News and Views

Routine PCR Testing in Patients with Suspected Community-Acquired Pneumonia

The use of polymerase chain reaction (PCR) testing on lower respiratory tract samples led to a significant reduction in the time to provision of pathogen-directed treatment in patients with suspected community-acquired pneumonia (CAP) in the emergency room (ER). Those who underwent PCR testing also received more targeted microbial treatment based on the specific pathogens identified. These findings from a single center trial were published in the journal *JAMA Network Open*[1].

Through this single-center study, the researchers aimed to assess the impact of syndromic PCR-based panel testing on the management of CAP. The study with a parallel-arm, single-blinded design was conducted between September 2020 and June 2022 in the emergency department (ED) of a tertiary hospital in Norway. The 374 patients, with median age 72 years, with suspected CAP were randomized 1:1 to either the intervention arm (rapid syndromic PCR testing + standard care) or the control arm (standard microbiological testing + standard care). Men comprised ~70% of the study population.

The primary outcome was pathogen-directed treatment tailored according to the specific pathogens identified in the PCR-based panel testing. The second primary outcome was time to provision of pathogen-directed treatment, i.e., efficiency of the intervention in facilitating timely initiation of appropriate treatment within 48 hours of randomization.

In the intervention arm, 66 out of 187 patients (35.3%) received pathogen-directed treatment based on the microbiological test results. In contrast, only 25 out of 187 patients (13.4%) in the control arm received pathogen-directed treatment. This corresponds to a reduction in the absolute risk of 21.9% points in the intervention arm compared to the standard-of-care arm. Participants in the intervention arm were at least thrice more likely to receive pathogen-directed treatment compared to those in the standard-of-care arm with odds ratio (OR) of 3.53.

In the intervention arm (PCR-based panel testing), the median time to provision of pathogen-directed treatment within 48 hours was 34.5 hours versus 43.8 hours in the control arm. The mean difference in time to provision of treatment between the two arms was −9.4 hours. The hazard ratio (HR) for intervention compared with standard of care was 3.08. These findings remained statistically significant even after adjustment for season.

These findings underscore the clinical utility of molecular testing in expediting the diagnosis thereby optimizing the management of CAP leading to improved clinical management and potentially better outcomes. The rapid turnaround time and ability to identify multiple pathogens simultaneously make PCR testing a valuable complementary or even a potential alternate test for selected standard, time-consuming laboratory-based diagnostics. By reducing unnecessary empirical antibiotic use it has the potential of mitigating the risk of antibiotic resistance.

Reference

1. Markussen DL, et al. Diagnostic stewardship in community-acquired pneumonia with syndromic molecular testing: a randomized clinical trial. JAMA Netw Open. 2024;7(3):e240830.

Impact of 24-hour Physical Behaviors on Type 2 Diabetes

Patients with obesity-related subtype of type 2 diabetes tend to have poorer sleep quality, lower overall physical activity levels, higher sedentary time, and lower intensity of movement compared to those with age-related diabetes subtype, suggests a study published in the April 2024 issue of the journal *Diabetes, Obesity and Metabolism*[1].

The objective of this 7-day study was to explore how physical behaviors differed across four different subtypes of type 2 diabetes namely insulin-deficient diabetes (INS-D), insulin-resistant diabetes (INS-R), obesity-related diabetes (OB), and age-related diabetes (AGE). The participants were part of the ongoing Chronotype of Patients with Type 2 Diabetes and Effect on Glycaemic Control (CODEC) observational study. Participants wore accelerometers for 7 days to track their physical behaviors throughout the day.

The 564 study participants, with mean age 63.6 years and ~40% females, were categorized into four subtypes based on clinical data such as age at onset of diabetes, glycated hemoglobin (HbA1c) level, homeostatic model assessment index of beta-cell function, homeostatic

model assessment index of insulin resistance and body mass index (BMI). The AGE cluster served as the reference group. There were 35 subjects (6.2%) in the INS-D, 88 (15.6%) in the INS-R group, 166 (29.4%) had OB, while 275 (48.8%) had AGE.

