sample entropy

None declared.

ID 286. Predicting acute adverse events in neonates using automated vital sign pattern analysis

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Background: Infants in a neonatal intensive care unit (NICU) are at risk of a variety of adverse events, such as systemic infections, necrotizing enterocolitis and major bleeding. These usually present with initial subtle changes of physiological parameters but may lead to life-threatening situations. Earlier recognition of such events would be of importance in daily clinical practice. Recent development of Clinical Decisions Support Systems indicate that the use of machine learning to detect changes in vital sign patterns enable early diagnosis of neonatal pathologies. Most studies have focused on sepsis and specific subgroups of the NICU population, such as very low birth weight infants. Earlier detection of adverse events in the whole NICU population could reduce morbidity and mortality.

Methods: We performed an observational study on a representative NICU cohort admitted to Karolinska University Hospital, using high frequency vital signs including heart rate, respiratory rate and oxygen saturation. We assessed the ability of a Gaussian Mixture Model based machine learning algorithm to detect sepsis, necrotizing enterocolitis, central nervous system infection, pneumonia, intraventricular hemorrhage and lung bleeding up to 24 h before clinical suspicion.

We compared the ability of the algorithm to detect all adverse events to detection in subgroups of infections and sepsis.

Results: Our study included 342 infants with 41 patients experiencing 52 adverse events. Our algorithm could detect events 24 h before diagnosis with an area under the receiver operating characteristics curve of 0.69 for the prediction of all adverse events, 0.80 for infections and 0.75 for sepsis.

Conclusion: Several adverse events in NICU patients can be predicted 24 h before clinical discovery with a machine learning algorithm based on continuous vital sign characteristics. The algorithm is more useful to detect systemic infections, probably since they constitute a more uniform group compared to all adverse events in this study. We use several parameters from standard monitoring in a representative NICU cohort to detect a broader spectrum of complications compared to earlier investigations, and thus explore new applications of vital sign pattern analysis. This potentially provides new tools for the clinician in the diagnosis of neonatal disease, enabling earlier therapeutic interventions and saved lives.

None declared.

ID 367. Case report of septic pulmonary embolization in a neonate: could it be a manifestation of MIS-N?

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Background: Multisystem inflammatory syndrome in children is characterized by fever, MODS and elevated inflammatory markers following COVID-19 infection. So far, three cases of Neonatal MIS-C (MIS-N) are reported. A 33 week preterm with pericardial effusion and two cases of neonates with respiratory failure and pulmonary hypertension. All mothers had COVID-19 infection, and neonates had elevated inflammatory markers, reported as possible MIS-N. Micro-organisms can cause pulmonary cavities either by entering via oropharynx, causing necrotizing pneumonia, or via the bloodstream as septic pulmonary emboli. We report a neonate who had multiple cavity lesions in lung, which we suspect could be a presentation of MIS-N.

Case report: Term, male, 2.4 kg, born by C-Section, referred on 8th day with fever and fast breathing. Mother positive for COVID-19 in 29th week of pregnancy. Neonate was started on oxygen in view of 89% saturation. The total leukocyte count was 31200/cu.mm, CRP 9.8 mg% and procalcitonin 6.34 ng/ml. Antibiotics were started, but BACTEC, urine and CSF cultures were sterile. Chest-radiograph showed bilateral, perihilar opacities. COVID-19 RT-PCR was negative. In view of persisting fever and history of maternal COVID infection, baby was investigated for Inflammatory syndrome. The COVID antibodies were positive with raised Ferritin and LDH. Echocardiogram normal. The HRCT thorax showed multiple nodules with evidence of cavitation in both lungs, suggestive of septic emboli. Workup for tuberculosis was negative. Full body contrast scan to rule out rare possibility of metastatic spread did not find anything significant. Since the cultures were negative and neonate was not responding to antibiotics, along with raised inflammatory markers, a possible diagnosis of MIS-N was made. Intravenous Immunoglobulin was administered to the neonate after which resolution of respiratory symptoms was noted.

