

Workshop for "aktive" forskere

Torsdag den 18. og fredag den 19. november 2010

Torvehallerne
Kirketorvet 10-16
7100 Vejle



Dr Jaime Ferrán, opfinder af cholera-vaccinen, så til 50.000 blev vaccineret under cholera-epidemien i Valencia i 1885

Program

Torsdag d. 18.11.2010

Chairman, Jens Lundgren

- 14.00-14.15 Lars Haukali Omland, Rigshospitalet. Levercancer og Non-Hodgkin Lymfom blandt Hepatitis C Virus-inficerede patienter: Resultater fra DANVIR kohorten.
- 14.15-14.30 Lene Ryom, CHIP, Københavns Universitet. Chronic kidney disease in HIV patients with normal eGFR at baseline - results from EuroSIDA.
- 14.30-14.45 Thomas A Rasmussen, Århus Universitets Hospital. Serum Procalcitonin in Pulmonary Tuberculosis
- 14.45-15.00 Lilian Kolte, Hvidovre Hospital. Increase in CD4+CD25+CD127^{low} FOXP3+Regulatory T-cells (Tregs) during second Trimester: Comparison of Immunological measurements in HIV-infected and HIV-negative Pregnant Women.
- 15.00–15.15 Lotte Rodkjær, Århus Universitets Hospital. Changes in depression in a Cohort of Danish HIV-positive individuals: time for routine screening.
- 15.15–15.30 Katrine Meyer Jensen, Århus Universitets Hospital. Immunity against Nasopharyngeal Pneumococcal Colonization in Mice after administration of TLR9 Adjuvants and Pneumococcal Vaccination.

15.30 – 16.00 Pause

Chairman, Jens Ole Nielsen

- 16.00–16.15 Daria Podlekareva, University of Copenhagen, Copenhagen HIV Programme Health care index score and outcome following TB diagnosis in HIV-infected patients.
- 16.15–16.30 Ole Kirk, University of Copenhagen, Copenhagen HIV Programme Vitamin D and clinical disease progression in HIV infection: results from the EuroSIDA study.
- 16.30-16.45 Tavs Qvist, Rigshospitalet. No increase in the detection of non-tuberculous mycobacterial infections at the Copenhagen CF Centre over the last 19 years.
- 16.45-17.00 Peter Ellekvist, Københavns Universitet. Potassium channels as drug targets in Plasmodium parasites.

Chairman, Niels Obel

- 17.00-17.30 Professor Aase Bengaard Andersen, Odense Universitetshospital. Infektionsmedicinsk forskning: hvem, hvorfor, hvordan?
- 17.30-18.00 Professor Niels Frimodt-Møller, Statens Seruminstitut: Antibiotikaforskning med mere - på SSI anno 2010.
- 19.00 **Middag**

Fredag d. 19.11.2010

Chairman, Henrik Nielsen

- 9.00-09.15 Ann-Brit Eg Hansen, Rigshospitalet. Substitution af zidovudin med non nukleosid-analog eller lopinavir/ritonavir hos HIV positive som tidligere er behandlet med zidovudin, lamivudin og abacavir – indflydelse på metaboliske forstyrrelser. TRI-SPAR-studiet.
- 09.15-09.30 Jannie Pedersen, Hvidovre Hospital. The significance of neutralizing antibodies as predictor for achieving effect after treatment with pegylated interferon and ribavirin in patients with chronic hepatitis C.
- 09.30-09.45 Hans Jakob Hartling, Rigshospitalet. Betydning af regulatoriske T-celler for udvikling af inflammation og fibrose hos patienter med kronisk hepatitis C.
- 09.45-10.00 Jannik Helweg-Larsen, Rigshospitalet. Peroral antibiotisk behandling af endocarditis? – Metodologiske og historiske aspekter ved planlægning af et dansk non-inferiority trial.
- 10.00-10.15 Marianne H. Spanggaard, Ålborg Hospital. Short-term gentamicin therapy and risk of renal toxicity in medical patients with bacteraemia.
- 10.15-10.30 Hans Linde Nielsen, Ålborg Hospital. Clinical epidemiology and manifestations of *Campylobacter concisus*.
- 10.30-11.00 **Pause**

Chairman, Peter Skinhøj

- 11.00-11.15 Reimar W. Thomsen, Århus Universitets Hospital. Diabetes, Glycemic control and risk of bacteremia with hemolytic streptococci group A,B and G in adults: a 15-year population-based case-control study.
- 11.15-11.30 Jette Brommann Kornum, Århus Universitets Hospital. Alcohol drinking and risk of subsequent hospitalization with pneumonia.
- 11.30-11.45 Birgitte Lindegaard, Rigshospitalet. IL-18 increases intramuscular fat oxidation by activating AMPK.
- 11.45-12.00 Henriette S. Nielsen, Statens Seruminstitut. Antibody response to the 2009 pandemic H1N1 influenza virus following infection or vaccination.
- 12.00 **Frokost og afrejse**

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Patienters adhærens ved behandling af HIV – nye udfordringer

Toke Barfod og Jan Gerstoft

Epidemiklinikken M, Rigshospitalet.

Præsenterende forfatter: Toke Barfod, e-mail: Toke.barfod@dadlnet.dk

I perioden 2000- 2005 interviewedes 20 hiv-positive patienter på RH kvalitativt om deres medicinindtag. Hovedfundene var, at

- Mange faktorer interagerede, herunder bivirkninger, patientens holdninger til sygdommen og behandlingen, relationen til lægen, patientens livsstil, rutiner og vaner for medicinindtag og omverdenens reaktioner.
- Patienterne var ofte ikke selv opmærksomme på disse faktoreres betydning, før de blev afdækket i løbet af længere samtale
- Patienterne fortalte ofte ikke deres faste læge om deres manglende medicinindtag

Dengang i 2000 havde cirka halvdelen af patienterne virologisk behandlingssvigt. Nu her 10 år efter, er cirka 80 procent af patienterne velbehandlede.

Vi formoder, at flere faktorer spiller ind i den positive udvikling.

- Behandlingerne er blevet nemmere at tage, idet der er færre tabletter, færre daglige doser, ingen måltidsrestriktioner og der er færre bivirkninger
- Behandlingerne er blevet stærkere (mere "tilgivende")
- Behandlingssystemet er blevet mere opmærksomt på betydningen af adhærens og god kommunikation herom med patienten
- Stemningen blandt patienterne er vendt, idet subkulturene har accepteret behandlingen som god og nødvendig frem for at behandlingen havde et image som lægernes projekt og noget giftigt stads

Selvom det går bedre, er ufuldstændig adhærens dog stadigvæk den primære årsag til behandlingssvigt.

- Man har indtryk af, at de patienter, der aktuelt har adhærensproblemer har massive psykosociale problemer.
- Man har også indtryk af, at der blandt behandlere er opstået en træthed, således at man har vanskeligt ved at opretholde entusiasmen overfor rådgivning og vejledning i adhærens.

For at undersøge disse formodninger og indtryk, planlægges det derfor nu at gen-interviewe patienterne. Patienterne vil blive tilbudt en samtale, hvor der følges op på de specifikke faktorer, der gjorde det let eller vanskeligt for dem at tage deres medicin, og hvor de vil kunne fortælle om, hvad de oplever af ændringer. På workshoppen ønsker vi med deltagerne at diskutere styrker og svagheder ved studiets formål og metode.

Primary health care workers' perception of diagnostic challenges in childhood tuberculosis – Tanzania 2010

Stephanie Bjerrum¹, Michala V. Rose¹, Pernille Ravn¹ og Ib Bygbjerg²

1)Hvidovre Hospital, Infektionsmedicinsk afdeling og 2)Faculty Of Health Sciences, CSS
Presenting author: Stephanie Bjerrum, e-mail: steph@medicinsk.dk

Background: Diagnosing tuberculosis (TB) in children remains a great challenge in developing countries where access to diagnostic procedures is limited. Repeated visits at primary health care level without reaching correct diagnosis has been identified as a core reason for diagnostic delay. Being the first and often only contact to the health system, the primary health care (PHC) workers at community level have a crucial role in identifying suspect TB cases, and it is essential that they feel equipped to recognize signs and symptoms of childhood TB. This study aims to qualitatively explore PHC workers' opinions on the challenges they face in diagnosing children with TB, and how they wish to address those challenges.

Methods: Thirteen (13) semi structured interviews and three (3) focus group discussions were conducted with PHC workers in Tanga Region, Tanzania. All interviews and focus group discussions were recorded, translated and transcribed. The data was coded and thematically analysed using a framework approach.