Examination of sleep characteristics across different type 2 diabetes subtypes revealed that participants with the OB subtype had a shorter sleep duration with a difference of −0.3 hours compared to the AGE subtype. They also exhibited lower sleep efficiency (difference of −2%) and greater variability in sleep duration, with an increase of 17.9 minutes.

When physical activity profiles across different type 2 diabetes subtypes were compared, it was found that participants with OB engaged in less total physical activity, with a difference of −2.9 mg and also spent less time doing moderate to vigorous physical activity (MVPA). The average MVPA was >30% lower in the OB subtype compared to the AGE subtype, with a difference of −6.6 minutes.

Participants in the OB group spent longer time being sedentary (749.2 min) compared to those in the AGE group (717.4 min), with an increase of 31.9 minutes. Movement intensity during the most active continuous 10 and 30 minutes of the day was lower in the OB group compared to the AGE cluster. The intensity of the most active continuous periods of the day for the OB cluster was up to 15.8% lower than for the AGE cluster.

These findings show that sleep characteristics and physical behaviors differ across type 2 diabetes subtypes. Patients with obesity-related diabetes exhibited the least favorable sleep quality and lowest overall physical activity levels compared to those with age-related diabetes. Targeting these specific behaviors with personalized 24-hour lifestyle interventions and incorporating them into treatment plans could be particularly beneficial in improving health outcomes in type 2 diabetes patients, particularly those with obesity-related type 2 diabetes.

Reference

1. Henson J, et al. Twenty-four-hour physical behaviour profiles across type 2 diabetes mellitus subtypes. Diabetes Obes Metab. 2024;26(4):1355-65.

Predictors of Heart Failure in Type 2 Diabetes

N-terminal pro B-type natriuretic peptide (NT-proBNP) and troponin T (TnT) levels, and BMI are independent predictors of incident heart failure (HF) in patients with type 2 diabetes, including those on sodium-glucose co-transporter 2 (SGLT2) inhibitors, says a study published in the journal *Diabetes, Obesity and Metabolism*[1]. Use of calcium channel blockers, urine albumin-creatinine ratio, HbA1c, age, and hematocrit were also found to be significant predictors.

In this study, the researchers developed a prediction model that would effectively identify type 2 diabetes patients at high risk of incident HF, including those taking SGLT2 inhibitors. Data was obtained from the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) trial, focusing on type 2 diabetes patients with specific conditions like albuminuria or cardiovascular disease.

To validate the model, it was tested externally in two separate cohorts: the placebo arm of the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial, which included 996 participants with type 2 diabetes and high cardiovascular risk or established cardiovascular disease or, and another group comprising patients treated with canagliflozin. The study included 5,081 patients without HF and who had baseline measurements of NT-proBNP.

In the ALTITUDE trial, participants had a mean age of 64 years with a median serum NT-proBNP level of 157 pg/mL (with a range of 70-359 pg/mL). The study identified several significant and independent predictors of new-onset HF, including higher levels of NT-proBNP, TnT and BMI. Additionally, the model also incorporated urinary albumin-to-creatinine ratio, HbA1c, age, hematocrit, and the use of calcium channel blockers. The predictive model constructed from these variables demonstrated strong performance, with a C-statistic of 0.828 in the ALTITUDE. The validity of the model was further confirmed when applied to the CANVAS cohort, where it achieved a C-statistic of 0.800. When the model was applied to patients who received canagliflozin treatment for 1 year, its predictive performance improved, with a C-statistic of 0.847.

The development of a robust prediction model, as validated in this study, offers a promising clinical tool for early recognition of patients who are at a higher risk of new-onset HF. By leveraging these predictors, the treating clinicians can potentially stratify their type 2 diabetes according to their risk of developing HF. Early identification of the at-risk individuals enables timely personalized interventions including prevention strategies, ultimately improving clinical outcomes and reducing the burden of HF in patients with type 2 diabetes.

