Order of draw practices in venous blood sampling at clinical biochemistry departments in the Danish health care system

BACKGROUND: Deviation in blood collection procedures is a central source of preanalytical variation affecting overall analytical and diagnostic precision. The order of draw of venous sampling is suspected to affect analytical results, in particular for coagulation analysis. Here we compare the procedures in venous blood sampling among clinical biochemistry departments to assess the uniformity of order of blood draw and adherence to international guidelines in the Danish health care system.

METHODS: We collected venous order of draw procedures from 49 clinical biochemistry departments at 22 public hospitals in Denmark. Procedures were compared to the international guidelines from the Clinical Laboratory Standards Institute (CLSI) and World Health Organization (WHO), and assessed in relation to department ISO 15189:2012 accreditation.

RESULTS: We observed seven different order of draw procedures related to citrate, serum, heparin, and EDTA tubes, and the use of discard tubes in relation to coagulation assays. 31 departments (63.3%) were found to adhere to CLSI and WHO guidelines. A majority of departments instructs the use of discard tubes before collection for coagulation assays in citrate tubes (44 departments; 89.8%). The citrate tube was the first sample tube to be drawn for most departments (35 departments; 75.5%); and the preferred order of non-citrate tubes was serum-heparin-EDTA (36 departments; 73.5%). Adherence to the CLSI and WHO guidelines was not associated with department ISO 15189:2012 accreditation (p=.57).

CONCLUSIONS: Venous order of draw procedures is diverse at Danish clinical biochemistry departments and show moderate adherence to international guidelines.

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The immune response to Prevotella bacteria in chronic inflammatory disease
The microbiota plays a central role in human health and disease by shaping immune development, immune responses and metabolism, and by protecting from invading pathogens. Technical advances that allow comprehensive characterization of microbial communities by genetic sequencing have sparked the hunt for disease-modulating bacteria. Emerging studies in humans have linked the increased abundance of Prevotella species at mucosal sites to localized and systemic disease, including periodontitis, bacterial vaginosis, rheumatoid arthritis, metabolic disorders and low-grade systemic inflammation. Intriguingly, Prevotella abundance is reduced within the lung microbiota of patients with asthma and chronic obstructive pulmonary disease. Increased Prevotella abundance is associated with augmented T helper type 17 (Th17) -mediated mucosal inflammation, which is in line with the marked capacity of Prevotella in driving Th17 immune responses in vitro. Studies indicate that Prevotella predominantly activate Toll-like receptor 2, leading to production of Th17-polarizing cytokines by antigen-presenting cells, including interleukin-23 (IL-23) and IL-1. Furthermore, Prevotella stimulate epithelial cells to produce IL-8, IL-6 and CCL20, which can promote mucosal Th17 immune responses and neutrophil recruitment. Prevotella-mediated mucosal inflammation leads to systemic dissemination of inflammatory mediators, bacteria and bacterial products, which in turn may affect systemic disease outcomes. Studies in mice support a
causal role of Prevotella as colonization experiments promote clinical and inflammatory features of human disease. When compared with strict commensal bacteria, Prevotella exhibit increased inflammatory properties, as demonstrated by augmented release of inflammatory mediators from immune cells and various stromal cells. These findings indicate that some Prevotella strains may be clinically important pathobionts that can participate in human disease by promoting chronic inflammation.

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Divergent Response Profile in Activated Cord Blood T cells from First-born Child Implies Birth-order-associated in Utero Immune Programming