Results: The findings show, that PHC workers did not consider childhood TB to be a significant problem in the society. Establishment of the TB diagnosis was considered to require advanced medical skills and tests, which only were available in hospitals. PHC workers felt responsible for identifying suspected cases of childhood TB and referring these cases to the nearest hospital. Surprisingly, PHC workers claimed it unproblematic to differentiate TB from other common diseases with a similar clinical presentation, and they rarely found indication for referring cases to hospital. PHC workers primarily suspected TB in cases with long duration of pronounced symptoms and with inadequate response to antimalaria or regular antibiotic treatment. Low awareness of childhood TB among the PHC workers was ranked as the most important challenge and all PHC workers perceived effective guidelines and training in childhood TB to be urgently needed.

Conclusion: Our study revealed that PHC workers consider childhood TB to be a problem of limited public health relevance. Cases are primarily suspected based on symptoms characteristic for progressed disease, which could indicate a missed opportunity for case finding and early detection. Based on the PHC workers' expressed motivation, there seems to be an opportunity to improve case identification through training and guidelines, as well as drawing in evidence from other TB research projects.

***Staphylococcus aureus* skin and soft tissue infections in primary healthcare in Denmark: a 12-year population-based study**

Michael Dalager-Pedersen¹, Mette Sogaard^{1,2} and Henrik Carl Schönheyder¹

¹*Department of Clinical Microbiology, Aalborg Hospital, Aarhus University Hospital, Aalborg and*

²*Department of Clinical Epidemiology, Clinical Institute, Aarhus University Hospital, Aarhus, Denmark*

Corresponding author: Michael Dalager-Pedersen, Department of Infectious Diseases, Aalborg Hospital, Aarhus University Hospital, Aalborg, Hobrovej 18-22, 9000 Aalborg, Denmark

Telephone +45 9932 6536, telefax +45 9932 3216,

Presenting author: Michael Dalager-Pedersen, e-mail: midp@rn.dk

SUMMARY

A rise in community-onset *Staphylococcus aureus* infections has been observed in European countries. To ascertain secular trends of *S. aureus* infections in primary healthcare in Denmark, we conducted this register-based study in North Denmark Region, 1997-2008. We identified all skin and mucosa specimens obtained by general practitioners and all dicloxacillin prescriptions redeemed at local pharmacies. Repeat observations within a 12 month period were excluded prior to calculation of age and gender standardized incidence rates per 100.000 person-years.

We included 108,758 specimens of which 42,778 (39%) yielded *S. aureus*. The annual incidence rate of specimens doubled during the study period reaching 2,399 in 2008. The overall rate of *S. aureus* isolates increased 2-fold to a stable rate at about 850, but for isolates from children and impetigo specimens the increase was higher with a peak in 2002. A total of 156,462 dicloxacillin prescriptions had been prescribed; the annual prescription rate increased 2.5-fold from 1997-2008, peaking at 3,714 in 2007.

In conclusion, annual rates of specimens, *S. aureus* infections and dicloxacillin prescriptions more than doubled in primary healthcare during the study period. Most likely underlying factors were an impetigo epidemic and awareness of emerging antimicrobial resistance.

Potassium channels as drug targets in *Plasmodium* parasites.

Ellekvist P¹, Mlambo G², Maciel J², Luciani MH¹, Klaerke DA¹, and Kumar N²

¹Dept. of Physiology & Biochemistry, LIFE faculty, University of Copenhagen, DK1870-Frederiksberg;

²Malaria Research Institute, Johns Hopkins Bloomberg School of Public Health, MD-21205 Baltimore.

Presenting author: Peter Ellekvist, e-mail: p.ellekvist@dadlnet.dk

Background: Potassium channels are integral membrane proteins, which contribute to maintain vital parameters such as the cellular membrane potential and cell volume. Malaria parasites encode two K⁺ channel homologues, Kch1 and Kch2, which are well-conserved among members of the *Plasmodium* genus.

Methods: In the rodent malaria parasite *P. berghei*, the two K⁺ channel homologues, PbKch1 and PbKch2, were studied using targeted gene knock-out. The transgenic parasites were characterized in a mouse model in terms of growth-kinetics and transmission potential. Second, using a tracer-uptake technique and ⁸⁶Rb⁺ as a K⁺ congener, the K⁺ transporting properties of the transgenic parasites were assessed. Third, the impact on parasite membrane potential of the two K⁺ channels was investigated using a potential-dependent fluorophore DiBAC4 bis-oxonol.

Results: Knock-out of either K⁺ channel did not grossly affect the phenotypes in terms of asexual replication and pathogenicity in a mouse model. However, *P. berghei* parasites deficient in PbKch1 (PbKch1-null parasites), but not PbKch2-null parasites, were unable to form oocysts in female *Anopheles stephensi* mosquitoes. PbKch1-null parasites, but not PbKch2-null parasites, had a low ⁸⁶Rb⁺ uptake, when compared to wild-type (WT) parasites. The Kch1-mediated ⁸⁶Rb⁺ uptake was inhibited by K⁺ channel blockers; the residual, non-Kch1-mediated, ⁸⁶Rb⁺ uptake was not sensitive to further inhibition by K⁺ channel blockers. Finally, Kch1, but not Kch2, apparently influenced the membrane potential of the parasites.

Conclusion: Our studies suggest unequivocally that *Plasmodium* K⁺ channel 1 homologue is a functioning K⁺ channel, which contributes to the K⁺ permeability of the parasites plasma membrane. The channel is, for yet unknown reasons, necessary for sexual replication of *P. berghei* parasites in the mosquito midgut. These studies provide a rationale for pharmacological inhibition of the Kch1 orthologue in human parasites as a novel strategy to disrupt malaria transmission.

Lung cancer in HIV patients and their parents: A Danish cohort study.

Frederik N Engsig¹, Gitte Kronborg², Carsten S Larsen³, Gitte Pedersen⁴, Jan Gerstoft¹, Niels Obel¹.

¹*Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet*

²*Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre*

³*Department of Infectious Diseases, Aarhus University Hospital*

⁴*Department of Infectious Diseases, Aalborg University Hospital*

Background: The mechanism for the increased risk of lung cancer observed in HIV patients is controversial.

Methods: We estimated the cumulative incidence and relative risk of lung cancer in 1) a population of all Danish HIV patients identified from the Danish HIV Cohort Study (n=4571) and a cohort of population controls matched on age and gender (n=63,994) (study period; 1995 – 2007) and 2) these individuals parents (study period; 1969 – 2007). Mortality and relative risk of death after a diagnosis of lung cancer was estimated in both populations.

Results: 29 (0.6%) HIV patients vs. 183 (0.4%) population controls were diagnosed with lung cancer in the observation period. HIV patients had an increased risk of lung cancer (unadjusted incidence rate ratio (IRR): 2.10 (95% CI; 1.37 – 2.65) adjusted IRR 2.50 (95% CI; 1.68 – 3.70) adjusted). The IRR was considerably increased in HIV patients with heterosexual route of infection (Unadjusted IRR; 2.80 (1.38 – 5.67), adjusted IRR; 3.44 (1.69 – 6.99)) and prior AIDS defining events (Unadjusted IRR; 5.51 (2.10 – 14.47), adjusted IRR; 6.21 (2.35 – 16.42)) whereas low baseline CD4 cell count did not affect the IRR. Both fathers and mothers of HIV patients had an increased risk of lung cancer but only significantly for the fathers (IRR: 1.36 (95% CI: 1.11 - 1.66) and adjusted 1.29 (95% CI: 1.05 – 1.59)). Mortality after lung cancer diagnose was increased in HIV patients (unadjusted mortality rate ratio 2.26 (95%CI; 1.39 – 3.69), adjusted 2.28 (95%CI; 1.40 – 3.71)). The parents of HIV patients diagnosed with lung cancer were not at increased risk for death.

Conclusion: HIV appears to be a marker of environmental or familiar risk factors that affect the incidence of lung cancer in HIV infected individuals independently of immunosuppression.

Depression og hepatitis C blandt stofmisbrugere

Thilde Fabricius , Lone Wulff Madsen , Peer Brehm Christensen

Infektionsmedicinsk afd Q, Odense Universitets Hospital

Præsenterende forfatter: Thilde Fabricius, e-mail: thif@mail.dk

Behandling for hepatitis C med pegyleret interferon (pegasys) i kombination med ribavirin har vist at kunne øge risikoen for udvikling af depression, og dermed være en medvirkende årsag til forringet compliance og for tidligt ophør af den antivirale behandling. I et nyligt skandinavisk arbejde udviklede 1/3 af patienterne i behandling for hepatitis C depression under interferon behandling og kun 1/3 af disse blev erkendt af de behandlende læger (Leutscher et al). Der er evidens for at behandlingen af hepatitis C øger risikoen for udvikling af depression. Flere studier har desuden antydnet, at HCV i sig selv påvirker hjernen og kan være en medvirkende årsag til depression. Imidlertid er de fleste screeningsredskaber udviklet blandt psykiatriske patienter og afprøvet på normalbefolkningen, og ikke blandt gruppen med den højeste forekomst af hepatitis C – nemlig intravenøse stofmisbrugere - hvor halvdelen er kronisk inficeret med HCV [2].