Reference

1. Said F, et al. Prediction of new-onset heart failure in patients with type 2 diabetes derived from ALTITUDE and CANVAS. Diabetes Obes Metab. 2024;26(7):2741-51.

Factors Influencing Time to Clinical Stability in Pediatric Pneumonia

Children with suspected CAP who were older or were dehydrated took longer to recover and reach clinical stability within 24 hours, according to new study published online on April 15, 2024 in the journal *Pediatrics*[1]. Younger age, absence of vomiting, decreased breath sounds and normal capillary refilling were the factors indicative of clinical stability.

The prospective cohort study included 571 children, aged 3 months to 18 years, from the CARPE DIEM (Catalyzing Ambulatory Research in Pneumonia Etiology and Diagnostic Innovations in Emergency Medicine) study, who had been hospitalized with suspected CAP from July 2013 to December 2017. The time from hospitalization to normalization of temperature, heart rate, respiratory rate, and oxygen saturation were the four parameters used to assess clinical stability. Through this study, the researchers aimed to understand the association between time to clinical stability (TCS) and disease severity, as well as to identify the factors that contribute to attaining early stability in children with suspected CAP.

Nearly one-third of the children (32.7%) had at least one abnormal parameter at discharge. Approximately 67% of children met all four criteria for clinical stability at discharge, while 7% had two abnormalities and 25% had one abnormality. None of the participants had ≥3 abnormal discharge parameters. The average hospitalization duration for patients with mild disease was 18.2 hours, while those with moderate disease including those receiving intravenous (IV) hydration or oxygen support had hospital stay of 40.8 hours. The length of stay was 70 hours for patients with serious disease.

Infants exhibited a higher proportion of having all four parameters stable at discharge compared to older children aged 12 to 18 years; 93% versus 49%, respectively. The median TCS for each parameter was <24 hours, indicating that most children achieved clinical stability relatively quickly after admission. "The median TCS for each parameter was <24 hours; respiratory rate was the least likely factor to reach stability at hospital release (65%), followed by heart rate (84%), temperature (95%), and oxygenation (97%)".

Clinical factors associated with earlier TCS during the course of the study were also identified. These were younger age, no vomiting, normal capillary refill and diffusely decreased breath sounds. Failure to attain stability did not necessarily correlate with the risk of post-discharge complications or disease recurrence.

Older children were less likely to reach clinical stability within 24 hours with adjusted odds ratio (aOR) of 0.96. Other factors associated with lower likelihood of reaching clinical stability within 24 hours were vomiting (aOR 0.77) and prolonged capillary refill (aOR 0.77).

This study found that several patient characteristics were associated with prolonged TCS. Older children were more likely to have 1 to 2 parameters that were unstable at discharge, as opposed to infants who were more typically discharged with all parameters stable. "*Older children and those admitted for IV fluids and potential dehydration may improve slower than other patients. Patients without these factors might be candidates for management on an observation or short-stay unit,*" write the authors.

Hence, all 4 parameters should be considered together for children hospitalized with CAP. This offers several benefits including improved assessment of disease recovery, optimized discharge planning, and potentially reduced health care resource utilization leading to more efficient health care delivery. By ensuring that all physiological parameters have normalized, TCS helps minimize the risk of premature discharge and reduces the likelihood of post-discharge complications or relapse.

Reference

1. Field MR, et al. Time to clinical stability in children with community-acquired pneumonia. Pediatrics. 2024;153(5):e2023063480.

Pediatric Hypertension and Long-Term Cardiovascular Outcomes

Is childhood hypertension associated with greater risk of adverse cardiovascular outcomes in the long-term? To answer this question, a team of researchers from Canada, South Africa, and the United States conducted a population-based, retrospective, matched cohort study of all Canadian children, aged 3 to 18 years, from 1996 to 2022[1]. Children undergoing dialysis or with kidney transplant were not included in the study group. Data for the study was obtained from provincial administrative health databases.