Background: First-born children are at higher risk for development of a range of immune-mediated diseases. The underlying mechanism of 'birth-order-effects' on disease risk is largely unknown, but in utero programming of the child's immune system may play a role. Objective: We studied the association between birth-order and the functional response of stimulated cord blood T cells. Method: Purified cord blood T cells were polyclonally activated with anti-CD3/CD28-coated beads in a subgroup of 28 children enrolled in the COPSAC 2010 birth cohort. Expression levels of seven activation markers on helper and cytotoxic T cells as well as the percentage of CD4^+CD25^+ T cells were assessed by flow cytometry. Production of IFN-γ, TNF-α, IL-17, IL-4, IL-5, IL-13 and IL-10 was measured in supernatants. Results: IL-10 secretion (P = 0.007) and CD25 expression on CD4^+ T cells (P = 0.0003) in activated cord blood T cells were selectively reduced in first-born children, while the percentage of CD4^+CD25^+ cord blood T cells was independent of birth-order. Conclusion: First-born infants display a reduced anti-inflammatory profile in T cells at birth. This possible in utero 'birth-order' T cell programming may contribute to later development of immune-mediated diseases by increasing overall immune reactivity in first-born children as compared to younger siblings.

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Season of birth shapes neonatal immune function

Birth season has been reported to be a risk factor for several immune-mediated diseases. We hypothesized that this association is mediated by differential changes in neonatal immune phenotype and function with birth season. We sought to investigate the influence of season of birth on cord blood immune cell subsets and inflammatory mediators in neonatal airways. Cord blood was phenotyped for 26 different immune cell subsets, and at 1 month of age, 20 cytokines and chemokines were quantified in airway mucosal lining fluid. Multivariate partial least squares discriminant analyses were applied to determine whether certain immune profiles dominate by birth season, and correlations between individual cord blood immune cells and early airway immune mediators were defined. We found a birth season-related fluctuation in neonatal immune cell subsets and in early-life airway mucosal immune function. The seasonal airway immune pattern was associated with the number of activated and regulatory T cells in cord blood whereas it was independent of concomitant presence of pathogenic airway microbes. Specifically, summer newborns presented with the lowest levels of all cell types and mediators; fall newborns displayed high levels of activated T cells and mucosal IL-12p70, TNF-α, IL-13, IL-10, and IL-
and winter newborns had the highest levels of innate immune cells, IL-5, type 17-related immune mediators, and activated T cells. Birth season fluctuations seem to affect neonatal immune development and result in differential potentiation of cord blood immune cells and early airway mucosal immune function.
Susceptibility to Lower Respiratory Infections in Childhood is Associated with Perturbation of the Cytokine Response to Pathogenic Airway Bacteria

BACKGROUND: Neonatal colonization of the airways with respiratory pathogens is associated with increased risk of lower respiratory infections (LRI) in early childhood. Therefore, we hypothesized that children developing LRI have an aberrant immune response to pathogenic bacteria in infancy. OBJECTIVE: To characterize in vitro the early life systemic immune response to pathogenic bacteria and study the possible association with incidence of LRI during the first 3 years of life. METHODS: The Copenhagen Prospective Study on Asthma in Childhood2000 (COPSAC2000) is a clinical birth cohort study of 411 children born of mothers with asthma. LRI incidence was prospectively captured from 6-monthly planned visits and visits at acute respiratory episodes. The in vitro systemic immune response to H. influenzae, M. catarrhalis and S. pneumoniae was characterized by the production of TNF-α, IFN-γ, IL-2, IL-5, IL-10, IL-13, and IL-17 in peripheral blood mononuclear cells isolated at age 6 months from 291 infants. Data were analyzed by Poisson regression against incidence of LRI in infancy. RESULTS:: A multivariable model including all cytokine responses from the three different bacterial stimulations significantly identified children at risk of LRI (p=0.006). The immune response pattern associated with LRI was characterized by perturbed production of several cytokines rather than production of one specific cytokine, and was independent of concurrent asthma. TNF-α and IL-5 were key drivers but did not explain the entire variation in LRI susceptibility. CONCLUSIONS: Children at risk of future LRI present a perturbed systemic immune response upon exposure to common airway pathogens in early life.
Chronic obstructive pulmonary disease and asthma-associated Proteobacteria, but not commensal Prevotella spp., promote Toll-like receptor 2-independent lung inflammation and pathology