Denne gruppe adskiller sig på en række punkter fra de ovennævnte undersøgte grupper, ved, udover selve sygdommen, at have flere disponerende faktorer for udvikling af depression.

Vi har derfor valgt at lave et tværsnitsstudie blandt klienter tilknyttet rusmiddelcentrene på Fyn, hvor der i perioden fra oktober 2010 til januar 2011 skal foretages depressions scoring ved hjælp af MDI skemaet blandt alle klienterne uafhængigt af HCV status. Vores mål er at få inkluderet minimum 400 misbrugere. Efterfølgende indsamles data omfattende oplysninger om stofmisbrug, hepatitis- og HIV status, psykiatriske diagnoser og indlæggelser samt psykofarmakaforbrug. Desuden skal der indhentes oplysninger om psykosociale forhold der kan have en betydning for udfaldet af resultaterne på depressions scoren.

Ud fra disse oplysninger skal vi forsøge at belyse hvorvidt MDI skemaet er et brugbart værktøj i screeningen for depression blandt stofmisbrugere, samt forsøge at belyse en eventuel sammenhæng mellem depression og hepatitis C status.

Ud fra MDI skemaet klassificeres klienterne i kategorierne let, moderat eller svær depression, og denne inddeling sammenholdes med de allerede eksisterende depressionsdiagnoser stillet af rusmiddelcentrets læger.

Projektet gennemføres som et tillæg til igangværende projekter vedrørende hepatitis blandt stofmisbrugere (fibrosescreening og Best studierne).

Substitution af zidovudin med non nukleosid-analog eller lopinavir/ritonavir hos HIV positive som tidligere er behandlet med zidovudin, lamivudin og abacavir – indflydelse på metaboliske forstyrrelser. TRI-SPAR studiet

Ann-Brit Eg Hansen, Niels Obel, Lars Mathiesen, Court Pedersen, Alex Laursen, Jan Gerstoft

Presenting author: Ann-Britt Eg Hansen, e-mail: ann-brit.eg.hansen@rh.regionh.dk

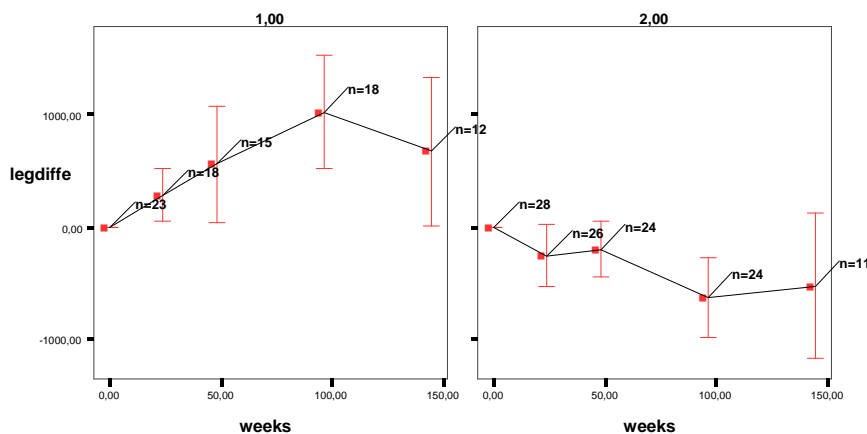
Objective: To assess metabolic changes after discontinuation of zidovudine including evolution of peripheral fat mass and bone mineral density (BMD).

Methods: HIV-1 infected patients with undetectable viral load receiving treatment with zidovudine/lamivudine/abacavir (Trizivir) were eligible for this non-randomised prospective study. Patients were offered to switch zidovudine to efavirenz, nevirapine or lopinavir/ritonavir [the non-Trizivir group] or to continue Trizivir. Patients were evaluated at 12 week intervals until week 144. We used dual energy X-ray absorptiometry (DEXA) to assess regional body composition as well as lumbar spine and femoral neck (hip) BMD at baseline, week 24, 48, 96 and 144.

Results: 60 patients were included, of whom 26 switched zidovudine to efavirenz (N=14), nevirapine (N=8) or lopinavir/ritonavir (N=4) while 34 patients continued Trizivir.

Antiretroviral efficacy: There was no difference between the two groups in proportion of patients with undetectable viral load (<40) at any time point. Two patients in the non-Trizivir group developed virological failure (both on efavirenz). CD4 cell count increased more in the non-Trizivir group compared with the Trizivir group: the median values were (68 vs. 0 cells/ μ l, $p=0.2$), (98 vs. 21 cells/ μ l, $p=0.04$), (130 vs. 40 cells/ μ l, $p=0.05$) and (117 vs. 60 cells/ μ l, $p=0.2$) at week 24, 48, 96, and 144 respectively.

Body composition and BMD: Patients in the non-Trizivir group gained peripheral fat measured as leg fat while peripheral fat mass decreased in the Trizivir group. Figure 1 displays the changes in leg fat mass compared with baseline (1 non-Trizivir; 2 Trizivir).



Both spine and hip BMD were stable over time with no significant differences between arms at any time point. The mean percentage changes from baseline in spine BMD were 0.6% (95% CI; -0.9 to 2.1) at week 96 and 2.3% (95% CI; -0.1 to 4.7) at week 144. For hip BMD the mean percentage changes from baseline were 1.3% (95% CI; -1.1 to 3.8) at week 96 and 1.5% (95% CI; -1.5 to 4.5) at week 144, respectively.

Conclusion: Discontinuation of zidovudine was followed by an increase in CD4 cell count and by increase in peripheral fat mass. We did not observe an adverse effect of ongoing HAART on spine or hip BMD during three years of follow-up.

Betydning af regulatoriske T-celler for udvikling af inflammation og fibrose hos patienter med kronisk hepatitis C

Hans Jakob Hartling¹, Julie Christine Gaardbo¹, Lene Surland Knudsen¹, Henrik Ullum², Ben Vainer³, Helle Bruunsgaard⁴, Mette Rye Clausen⁵, Jan Gerstoft¹, Susanne Dam Nielsen¹

(1) Epidemiklinikken, (2) Blodbanken, (3) Patologifdelingen, (4) Center for Inflammation og Metabolisme, (5) Hepatologisk Afdeling, Rigshospitalet

Præsenterende forfatter: Hans Jakob Hartling, e-mail: hj@hartling.dk

Introduktion: Hepatitis C virus (HCV) vil hos 70 % af smittede forårsage kronisk hepatitis med gradvis udvikling af leverfibrose. Hos omkring en tredjedel vil dette føre til cirrose inden for 20-30 år. Heraf vil 1-4 % pr. år udvikle hepatocellulært karcinom. Der er endnu ingen god forklaring på, hvorfor nogle individer med kronisk infektion med HCV ikke udvikler fibrose, mens andre udvikler alvorlig lever-påvirkning med fibrose og cirrose. En mulighed er, at de såkaldte regulatoriske T-celler (Tregs) spiller en rolle.

Tregs er en undergruppe af CD4+ celler, der menes at have en vigtig immunmodulerende rolle, idet Tregs har en suppresserende effekt på T-celler og hæmmer CD4+ såvel som CD8+ celler.

Et for lavt Treg-niveau kan være en vigtig del af den proces, der fører til udvikling af inflammation og fibrose. Ligeledes er det vist, at patienter med kronisk HCV infektion har et højere Treg-niveau end patienter med clearret HCV infektion og raske kontroller, hvilket på samme vis kan være en fordel for patienten med kronisk HCV infektion ved at inflammation og fibrose begrænses.

Formålet med dette studie er at undersøge en eventuel sammenhæng mellem Tregs, inflammation og leverfibrose hos patienter med kronisk HCV.

Materiale/metode: Ved et tværsnitstudie sammenlignes en immunologisk profil (inkl. Tregs) og fibrosegraden hos 120 patienter fordelt i fire grupper, hhv. (1) patienter med kronisk hepatitis C med fibrose, (2) patienter med kronisk hepatitis C uden fibrose, (3) patienter co-inficeret med HCV og HIV og (4) alders- og køns-matchedde raske kontroller.

Ved flowcytometri undersøges for Tregs (CD4+CD25+CD127^{low} og FOXP3⁺), aktiverede T-celler (CD38+HLA-DR⁺), naive T-celler (CD45RA+CD27+CCR7⁺) og aldrende T-celler (CD8+CD57+CD28⁻). Derudover undersøges pro- og anti-inflammatoriske cytokiner samt cytokiner for Th1 (IFN- γ , IL-12, TNF- α), Th2 (IL-10, IL-4), Th17 (IL-17, IL-23) og Tregs (TGF- β , IL-10) via luminex.