The study population comprised 25,605 children with hypertension and 1,28,025 controls without hypertension. The median age in the hypertensive group was 15 years and nearly 60% were boys. Each case was matched by age, sex, birth weight, maternal gestational hypertension, and prior comorbidities such as diabetes, chronic kidney disease (CKD), cardiovascular surgery with 5 nonhypertensive controls to control for potential confounding variables, and a propensity score for hypertension. Occurrence of major adverse cardiac events (MACE), a composite of cardiovascular death,

stroke, hospitalization for myocardial infarction or unstable angina, or coronary intervention was the primary study outcome. The baseline characteristics were well-balanced between the two groups after propensity score matching and prior comorbidities were uncommon (hypertension vs. control cohort: malignancy, 5.7% vs. 6.2%; congenital heart disease, 4.3% vs. 4.2%; diabetes, 1.9% vs. 1.9%).

Results published in *JAMA Pediatrics* show that over a follow-up period of ~14 years, the incidence of MACE, including stroke, myocardial infarction, unstable angina, coronary intervention and congestive HF was significantly higher in children with hypertension when compared with controls; 4.6 per 1,000 person-years in children with hypertension versus 2.2 per 1,000 person-years in controls with HR of 2.1. The probability of experiencing MACE was higher in children younger than 13 years of age and those with CKD.

Children with hypertension were at elevated risk for stroke (HR 2.7), hospitalization for myocardial infarction or unstable angina (HR 1.8), coronary intervention (HR 4.1), and congestive HF (HR 2.6) compared to nonhypertensive controls. They also had a higher likelihood of other cardiovascular diagnoses (HR 1.7) and undergoing cardiovascular procedures (HR 2.6) versus controls. Interestingly, there was no significant difference in the risk of cardiovascular death between children with hypertension and nonhypertensive controls.

According to this study, children with hypertension were found to be at double the risk of developing MACE than the control group without hypertension.

These findings point out the profound impact of elevated blood pressure (BP) in childhood on long-term cardiovascular health and emphasize the importance of proactive management early in life to prevent or delay future cardiovascular events in this population group. The median age of the study subjects at last follow-up was 27 in both groups. This is relatively younger than the age at which cardiovascular events are expected to occur. Early detection, follow-up, and management of hypertension in pediatric patients is therefore critical. Regular BP monitoring, lifestyle modification, and appropriate pharmacological interventions should be initiated and maintained throughout childhood and into adulthood to ensure optimal management of BP to optimize cardiovascular health outcomes.

Reference

1. Robinson CH, et al. Long-term cardiovascular outcomes in children and adolescents with hypertension. JAMA Pediatr. 2024 May 6.

Antibiotic Exposure and Risk of Atopic Dermatitis in Infants

Use of systemic antibiotics during the first year of life is associated with an increased risk of atopic dermatitis (AD). This heightened risk is likely mediated by disruption in the gut microbiome due to exposure to antibiotics. These findings were published online April 24, 2024 in the *Journal of Allergy and Clinical Immunology*[1].

Courtney Hoskinson, from the University of British Columbia in Vancouver, Canada, and colleagues conducted this study to understand the timing of antibiotic exposure, oral or IV, its impact on the early-life gut microbiome and their relationship with AD development. For this, they used participants from the CHILD study, a nationwide birth cohort study involving 3,621 pregnant women and 3,455 Canadian infants who were born at 34 weeks of gestation (minimum) and did not have any congenital malformation. It explores how genetics and environmental exposures in early childhood influence the development of asthma, allergies, and other chronic childhood diseases. Stool samples from a subgroup of infants with a complete antibiotic history were collected at 1 year and species abundance were compared.

It was observed that compared to antibiotic usage later in life, antibiotic exposure during infancy was linked with an increased risk of AD, with an aOR of 1.81. A dose-response relationship between the number of antibiotic courses and AD risk was noted. Infants who received one course of antibiotics had an aOR of 1.67 for developing AD, while those who received two or more courses had a higher aOR of 2.16.