Conclusion: MIS-N can occur following in-utero exposure to SARS-CoV-2. It's known that hyperinflammatory state of MIS-C predisposes thromboembolic complications, including pulmonary emboli. After having ruled out bacterial sepsis, the case reported by us, could be a possible inflammatory response to antenatal exposure to COVID-19 causing pulmonary emboli. Hence, in future, neonates exposed to COVID-19 should also be evaluated for thromboembolic complications.

(ID 367)- HRCT shows multiple nodules of varying sizes, conglomerate at places noted in both lungs. Most of the nodules so evidence of cavitation. Findings suggestive of septic embolization.

None declared.

ID 438. Three peaks COVID-challenge and neonatal outcomes in a large UK tertiary centre with a high BAME population

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Background: The risk of perinatal transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been eluded to but still remains somewhat unknown. COVID-19 has caused significant morbidity and mortality particularly within Black, Asian and Minority Ethnic (BAME) population. Yet published evidence of perinatal outcomes of affected BAME pregnancies is limited.

Methods: Retrospective cohort study was conducted of all neonates born to mothers testing positive for SARS-CoV-2 within 7 days of delivery at a large perinatal centre between March

2020–March 2021 encompassing the three peaks in the UK of SARS-CoV-2. A subgroup analysis on BAME pregnancies was also performed. Since May 2021, all mothers were swabbed at admission with RT-PCR (prior to this, only symptomatic women were tested with RT-PCR). All infants admitted to NNU born to positive or suspected mothers were swabbed on day 3 and day 5. Routine weekly RT-PCR of admitted neonates began in Nov 2021.

Results: Of approximately 9000 births during the study period, 88 COVID positive mothers delivered 89 neonates. 67 mothers (76%) were from BAME groups. Of the 89 neonates, 13 (15%) required NNU admission, 5 of which were pre-term. 8 had respiratory distress syndrome requiring respiratory support, all but one of these were born to BAME mothers. These infants followed usual neonatal clinical course. Only two infants tested positive during this time: one tested positive at day 3 and day 5 and remained positive till day 20 which is likely vertical transmission. The other infant tested positive at 2 months of age having previously tested negative; likely horizontal transmission however was asymptomatic during the time and were picked on routine weekly PCR swabs. No other infants tested positive on symptomatic screening for COVID. The other 76 babies remained well and stayed on the postnatal wards with their mothers. 55% of infants were breast fed, none of whom went on to develop symptoms of COVID.

Conclusion: The BAME pregnancies appear to have been disproportionately affected by COVID-19, significant numbers delivered prematurely and needing admission to neonatal unit. However, reassuringly, insignificant perinatal transmission and severity was noted in neonates and breast feeding appeared safe with appropriate infection control measures.

None declared.

ID 506. Early postnatal antibiotics induce later blood transcriptomic changes in preterm pigs

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Background: Antibiotics (AB) are commonly used for preterm infants. Prolonged treatment is associated with later immune-related dysfunctions and morbidities (NEC, LOS). We hypothesized that 4 days of early postnatal AB treatment affects later immune status, potentially via gut microbiota changes, as reflected by blood cell transcriptional responses.

Methods: Using preterm pigs as a model for infants, newborn caesarean-delivered animals were treated with broad spectrum AB (amoxicillin/clavulanic acid 50/25 mg/kg/d; neomycin 50 mg/kg/d, oral administration) on day 1–4, and blood was collected at intervals until day 9. Temporal gene expression was analyzed by qPCR for selected genes related to immunity and cellular energy metabolism. Immune gene expressions (day 5–9) and whole blood transcriptome (RNAseq) and gut microbiota (day 9) were analyzed.

Results: Expression of genes related to immunity and energy metabolism (TLR2, TLR4, CXCL10, IFNG, IL10, S100A9, PKM, HK1) increased at day 5–9 in controls (vs day 1, Fig. 1). AB-treated pigs showed less gene responses over time, with persistently low expression of TLR2 and TLR4 at day 5–9. Targets related to Th1 polarization showed lower levels in AB-treated vs. control animals (CXCL9, CXCL10, IFNG, IFNG/IL4, TBET/GATA3). Th17 related targets showed decreasing expression on day 9 (TGFB1, RORC) and lower levels of IL17A in AB-treated pigs. Temporary lower expression of S100A9 was seen in the AB-treated on days 5–7 (all $p < 0.05$). Transcriptomics showed 1487 differentially expressed genes (DEGs, 273 up, 1214 down) in AB-treated pigs. IL17A, IL17F, IFNG, and IL22 expression were among top 20 DEGs and AB affected pathways related to adaptive immunity, JAK-STAT-signaling, glycolysis, GPCR signaling, and ribosome function. The gut microbiota was minimally affected on day 9.