Fibrosegraden vurderes ved fibroskanning.

Resultater: Analyserne af flowcytometri-data er påbegyndt og de første resultater vil være klar til præsentation til workshop d. 18. november. I henhold til vores hypotese forventer vi at finde et højere niveau af Tregs hos HCV-patienter sammenlignet med raske kontroller og et højere niveau af Tregs hos HCV-patienter uden fibrose sammenlignet med HCV-patienter med fibrose.

Diskussion/Perspektivering: Studiet er hypotesegenerende og forøget viden om interaktionen mellem HCV og immunsystemet vil på sigt kunne medvirke til at afklare spørgsmålet om, hvorfor nogle med kronisk HCV bliver syge, mens andre forbliver raske.

Peroral antibiotisk behandling af endocarditis?- Metodologiske og historiske aspekter ved planlægning af et dansk non-inferiority trial.

Jannik Helweg-Larsen

Epidemiklinikken, Rigshospitalet

Præsenterende forfatter: Jannik Helweg-Larsen, e-mail: jhelweg@dadlnet.dk

Traditionelt gives ved endokardit langvarig intravenøs antibiotisk behandling. Afkortning af intravenøs antibiotisk behandling med overgang til peroral antibiotisk behandling burde være muligt, men der foreligger kun relativt sporadisk dokumentation af dette, primært for højresidig endokardit.

Med udgangspunkt i en- forhåbentligt- kommende dansk undersøgelse af peroral antibiotisk behandling, som aktuelt er under planlægning (præliminær arbejdsgruppe: RH: Kardiologisk afdeling: Kasper Iversen, Henning Bundgaard, Christian Hassager; KMA: Claus Moser og Epidemiafdelingen: Jannik Helweg-Larsen, samt BBH: Kardiologisk afdeling: Nis Høst) , vil jeg diskutere metodologiske problemer/aspekter ved planlægning af et non-inferiority trial med udgangspunkt i historiske data for effekt af antibiotika ved infektiøs endokardit. Diskussionen vil også berøre EMEA+ FDAs guidelines for non-inferiority trials.

SIRS og sepsis blandt akutte medicinske patienter

Daniel Henriksen¹, Annmarie Lassen², Hanne Madsen², Court Pedersen³

¹Klinisk Institut, Det Sundhedsvidenskabelige Fakultet, Syddansk Universitet, ²Akut Medicinsk Modtageafdeling AMA, OUH, ³Infektionsmedicinsk afdeling Q, OUH

Præsenterende forfatter: Daniel Henriksen, e-mail: henriksen.dp@gmail.com

Baggrund: Svær sepsis og septisk shock er livstruende tilstande men den eksakte hyppighed i Danmark og resten af Europa er ukendt. Forekomst og anvendelighed af symptomer på systemisk inflammatorisk respons (SIRS) i den primære vurdering hos akutte medicinske patienter er ligeledes ukendt.

Formål: At beskrive incidens, risikofaktorer og prognose af SIRS, samfundserhvervet infektion, sepsis, svær sepsis og septisk shock blandt uselekterede akut indlagte medicinske patienter.

Metode: Et prospektivt studie af alle patienter, der bliver indlagt i akut medicinsk modtageafdeling samt alle patienter indlagt via skadestue/lægeambulance direkte i medicinsk intensivt regi på OUH i en etårig periode. Alle indlagte patienter får rutinemæssigt registreret vital-værdier ved ankomst (blodtryk, puls, respirationsfrekvens, temperatur) samt taget blodprøver inklusiv leukocytal. På basis af journaloplysninger afgøres det om patienten - i henhold til prædefinerede kriterier - har SIRS, infektion, sepsis, svær sepsis samt septisk shock ved ankomst eller udviklet indenfor det første døgn.

Alle, der på et eller andet tidspunkt indenfor inklusionsperioden har været beboer i OUHs optageområde, fungerer som kontroller og tildeles en indexdato indenfor rekrutteringsperioden.

For patienter og kontroller indhentes data fra landspatientregistret, cancerregistret, alkohol- og narkobehandlingsregistret, Odense pharmakoepidemiologiske database og CPR registret.

Analyseplan: Der planlægges 3 hovedstudier:

- 1) Tværnsnitsbeskrivelse af patienter i akut medicinsk regi med beskrivelse af total antal indlæggelser for SIRS, samfundserhvervet infektion, SIRS uden infektion, sepsis, svær sepsis og septisk shock pr. 1000 akutte medicinske indlæggelser samt pr. 100.000 personer i baggrundsbefolkningen.
- 2) Case-kontrolundersøgelse med henblik på afklaring af risikofaktorer for indlæggelse med SIRS, samfundserhvervet infektion, sepsis, svær sepsis og septisk shock.
- 3) Kohorte undersøgelse til beskrivelse af 30 dages mortalitet for indlæggelse med SIRS, samfundserhvervet infektion, sepsis, svær sepsis og septisk shock.

Status: Dataindsamlingsmodulet er etableret med semi automatisk rekruttering af data fra elektronisk patientjournal. Indskrevet som Ph.d. studerende pr. 1/8 2010. Pilotstudie med dataindsamling afsluttet vellykket 1/8 2010. Start på et årigt patientregistreringsforløb 1/9 2010.

Immunity against Nasopharyngeal Pneumococcal Colonization in Mice after administration of TLR9 Adjuvants and Pneumococcal Vaccination

Katrine M. Jensen¹, Martin Tolstrup¹, Frederik Dagnaes-Hansen², Uffe S. Sørensen², Jesper Melchjorsen¹, Lars Østergaard¹ and Ole S. Søgaard¹

¹*Department of Infectious Diseases, Aarhus University Hospital, Skejby, Denmark*

²*Department of Medical Microbiology and Immunology, Aarhus University, Aarhus C, Denmark*

Presenting author: Katrine Meyer Jensen, e-mail: katrine_meyer@hotmail.com

Introduction: Based on previous studies we hypothesized, that cellular immunity following pneumococcal conjugated vaccination in mice could be enhanced by coadministration of a TLR9 adjuvant, leading to reduced nasopharyngeal pneumococcal colonization.

Material and methods: Four groups of 12 female Balb/c mice were immunized twice with either the 7-valent pneumococcal conjugate vaccine, prevenar (7vPnC) alone; ODN 1826 (TLR9 adjuvant) alone, 7vPnC+ODN 1826, or PBS buffer. After 5 weeks serum samples were obtained to quantify antibodies against pneumococcus polysaccharide type 6B and 14 by ELISA. Six weeks after the first immunization the mice were challenged intranasally with $\approx 10^6$ cfu of pneumococcus serotype 6B strain O603. We performed an upper respiratory wash one week after challenge through the transected trachea, and collected the first six drops from the nostrils. After serial dilution and culturing on blood agar plates containing 5 mg/mL gentamycin, pneumococcal colony forming units were counted in the tracheal wash. We used capsular reaction test with diagnostic pneumococcal antiserum to verify that counted colonies represented pneumococcus serotype 6B.

Results: The colonization study indicated that mice vaccinated with ODN1826 alone were least colonized and hence display the best protection. Furthermore, it seemed that 7vPnC in combination with ODN1826 off set the protective effect of both the vaccine ($p = 0,056$) and the adjuvant ($p = 0,007$). Colonization was significantly higher in the PBS group compared to the ODN 1826 group ($p = 0,014$). Correlations were made with the Mann-Whitney test. We found no difference in antibody responses between the 7vPnC and 7vPnC+ODN 1826 groups. As expected neither ODN 1826 alone nor PBS raised antibodies. A correlation analysis with Pearsons test of the antibody level and colonization indicated, that it may be a disadvantage to have high levels of antibodies against type 6B in terms of protection against pneumococcal nasopharyngeal colonization, although, this was not statistically significant.

Perspective and further investigation: The results are somewhat surprising but data appear valid and consistent. The levels of CFU recovered after colonization are very similar to observations in other studies and the intra-group variation was satisfactory. Based on recently published studies we now have the presumption, that the time of administration of ODN 1826 is essential for its possible potentiating effect on 7vPnC. The observation of ODN 1826 being the most protective intervention of all given alone, and the confirmation that it is not inducing any antibody response, makes it really interesting to investigate in greater detail. The fact that co-administration of vaccine antigen and adjuvant appear inferior to adjuvant alone is puzzling.

We intend to investigate whether ODN 1826 is also mediating protection in B-cell depleted mice. Furthermore we have initiated a study to explore how the vaccine dosing influences T-cell immunology. It has been suggested that vaccination with polysaccharides induce CD4 T cell memory.