Eighteen out of the 72 species tested were significantly altered in participants with AD and 15 were altered by antibiotic exposure. Certain alterations in the 1-year infant gut microbiome were identified to be associated with later development of AD. These included increase in *Tyzzerella nexilis*, increased monosaccharide utilization along with decrease in *Bifidobacterium* and *Eubacterium* spp. as well as decreased fermentative pathways.

Atopic dermatitis is the most prevalent chronic inflammatory skin condition. Its multifactorial etiology involves a complex interplay of genetic predisposition and environmental factors. Pediatric AD is also the first step in the allergic march followed by other allergic conditions such as food allergy, allergic rhinitis and allergic asthma.

This study demonstrates a significant association between systemic antibiotics administered during the first year of life and an increased risk of AD. It elucidates

that early antibiotic use alters the microbial taxa, which subsequently contribute to the pathogenesis of AD. "*Microbiome alterations associated with both AD and systemic antibiotic usage fully mediate the effect of antibiotic usage on the development of AD*", write the authors.

These findings highlight the importance of the gut microbiome in modulating immune function and increasing susceptibility to inflammatory skin diseases like AD. It underscores the need for minimizing unnecessary antibiotic usage during infancy and the potential for microbiome-targeted preventative strategies to mitigate the adverse effects of antibiotic exposure on immune health and reduce the risk of developing AD in infancy.

Reference

1. Hoskinson C, et al. Antibiotics within first year are linked to infant gut microbiome disruption and elevated atopic dermatitis risk. J Allergy Clin Immunol. 2024 Apr 24:S0091-6749(24)00409-3.

Dry Eye Disease and Type 2 Diabetic Nephropathy

More than half of patients with type 2 diabetic nephropathy have dry eye disease, suggests a study from Vietnam published May 6, 2024 in the journal *Clinical Ophthalmology*[1]. Advanced age, high HbA1c levels and decreased estimated glomerular filtration rate (eGFR) were identified as factors that were independently associated with dry eye disease.

A total of 338 individuals, consisting of 169 patients with type 2 diabetic nephropathy and 169 patients with type 2 diabetes but without renal complications as a control group, were included in this cross-sectional study. All subjects were evaluated for Ocular Surface Disease Index (OSDI) via a questionnaire and test fluorescein tear-film break-up time (TBUT). Patients with OSDI scores <13 and TBUT values ≤10 seconds were diagnosed with dry eye. The aim of this cross-sectional study was to determine the prevalence of dry eye among patients with type 2 diabetic nephropathy and also identify factors potentially associated with dry eye in these patients.

The prevalence of dry eye among type 2 diabetic nephropathy patients was found to be significantly higher than the control group, with rates of 55.6% versus 37.3%, respectively. They had higher OSDI scores but lower TBUT than the type 2 diabetes alone group.

The type 2 diabetic nephropathy patients with dry eye were older and had a longer duration of diabetes. They also had a higher percentage of participants with hypertension, peripheral nerve complications, anemia including insulin users compared with those without dry eye in the group. This subgroup also had higher levels of plasma glucose, HbA1c, urea, creatinine and high-sensitivity C-reactive protein.

Advanced age, high HbA1c level and decreased eGFR were identified as independent factors associated with dry eye in type 2 diabetic nephropathy patients.

This study highlights dry eye as a common condition in patients with type 2 diabetic nephropathy compared to those with type 2 diabetes mellitus without renal complications. The authors note, "*kidney complications and eye complications often go together, and 'renal-retinal syndrome' originates from this coincidence*". It further elucidates on potential risk factors contributing to a better understanding of ocular complications in this population.

Reference

1. Tran Tat T, et al. Dry eye and some related factors in patients with type 2 diabetic nephropathy: a cross-sectional study in Vietnam. Clin Ophthalmol. 2024:18:1217-24.

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