Recent studies of healthy human airways have revealed colonization by a distinct commensal bacterial microbiota containing Gram-negative Prevotella spp. However, the immunological properties of these bacteria in the respiratory system remain unknown. Here we compare the innate respiratory immune response to three Gram-negative commensal Prevotella strains (Prevotella melaninogenica, Prevotella nanceiensis and Prevotella salivae) and three Gram-negative pathogenic Proteobacteria known to colonize lungs of patients with chronic obstructive pulmonary disease (COPD) and asthma (Haemophilus influenzae B, non-typeable Haemophilus influenzae and Moraxella catarrhalis). The commensal Prevotella spp. and pathogenic Proteobacteria were found to exhibit intrinsic differences in innate inflammatory capacities on murine lung cells in vitro. In vivo in mice, non-typeable H. influenzae induced severe Toll-like receptor 2 (TLR2)-independent COPD-like inflammation characterized by predominant airway neutrophilia, expression of a neutrophilic cytokine/chemokine profile in lung tissue, and lung immunopathology. In comparison, P. nanceiensis induced a diminished neutrophilic airway inflammation and no detectable lung pathology. Interestingly, the inflammatory airway response to the Gram-negative bacteria P. nanceiensis was completely TLR2-dependent. These findings demonstrate weak inflammatory properties of Gram-negative airway commensal Prevotella spp. that may make colonization by these bacteria tolerable by the respiratory immune system.
Asthma, Microbiota, Chronic obstructive pulmonary disease, Lung immunopathology, Respiratory inflammation
Maternal fatty acid desaturase genotype correlates with infant immune responses at 6 months

Breast milk long-chain PUFA (LCPUFA) have been associated with changes in early life immune responses and may modulate T-cell function in infancy. We studied the effect of maternal fatty acid desaturase (FADS) genotype and breast milk LCPUFA levels on infants’ blood T-cell profiles and ex vivo-produced cytokines after anti-CD3/CD28 stimulation of peripheral blood mononuclear cells in 6-month-old infants from the Copenhagen Prospective Study of Asthma in Childhood birth cohort. LCPUFA concentrations of breast milk were assessed at 4 weeks of age, and FADS SNP were determined in both mothers and infants (n 109). In general, breast milk arachidonic acid (AA) levels were inversely correlated with the production of IL-10 (r -0.25; P=0.004), IL-17 (r -0.24; P=0.005), IL-5 (r -0.21; P=0.014) and IL-13 (r -0.17; P=0.047), whereas EPA was positively correlated with the counts of blood regulatory T-cells and cytotoxic T-cells and decreased T-helper cell counts. The minor FADS alleles were associated with lower breast milk AA and EPA, and infants of mothers carrying the minor allele of FADS SNP rs174556 had higher production of IL-10 (r -0.23; P=0.018), IL-17 (r -0.25; P=0.009) and IL-5 (r -0.21; P=0.038) from ex vivo-activated immune cells. We observed no association between T-cell distribution and maternal or infant FADS gene variants. We conclude that increased maternal LCPUFA synthesis and breast milk AA are associated with decreased levels of IL-5, IL-13 (type-2 related), IL-17 (type-17 related) and IL-10 (regulatory immune responses), but not with interferon-γ and TNF-α, which could be due to an effect of the maternal FADS variants on the offspring immune response transferred via breast milk LCPUFA. Copyright © The Authors 2015.
Metagenomic heterogeneity explains dual immune effects of endotoxins

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Cesarean section imprints cord blood immune cell distributions
Immune programming in early life may affect the risk of developing immune-related diseases later in life. Children born by cesarean section seem to be at higher risk of asthma, allergic rhinitis, and type-1 diabetes. We hypothesized that delivery by cesarean section may affect immune maturation in newborns. The objective of the study was to profile innate and adaptive immune cell subsets in cord blood of children born by cesarean section or natural birth.