The Cooling And Surviving Septic shock study (CASS): Protokolabstract

J.U. Jensen^{1,2}, M. E. Johansen^{1,2}, E.K. Tønnesen³, L. Hein⁴, M. Bestle⁴, T. Mohr⁵, K. M. Larsen³, J. Løken⁶, M. Steensen⁶, P. Carl⁶, Z. Fox^{1,7}, H. Toubi⁸, P. Sjøe-Jensen⁸, H.C. Boesen⁹, D. Strange⁹, N. Reiter¹⁰, K. Thormar⁵, P. Fjeldborg¹¹, M. H. Andersen³, N.E. Drenck¹⁰, C. Ostergaard¹², P. Toft¹³, B. Lundgren¹⁴, J. Grarup, D¹, J. D. Lundgren¹

1. Copenhagen HIV Programme, Det Sundhedsvidenskabelige Fakultet, Kbh. Universitet, 2. Klinisk Mikrobiologisk Afd. 445, Hvidovre Hospital*, 3. Anæstesiologisk Afdeling, Århus Sygehus**, 4. Anæstesiologisk Afdeling, Hillerød Hospital*, 5. Anæstesiologisk Afdeling, Gentofte Hospital*, 6. Anæstesiologisk Afdeling, Hvidovre Hospital*, 7. Royal Free Hospital School of Medicine in London, 8. Anæstesiologisk Afdeling, Herlev Hospital*, 9. Anæstesiologisk Afdeling, Glostrup Hospital*, 10. Anæstesiologisk Afdeling, Roskilde Sygehus*, 11. Anæstesiologisk Afdeling, Skejby Sygehus**. 12. Klinisk Mikrobiologisk Afd., Herlev Hospital, 13. Anæstesiologisk Afdeling, Odense Universitetshospital, 14. Diagnostisk Center, Rigshospitalet. Alle: På vegne af The Cooling And Surviving Septic shock (CASS) study & Procalcitonin And Survival Study (PASS) Group. *Kbh. universitetshospital. **Århus Universitetshospital.

E-mail: Jens-Ulrik Jensen: juj@cphiv.dk, Maria Johansen: maegjo@gmail.com

Baggrund: For alvorligt syge patienter med svære infektioner samt kredsløbssvigt (septisk shock) er dødeligheden og forekomsten af organrelaterede komplikationer fortsat overordentlig høj. Mild induceret hypothermi (MIH) har ved hjerrestop samt neonatal asfyxi vist et at kunne: a. nedsætte apoptose i truede væv direkte på gen-niveau (via bl.a. cold shock proteiner), b. nedsætte metabolisme og dermed mindske iskæmien i vævene, c. mildt antikoagulere (primært ved at hæmme trombocyttaggregation). Ved behandling af brandsår er hurtig lokal køling dokumenteret at mindske apoptose på samme baggrund og med betydelig klinisk effekt. Iskæmi-udløst apoptose er ligesom ved hjerrestop en vigtig årsag til organsvigt ved septisk shock, og antikoagulation er en eftertragtet effekt i de væv, som er ramt af mikrocirkulationsnedbrud (forsøgt påvirket i interventionsstudier med AT-III, Drotrecogin- α , heparin). Dyrestudier med sepsismodeller (endotoxin og coecal ligatur) og MIH i 24 timer har vist markant forbedring i overlevelse ved mild induceret hypothermi. Det er nyligt vist hos 200 patienter med septisk shock, at ekstern køling fra feber (38,4° C) til normothermi (36,8° C) kan nedsætte varigheden af kredsløbsnedbrud (målt ved behov for vasopressor/inotropi).

Formål: At bestemme om mild induceret hypothermi ved septisk shock kan reducere dødeligheden ved at påvirke ovenfor nævnte patofysiologiske mekanismer.

Design: Randomiseret GCP-kontrolleret, "open label" studie, som udgående fra Copenhagen HIV Programme, Københavns Universitet og ti intensivafdelinger fra tre regioner i Danmark i perioden 2011-13.

Patienter: 550 intensivpatienter med mistanke om alvorlig infektion og hypotension ved ankomst til intensivafdelingen samt indikation for intubation. PCT-Q skal være >2.0 ng/ml og patienterne skal være 50 år eller derover. Patienter skal randomiseres indenfor de første 2 timer efter ankomst til intensivafdelingen.

Interventioner: For MIH-interventionsarmen, skal patienter køles til 32° C – 34° C (målsætning: kølet indenfor 120 min) og derefter fortsat været kølet i 24 timer. Herefter langsom genopvarmning (0,25° C/time). Patienter følger alle (kontrol og interventionsgruppe) surviving sepsis campaign guidelines. Antibiotika gives max. 30 min efter syndrom-diagnosen er stillet.

Primært effektmål: Død af alle årsager på dag 28.

Perspektiv: Udover det primære effektmål vil studiet kunne afklare en række spørgsmål vedr. MIH's effekt ved infektioner på en række organfunktioner på både kortere og længere sigt. En række molekylære patofysiologiske effekter vil ligeledes kunne afklares, herunder gen-aktivering og hæmning og aktiviteten af cold shock proteiner, koagulationsproteiner m.fl.

Klinisk vil et positivt resultat have stor indflydelse på behandlingen af alvorligt inficerede patienter fremover.

Status: Detaljeret protokol foreligger inkl. omfattende sikkerhedssetup med direkte opdatering af databasen for hver patient real-time på 7 organrelaterede parametre og dødelighed, automatisk genereret ad hoc interimanalyse og pause i rekruttering indtil Data and Safety Monitoring Board har taget stilling. Videnskabetisk godkendelse foreligger. Projektgruppe er dannet med basis i PASS-gruppen (kan udvides). Lundbeckfonden har doneret 1 mio kr.

T cell polyfunctionality – The Effect of a TLR9 Agonist on Pneumococcal Vaccine Response

Johannesson T^{1,2}, Sogaard O¹, Tolstrup M¹, Petersen M², Ribeiro L², Østergaard L², Erikstrup C²

¹*Department of infectious Diseases, Århus University Hospital, Skejby, Denmark*

²*Department of clinical immunology, Århus University Hospital, Skejby, Denmark*

Participating authors:

Thomas Gravesen Johannesson, tgjohannesson@gmail.com

Ole Sogaard, olesoega@rm.dk

Background: Vaccination is the most efficient way to prevent infectious diseases. In pneumococcal vaccination, the B- and T-cells characteristics that predict vaccine responses are poorly understood. Furthermore, finding therapeutic ways to achieve a better antigen-specific T-cell response, especially in immune-compromised individuals, e.g. HIV-positives, is of tremendous importance.

Materials and Methods: We use stored PBMCs from persons with HIV who were randomized to conjugate pneumococcal vaccination with or without a Toll-like receptor 9 (TLR9) agonist. Twenty vaccinees, equally divided between placebo or TLR 9 agonist, are included. Flow cytometry is used to establish B- and T-cell phenotype at baseline and these phenotypes are compared to vaccine antibody responses. Flow cytometry is also used to establish expression of CD 3, CD 4 and CD 8, IL 2, IFN γ and TNF α before and after immunization, thereby establishing the proportion of antigen-specific polyfunctional T-cells.

Results: The flow analyses are ongoing and results will be presented. We expect to find an association between antibody responses following vaccination and the pre-vaccination proportion of circulating naïve CD4+ T-cells and memory B-cells. We also expect a higher fraction of antigen-specific polyfunctional T-cells in the group receiving the TLR 9 agonist compared to the placebo group.

Perspective: These results will improve our understanding of cellular and humoral immunity development and also contribute to our understanding of how adjuvants affect the immune system. This may, on a larger scale, help in the development of new and more effective vaccines.

Funding source: The Danish Council for Independent Research | Medical Sciences and the Aase og Ejnar Danielsen Foundation

Vitamin D and clinical disease progression in HIV infection : results from the EuroSIDA study

Ole Kirk, Amanda Mocroft, Jean-Paul Viard, Jean-Claude Souberbielle, Jens D Lundgren, for the EuroSIDA study group. Presenting author: Ole Kirk, e-mail: okj@cphiv.dk

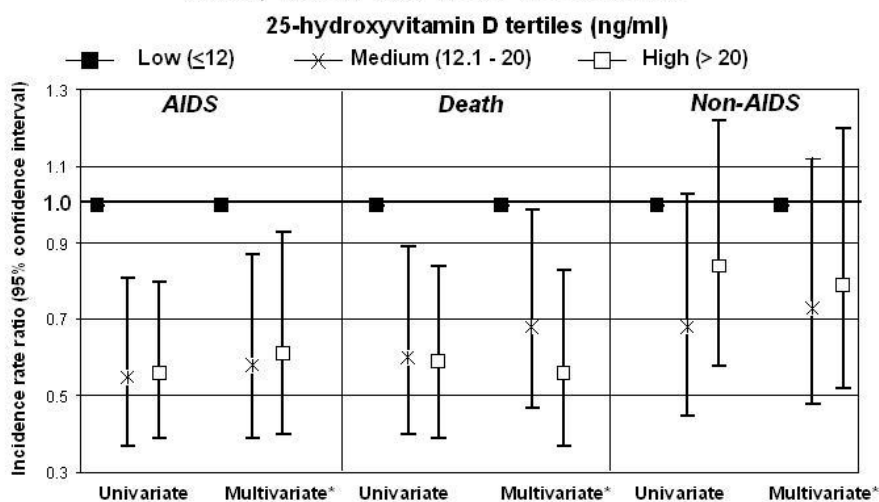
Purpose of Study: Since 25-hydroxy vitamin D (25(OH)D) deficiency has been associated with higher risk of morbidity and mortality in different settings, this study examined the association between 25(OH)D level and disease progression in HIV-infected patients with prospective follow-up in the EuroSIDA study.