Conclusion: Early postnatal AB treatment reduces expression of multiple immune-related genes, even after cessation of treatment and without notable effects to gut microbiota in preterm pigs. In a translational perspective, AB treatment of newborn preterm infants may be associated with immune suppression, potentially affecting later response to infection. Understanding how and when AB treatment affects immune maturation will help to improve ways to combat neonatal infections without inducing negative effects on the developing immune system and gut microbiota, thereby improving antibiotic stewardship.

(ID 506) - Temporal gene expression (vs day 1) in preterm pigs without and with antibiotic treatment on day 1–4 (CON and AB, respectively) and group comparison (AB vs CON, log2-fold-change, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$)

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ID 539. Addition of pentoxifylline to gentamicin enhances anti-inflammatory and pro-resolution cytokines in brain tissue of 1 week old mice with *Escherichia coli* sepsis

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Background: Neonatal sepsis triggers an inflammatory response that contributes to high mortality and brain injury. Pentoxifylline (PTX), a phosphodiesterase inhibitor that suppresses pro-inflammatory cytokine production, is a candidate adjunctive therapy for newborn sepsis that has shown improved survival in small clinical studies. The effects of adjunctive PTX on sepsis-induced cerebral inflammation in the newborn remain poorly understood. We hypothesized that the addition of PTX to gentamicin (GENT) compared to GENT alone inhibits the concentrations of pro-inflammatory and/or augments anti-inflammatory and pro-resolution cytokines and chemokines in cerebral tissue of one week old mice with *Escherichia coli* sepsis.

Methods: *E. coli* K1 (ATCC #700973) 10^5 colony forming units (CFU)/g weight or no bacteria control (CTL) were injected intraperitoneally into 7 days old C57BL/6J pups, corresponding immunologically to term human newborns. After 1.5 h, *E. coli*-septic pups were treated with GENT, PTX, (GENT+PTX) or saline (SAL), and euthanized after an additional 4 h. CFUs, cytokines and chemokines were measured in homogenized brain tissue, and comparisons employed 1-way ANOVA or Kruskal–Wallis tests.

Results: Cerebral tissue CFUs from untreated *E. coli*-septic pups were significantly lower (median 14 CFUs/mg tissue, IQR 8–34) compared to other organs (e.g., liver: median 11923 CFUs/mg tissue) or blood (median 1970 CFUs/ μ l), and were mostly undetectable in pups treated with GENT, whereby the addition of PTX did not augment bacterial growth. Cerebral concentrations of pro-inflammatory cytokines significantly increased in untreated septic compared to CTL mice (mean TNF: 697 vs 396 pg/g tissue, $p < 0.05$). GENT and (GENT+PTX) significantly decreased the cerebral chemokines CXCL1 (keratinocyte-derived chemokine) and CCL2. GENT alone suppressed cerebral CCL3, while (GENT+PTX) showed a non-significant trend towards reduced CCL3 concentration. CCL4 and TNF in cerebral tissue were not changed by GENT or (GENT+PTX). (GENT+PTX) and PTX alone enhanced cerebral concentrations of the anti-inflammatory and pro-resolution cytokines IL-10, IL-6 (Jones, *J. Immunol.* 2005) and G-CSF (Kitabayashi, *Blood* 1995), whereas GENT alone did not change IL-10 and significantly decreased IL-6 and G-CSF.

Conclusion: Addition of PTX to GENT in one-week-old mice with *E. coli* sepsis enhances cerebral concentrations of anti-inflammatory and pro-resolution cytokines without augmenting bacterial growth, suggesting potential protection from sepsis-induced cerebral injury.

None declared.