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Children developing asthma by school-age display aberrant immune responses to pathogenic airway bacteria as infants

Asthma is a highly prevalent chronic lung disease that commonly originates in early childhood. Colonisation of neonatal airways with the pathogenic bacterial strains H. influenzae, M. catarrhalis and S. pneumoniae is associated with increased risk of later childhood asthma. We hypothesized that children developing asthma have an abnormal immune response to pathogenic bacteria in infancy. We aimed to assess the bacterial immune response in asymptomatic infants and the association with later development of asthma by age 7 years.

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Children with asthma by school age display aberrant immune responses to pathogenic airway bacteria as infants

Background: Asthma is a highly prevalent chronic lung disease that commonly originates in early childhood. Colonization of neonatal airways with the pathogenic bacterial strains Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae is associated with increased risk of later childhood asthma. We hypothesized that children with asthma have an abnormal immune response to pathogenic bacteria in infancy.

Objective: We aimed to assess the bacterial immune response in asymptomatic infants and the association with later development of asthma by age 7 years.

Methods: The Copenhagen Prospective Studies on Asthma in Childhood birth cohort was followed prospectively, and asthma was diagnosed at age 7 years. The immune response to H influenzae, M catarrhalis, and S pneumoniae was analyzed in 292 infants using PBMCs isolated and stored since the age of 6 months. The immune response was assessed based on the pattern of cytokines produced and T-cell activation.

Results: The immune response to pathogenic bacteria was different in
infants with asthma by 7 years of age (P = .0007). In particular, prospective asthmatic subjects had aberrant production of IL-5 (P = .008), IL-13 (P = .057), IL-17 (P = .001), and IL-10 (P = .028), whereas there were no differences in T-cell activation or peripheral T-cell composition. Conclusions Children with asthma by school age exhibited an aberrant immune response to pathogenic bacteria in infancy. We propose that an abnormal immune response to pathogenic bacteria colonizing the airways in early life might lead to chronic airway inflammation and childhood asthma.

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Early immune response patterns to pathogenic bacteria are associated to increased risk of lower respiratory infections in children

Neonatal colonisation of the airways with respiratory pathogen is associated with increased risk of lower respiratory infections (LRI) in early childhood (1). Therefore, we hypothesized that children developing LRI have an abnormal immune response to pathogenic bacteria in infancy. We aimed to characterise the systemic immune response to pathogenic bacteria at the age of 6 months and study the association with incidence of LRI during the first 3 years of life.

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Divergent pro-inflammatory profile of human dendritic cells in response to commensal and pathogenic bacteria associated with the airway microbiota.

Recent studies using culture-independent methods have characterized the human airway microbiota and report microbial communities distinct from other body sites. Changes in these airway bacterial communities appear to be associated with inflammatory lung disease, yet the pro-inflammatory properties of individual bacterial species are unknown. In this study, we compared the immune stimulatory capacity on human monocyte-derived dendritic cells (DCs) of selected airway commensal and pathogenic bacteria predominantly associated with lungs of asthma or COPD patients (pathogenic *Haemophilus* spp. and *Moraxella* spp.), healthy lungs (commensal *Prevotella* spp.) or both (commensal *Veillonella* spp. and pathogenic *Haemophilus* spp. and *Moraxella* spp.).
and Actinomyces spp.). All bacteria were found to induce activation of DCs as demonstrated by similar induction of CD83, CD40 and CD86 surface expression. However, asthma and COPD-associated pathogenic bacteria provoked a 3-5 fold higher production of IL-23, IL-12p70 and IL-10 cytokines compared to the commensal bacteria. Based on the differential cytokine production profiles, the studied airway bacteria could be segregated into three groups (Haemophilus spp. and Moraxella spp. vs. Prevotella spp. and Veillonella spp. vs. Actinomyces spp.) reflecting their pro-inflammatory effects on DCs. Co-culture experiments found that Prevotella spp. were able to reduce Haemophilus influenzae-induced IL-12p70 in DCs, whereas no effect was observed on IL-23 and IL-10 production. This study demonstrates intrinsic differences in DC stimulating properties of bacteria associated with the airway microbiota.