Methods: A group of 2000 patients were randomly selected from those with stored samples after stratification by region. 25(OH)D levels were measured in a single laboratory from stored plasma samples. The 1985 available 25(OH)D results were stratified into tertiles. Factors associated with 25(OH)D levels and associations of 25(OH) levels with subsequent risk of all-cause mortality, AIDS and non-AIDS events were analyzed, using Poisson regression.

Results: Thirty-six percent of patients had 25 (OH) levels below 12 ng/ml, 31,3% between 12.1 and 20 ng/ml, and 32.7% above 20 ng/ml. In a cross sectional analysis, older persons, patients of Black ethnic origin, living outside Southern Europe and Argentina, sampled during winter, and infected with HIV through non-homosexual exposure were at higher risk of having low 25(OH)D levels, while patients receiving protease inhibitors were at a lower risk. Compared to those in the lowest 25(OH)D tertile, those in the medium and high tertiles had a significantly lower risk of clinical progression. Adjusted incidence rate ratios (IRR; see figure) for all-cause mortality were 0.68 (95%CI : 0,47-0,99, P=0.045) and 0.56 (95%CI : 0.37-0.8, P=0.009), and for AIDS events were 0.58 (95%CI : 0,39-0,87, P=0.0086) and 0.61 (95%CI : 0.40-0.93, P=0.020), for the medium and high tertiles, respectively. There was a non-significant reduced incidence of non-AIDS defining events in the medium and high tertiles, and a significant lower IRR of non-AIDS related death in the highest 25(OH)D tertile : 0.60 (95%CI : 0.37-0.98, P=0.043).

Conclusions: This observational study demonstrated that 25(OH)D deficiency is frequent in HIV-infected patients, and is independently associated with a variety of outcomes, reflected by a higher risk of mortality and AIDS events. Whether the relationship between vitamin D deficiency and clinical events is causal should be addressed because of potentially major consequences in terms of public health.

Univariate and multivariate incidence rate ratios of AIDS, death and non-AIDS events



*Adjusted for baseline values of gender, ethnic origin, HIV risk group, region of Europe, HBsAg and HCV antibody status, prior AIDS, exposure to antiretrovirals, age, CD4 count, Nadir CD4, HIV-RNA viral load, date of baseline sample date, season of sample and date of recruitment to EuroSIDA.

Increase in CD4+CD25+CD127^{low}FOXP3+ Regulatory T-cells (Tregs) during Second Trimester: Comparison of Immunological Measurements in HIV-infected and HIV-negative Pregnant Women

Lilian Kolte^{1,2}, Julie Christine Gaardbo³, Ingrid Karlsson⁴, Anna Louise Sørensen¹, Lars Peter Ryder⁵, Kristin Skogstrand⁶, Steen Ladelund², Susanne Dam Nielsen³

Departments of Infectious Diseases¹ and Clinical Research Center², Copenhagen University Hospital, Hvidovre, Denmark

Department of Infectious Diseases³ and Clinical Immunology⁵, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Departments of Virology⁴ and Clinical Biochemistry and Immunology⁶, Statens Serum Institute, Copenhagen, Denmark

Presenting author: Lilian Kolte, e-mail: lilian@kolte.dk

Pregnancy represents a major challenge to immunological tolerance. How the fetal “semi-allograft” evades maternal immune attack is not known, but pregnancy success may involve alteration of both central (thymic) and peripheral tolerance mechanisms. HIV-infection is characterized by CD4+ T-cell depletion, chronic immune activation and altered lymphocyte subsets. We studied immunological consequences of pregnancy in 20 HIV-infected women receiving highly active anti-retroviral therapy (HAART), and for comparison in 16 HIV-negative women. Lymphocyte subsets, thymic output and cytokine profiles were measured prospectively during pregnancy and postpartum. A significant expansion of CD4+CD25+CD127^{low}FoxP3+ Regulatory T-cells indicating alteration of peripheral tolerance was seen during second trimester, but only in HIV-negative women. HIV-infected women had lower CD4 counts, lower thymic output and Th-2 cytokines, and more immune activation at all time points compared to controls. Immune activation was decreased in HIV-infected patients during pregnancy. In contrast, CD4 counts were increased in both groups. In conclusion, the study does not indicate that pregnancy adversely affects the immunological course of HIV-infection. However, despite HAART during pregnancy, HIV-infected women display different immunological profiles from HIV-negative women, which may have importance for the induction of fetal-maternal tolerance and in part explain the increased risk of abortion in HIV-infected women.

Alcohol Drinking and Risk of Subsequent Hospitalization with Pneumonia

Jette Brommann Kornum¹, Karen Margrete Due², Mette Nørgaard¹, Anne Tjønneland³, Kim Overvad^{4,5}, Henrik Toft Sørensen¹, Reimar Wernich Thomsen¹

¹ Department of Clinical Epidemiology, Clinical Institute, Aarhus University Hospital, Aarhus, Denmark.

² Department of Cardiology, Center for Cardiovascular Research, Aalborg Hospital, Aarhus University Hospital, Denmark. ³ Danish Cancer Society, Copenhagen, Denmark. ⁴ Department of Cardiology, Center for Cardiovascular Research, Aalborg Hospital, Aarhus University Hospital, Denmark. ⁵ Department of Epidemiology, School of Public Health, Aarhus University, Aarhus, Denmark

Presenting author: Jette Brommann Kornum, e-mail: j.kornum@rn.dk

Background: Alcohol abuse increases the risk of pneumonia, but the dose-response relationship between alcohol drinking and pneumonia risk is poorly understood.

Methods: We followed a cohort of 22,485 men and 24,682 women from the Danish Diet, Cancer and Health Study who were 50-64 years old and free from major chronic diseases at baseline (1993-1997), to identify first-time hospitalizations with pneumonia (median follow-up 12 years).

Results: During follow-up, 1,091 men and 944 women had a pneumonia-related hospitalization. After controlling for smoking and body mass index, the adjusted hazard ratios (HRs) of pneumonia among men were 1.49 (95% confidence interval (CI): 1.00-2.21) for 0 drinks per week, 0.88 (95% CI: 0.76-1.03) for 7-20 drinks, 0.87 (95% CI: 0.72-1.05) for 21-34 drinks, 1.15 (95% CI: 0.93-1.44) for 35-50 drinks, and 1.81 (95% CI: 1.40-2.33) for >50 drinks per week, compared with consumption of 1-6 drinks per week. Among women, adjusted HRs were 1.26 (95% CI: 0.89-1.79) for 0 drinks per week, 1.01 (95% CI: 0.88-1.17) for 7-20 drinks, 1.10 (95% CI: 0.88-1.37) for 21-35 drinks, and 0.54 (95% CI: 0.29-1.01) for >35 drinks. After adjusting for chronic diseases diagnosed during follow-up, the association between high alcohol intake and pneumonia risk was lowered but still present. For the same weekly amount of alcohol, infrequent intake was associated with higher pneumonia HRs than more regular intake.

Conclusion: High weekly alcohol consumption and infrequent heavy drinking are associated with increased risk of pneumonia-related hospitalization among men, explained not only by occurrence of chronic diseases.

CCL3L gene copy number and survival in an HIV-1 infected Zimbabwe African population

Larsen MH¹, Erikstrup C², Thørner LW¹, Zinyama R^{3,4}, Kallestrup P⁵, Gerstoft J⁵, Gomo E⁶, Ullum H¹

¹ Department of Clinical Immunology, Rigshospitalet, Denmark

² Department of Clinical Immunology, Aarhus University, Skejby Sygehus, Denmark

³ Medical Research Council of Zimbabwe, Ministry of Health and Child Welfare, Zimbabwe

⁴ Department of Medical Laboratory Sciences, University of Zimbabwe

⁵ Department of Infectious Diseases, Rigshospitalet, Denmark

⁶ Department of Medical Laboratory Sciences, University of Zimbabwe

Presenting author: Margit Hørup Larsen, e-mail: mahlarsen@gmail.com

Background: CC chemokine ligand 3-like1 (CCL3L1) is a protein that interacts with the chemokine receptor CCR5 which also function as a co-receptor for the human immunodeficiency virus (HIV). The CCL3L1 protein is therefore a potential HIV-1 suppressive chemokine. Copy number variations (CNVs) represents a copy number change involving a DNA fragment that is ~1 kilobases or larger. The copy number of the *CCL3L1* gene have shown to be varying especially among different ethnic populations. The copy number of the *CCL3L1* gene has shown to have an association to the level of *CCL3L1* protein, in that a higher number of *CCL3L1* copies lead to a higher CCL3L1 protein expression level in the blood.

CNVs of the *CCL3L1* gene have been implicated in HIV-1 susceptibility and progression to AIDS, but inconsistent results have been found. The methods used for CVN determinations have shown not to be specific for the *CCL3L1* gene only. Our purpose is to examine the possible association of *CCL3L1* CNV to HIV-1 progression and to survival in a Zimbabwe-African population that is comprised of a mixture of both HIV-1 infected ($n = 159$) and –uninfected ($n = 153$) individuals within a 5 years follow-up of survival rate.

Methods: The CNV of the *CCL3L1* gene is determined by duplex real-time polymerase chain reaction.

Results: In overall we find the absence of any significant association of *CCL3L* copy number variation on HIV-1 status ($P = 0.964$), viral load ($P = 2.816$) and survival in the South-African population.

Insulinresistens og inkretineffekt under infusion af TNF- α

Louise Lehrskov-Schmidt og Signe Tellerup Nielsen

Præsenterende forfatter: Louise Lehrskov-Schmidt, e-mail: louise@lehrskov.dk

Formål: Ved hjælp af TNF- α infusion ønskes det at fremkalde et standardiseret systemisk inflammatorisk stimulus og vurdere hvorvidt denne tilstand påvirker frigivelsen af plasmaglukose (PG), insulin GIP og GLP1 under glukosebelastning, dels ved oralt glukoseindtag og dels ved iv. infusion af glukose.

Fremgangsmåde: Der inkluderes 12 raske frivillige mænd i alderen 18-40 år.

Der foretages en forundersøgelse af forsøgspersoner for at sikre, at forsøgsparticipanterne er helt raske, og at der ikke foreligger tilstande, der medfører øget risiko forbundet med at deltage i forsøget.

Forsøget består af 4 forsøgsgange af 6 timers varighed (2 timers infusion forud for 4 timers test) med en uges mellemrum.

Dag 1: NaCl-infusion med oral glukosetolerancetest (OGTT)

Dag 2: TNF- α -infusion med OGTT

Dag 3: NaCl-infusion med isoglykæmisk intravenøs glukosetolerancetest (IGTT)

Dag 4: TNF- α -infusion med IGGT

PG måles hvert 5 min, mens insulin, c-peptid, katekolaminer, cortisol, væksthormon, glukagon, cytokiner, GLP-1 og GIP måles med større mellemrum.

Forsøgsplanen er ikke randomiseret. Dette gøres for at undgå, at en evt. resterende insulinresistens eller anden kaskade-aktivering efter TNF- α -infusion påvirker resultatet under NaCl-infusion.

Forventninger: Vi håber således at kunne påvise at det for raske forsøgspersoner gælder, at der under infusion af TNF- α sammenlignet med intravenøs infusion af isoton NaCl ved en OGTT ses nedsat GLP-1 sekretion, øget PG og reduceret insulinsekretion, dvs. en nedsat endogen inkretineffekt.

Desuden håber vi ved brug af en IGGT at kunne påvise en øget insulin sekretion samt en reduktion i forskellen på arealet under kurven ved OGTT og IGGT hos forsøgspersonerne som får TNF- α infusion sammenlignet med NaCl infusion.

IL-18 increases intramuscular fat oxidation by activating AMPK

Birgitte Lindegaard^{1,2,3}, Vance Matthews³, Claus Brandt¹, Pernille Hojmann¹, Tamara L Allen³, Henriette Pilegaard¹, Juan Hildalgo⁴, Clinton Bruce³, Mark Febbraio³, Bente Klarlund Pedersen^{1,2}.

¹Centre of Inflammation and Metabolism, ²Department of Infectious Diseases, Rigshospitalet, University of Copenhagen, Denmark, ³Cellular and Molecular Metabolism Laboratory, Diabetes and Metabolism Division, Baker Heart Research Institute, Melbourne, Australia, ⁴Institute of Neurosciences, Department of Cellular Biology, Faculty of Biosciences, Autonomous University of Barcelona, Barcelona, Spain.

Presenting author: Birgitte Lindegaard, e-mail: blindegaard@hotmail.com

AIM: Circulating levels of interleukin (IL)-18 are elevated in obesity and type 2 diabetes. Paradoxically, patients with HIV-associated lipodystrophy, characterized by low subcutaneous fat, also demonstrate increased levels of circulating IL-18. Therefore, the observation that mice deficient in IL-18 and IL-18R (IL-18R^{-/-}) are obese is of particular interest (Netea et al. Nat Med.12: 650-656, 2006), suggesting that IL-18 are mechanistically involved in reducing fat mass. IL-18 is thought to act centrally by increasing fat oxidation and reducing food intake. However, whether IL-18 affects metabolic processes in the periphery is not known. Accordingly, we examined the effect of IL-18 on the fat oxidation pathway in skeletal muscle *in vitro*, *ex vivo*, and *in vivo* in IL-18R^{-/-} mice and in mice over-expressing IL-18 in muscle during high-fat and normal-fat feeding.

METHODS: L6 myotubes and isolated soleus muscles were treated with IL-18 and phosphorylation of the proteins AMP-activated protein kinase (AMPK) and acetyl coenzyme A carboxylase β (ACC β) were analysed, as was fatty acid oxidation. We also analysed triglyceride accumulation and phosphorylation of AMPK and ACC β in muscle from IL-18R^{-/-} mice on a chow and a high fat diet. Finally, we over-expressed IL-18 by gene electrotransfer into the tibialis cranialis muscle of mice and followed adiposity gain after a high fat and normal diet.

RESULTS: Here, we show that IL-18 increases fatty-acid oxidation in soleus muscle *ex vivo* and increases AMPK phosphorylation. In L6 myotubes, IL-18 phosphorylated AMPK and ACC β . IL-18R^{-/-} mice demonstrate obesity-independent insulin resistance. Moreover, IL-18R^{-/-} mice have increased levels of triglycerides in skeletal muscle and this is accompanied by a reduced phosphorylation of ACC β in the *soleus* muscle. Electroporation of an IL-18 expression vector into muscle inhibit both diet-induced-adiposity and fat gain on a normal diet. Furthermore, electroporation of an IL-18 expression results in increased AMPK-activity and phosphorylation of ACC β .

CONCLUSIONS/INTERPRETATION: Our findings show that IL-18 acts in the periphery by enhancing lipid oxidation in skeletal muscle via activation of AMPK, resulting in fat loss and resistance to obesity.

Bedre HCV behandling af stofmisbrugere

Belinda K. Mössner¹, Tina R Jørgensen², Inge Birkemose², Merete Skamling³, Court Pedersen¹, Peer Brehm Christensen¹

¹Infektionsmedicinsk afdeling Q, Odense Universitetshospital, ²Behandlingscenter Odense, Odense kommune, ³Behandlingscenter Svendborg, Svendborg kommune

Præsenterende forfatter: Belinda K Mössner, e-mail: belinda.klemmensen@gmail.com

Baggrund: Ca. halvdelen af nuværende og tidligere intravenøse stofbrugere er kronisk inficeret med hepatitis C. Stofbrugere tilbydes principielt behandling efter samme retningslinjer som andre patienter, dog skal de have været uden aktivt misbrug i en periode på 6-12 måneder. Behandlingsrespons er på samme niveau som i andre patientgrupper. Desværre er stofbrugeres compliance lav, og selv i dedikerede centre opnås det sjældent at behandle mere end 10 % af potentielle behandlingkandidater. I 2007 blev klienter på fynske behandlingscentre tilbudt undersøgelse med fibroscanning og blodprøvetagning. Af 759 klienter fik 450 foretaget en fibroscanning, og der fandtes 111 klienter med en scanningsværdi > 8 kPa. Blandt de 25, hvor der blev fundet medicinsk behandlingsindikation, påbegyndte 5 behandling. Dette svarer til 5 % af potentielle behandlingkandidater identificeret ved scanning.

Formål: At undersøge om flytning af udredning og behandling fra hospitalsmiljø til behandlingscentre kan øge behandlings- og gennemførelsesraten hos HCV- inficerede patienter, der opfylder de gængse kriterier for antiviral behandling.

Metode: Prospektivt enkeltcenterstudie. Alle klienter >18 år, som følges på Behandlings-center Odense eller Svendborg og som er HCV-RNA positive tilbydes forløb i fremskudt "hepatitis-ambulatorium" med fibroscanning, rutineprøver og klinisk undersøgelse som ved fremmøde i infektionsmedicinsk afdeling. Alle klienter med kronisk hepatitis C uanset fibrosestadie tilbydes klinisk og paraklinisk kontrol hver 6. mdr. Klienter med medicinsk behandlingsindikation tilbydes behandling, hvis behandlingsegnete.

Primære effektmål: Antal patienter der gennemfører antiviral behandling.

Sekundære effektmål:

1. Antal patienter der opnår helbredelse (HCV-RNA negativ 6 måneder efter behandlingsophør)
2. Antal patienter evalueret for behandling
3. Antal patienter der starter behandling
4. % der opnår 20 % reduktion i fibroscanning efter endt behandling
5. Antal dødsfald (uanset årsag)

Resultater: Studiet er pågående og data er endnu ikke opgjort.

Løb og muskler

Mille Bækdal Nielsen, Louise Seier Hansen, Matthew Laye, Bente Klarlund Pedersen

Centre of Inflammation and Metabolism, Rigshospitalet

Præsenterende forfatter: Mille Bækdal Nielsen, e-mail: millebn@gmail.com

Baggrund og formål: Mange forskellige livsstilssygdomme, herunder diabetes, kardiovaskulære sygdomme og visse former for cancer er relateret til fysisk inaktivitet og dermed også akkumulation af visceralt fedt og dernæst kronisk, systemisk inflammation. Med henblik på at forstå de bagvedliggende mekanismer, hvorved fysisk inaktivitet forårsager sygdom, vil vi studere hele spektret af fysisk aktivitet, fra de mest inaktive til de mest aktive personer. Vi etablerer en kohorte af særdeles fysisk aktive langdistanceløbere. Vi vil sammenligne muskel-stamcellefunktion hos meget fysisk aktive personer og personer, der ikke dyrker struktureret fysisk aktivitet. Projektet vil inkludere karakterisering af kredsløbskondition, stofskiftefunktion, løbeøkonomi, kognitiv funktion hos maratonløbere og raske, utrænede kontrolpersoner. Vi vil bl.a. undersøge ekspresion af Myo-miR i muskelbiopsier og i satellitcellekulturer, samt differentierede myocytkulturer i relation til køn, alder og træning. Desuden vil vi vurdere om køn, alder eller træning påvirker metabolisk flexibilitet, samt undersøge om forskelle i ekspresion af kandidat Myo-miR er forårsaget af forskelle i DNA-methylering af specifikke promotorer. Herudover vil vi undersøge om fysiologiske mål for fysisk træningsgrad er relaterede til kognitiv funktion.

Metode: Studiet, som inkluderer i alt 200 forsøgspersoner, herunder 100 langdistanceløbere og 100 kontroller, som er matchede i forhold til køn, alder og BMI, vil være et case-kontrolstudie. Gruppen af løbere vil bestå af personer, som enten har løbet mange maratonløb eller generelt løber meget, svarende til 50 km eller mere pr. uge. Forsøget består af 3 forsøgsg dage, alle under 6 timers varighed. Alle personer vil få foretaget en forundersøgelse, som skal sikre, at de er raske og dermed kan deltage i forsøget. I løbet af forsøgsg dagene vil forsøgspersonerne bl.a. få foretaget udtagning af to muskelbiopsier, VO₂ max-test, to submaksimale tests, en måling af hvilestofskifte, måling af håndens gribestyrke, DXA- og MR-scanning samt forskellige neuropsykologiske tests.

Forventninger: Vi håber at kunne påvise løbetrænings beskyttende effekter i forhold til livsstilssygdomme på et cellulært niveau samt undersøge, hvilke elementer i løbetræningen der gør, at løbere i flere studier er fundet at have en bedre kognitiv funktion både hvad angår koncentration og intelligens set i forhold til baggrundsbefolkningen.

Clinical epidemiology and manifestations of *Campylobacter concisus*

Hans Linde Nielsen¹, Tove Ejlertsen², Jørgen Engberg³ and Henrik Nielsen¹

¹Department of Infectious Diseases, and ²Clinical Microbiology, Aalborg Hospital, Aarhus University hospital, Aalborg, ³Department of Clinical Microbiology, Slagelse Hospital, Slagelse, Denmark
Præsenterende forfatter: Hans Linde Nielsen, e-mail: halin@rn.dk

Introduction: *Campylobacter jejuni/coli* (95/5%) are currently the major causes of bacterial diarrhoea throughout the western world. After the acute gastroenteritis some patients have sequelae like irritable bowel syndrome, reactive arthritis, inflammatory bowel disease and Guillain Barré syndrome. For *Campylobacter concisus* the epidemiology and disease burden in humans are not clarified. *C. concisus* has been proposed to cause diarrhoea among children and immunocompromised patients, and recently it has been proposed to be an etiologic factor for the development of Crohn's disease.

Aim: In this study we will clarify the epidemiology and clinical manifestations caused by *C. concisus*. We will describe the differences and similarities of the clinical presentations caused by *C. jejuni/coli* and *C. concisus*.

Methods: Patients with *C. jejuni/coli* and *C. concisus* in the faecal sample are included in the study. The study period will be two years and started January 2009. The patient's clinical data are reviewed by use of the patient's medical records as well as a questionnaire survey with a follow up for six months.

Results: From the first 18 months preliminary results show that *C. concisus* is very common. It is only surpassed by *C. jejuni/coli* and is more frequent than other enteric pathogens such as *Salmonella spp.* Early results show that patients with *C. concisus* present a more prolonged disease history more like chronic diarrhoea rather than acute enteritis.

Discussion: The study should provide a greater understanding of the clinical consequences of infection with the emerging *C. concisus*. It will provide information on whether the bacterium is a human pathogen of the gut causing diarrhoea and any sequelae as evidenced by infection with *C. jejuni/coli*.

Nosokomial Bakteriæmi – epidemiologi og forløb

Stig Lønberg Nielsen¹, Annmarie Touborg Lassen², Hans Jørn Kolmos³, Court Pedersen¹

¹*Infektionsmedicinsk afd. Q,* ²*Akut Modtage Afdeling AMA,* ³*Klinisk Mikrobiologisk Afdeling Odense Universitets Hospital*

Præsenterende forfatter: Stig Lønberg Nielsen, e-mail: slnielsen@dadlnet.dk

Indledning: Nosokomielle infektioner er hyppige og på trods af kendskab til adskillige risikofaktorer er der observeret en stigende hyppighed af nosokomial bakteriæmi, som er tæt associeret med sepsis og høj morbiditet samt mortalitet.

Formål: Formålet med studiet er at beskrives forekomsten af hospitalserhvervet bakteriæmi over en 10 års periode med fokus på demografi, bakterieætiologi, risikofaktorer, morbiditet og mortalitet samt ændringer i disse forhold over tid med henblik på at opnå en ny og opdateret epidemiologisk viden om problemstillingen, som på sigt kan danne grundlag for tidlig diagnostik, effektive profylaktiske tiltag samt optimal valg af antibiotika.

Metode: Projektet tager udgangspunkt i et nyoprettet register, DORIS (Danish Observational Registry of Infectious Syndromes). Registeret indeholder godt 9.000 patienter fra OUH (1999-2008) med 1. gangs bakteriæmi, hvoraf knap 4.000 er nosokomielle, som vil udgøre datagrundlaget i delstudie 1+2. Der er indsamlet kliniske data for patienterne.

Studier

Ph.d studiet består af 4 delprojekter:

- 1) Nosokomial bakteriæmi hos patienter med 1. gangs bakteriæmi. Der beskrives demografi, ætiologi og risikofaktorer.
- 2) Nosokomial bakteriæmi hos patienter med 1. gangs bakteriæmi. Der beskrives forløb i form af 30 dages- og langtidsmortalitet i hele follow up perioden (1999-2010).
- 3) Nosokomial bakteriæmi hos patienter opstået efter akut/elektiv operation inden for grupperne CABG, PCI +/- stent, knæ/hoftealloplastik, colonresektion og tyndtarmsresektion. Der beskrives demografi, hyppighed, risikofaktorer og forløb.
- 4) 1. gangs nosokomial bakteriæmi. Der beskrives demografi, ætiologi, risikofaktorer, forløb og betydningen af tidligere samfundserhvervet bakteriæmi undersøges.

Grupperne sammenlignes med relevante kontrolgrupper med henblik på at belyse forskelle.

Status

Der søges om optagelse på ph.d studiet 1/11-2010 med planlagt indskrivning 1/9-2011.

Antibody response to the 2009 pandemic H1N1 influenza virus following infection or vaccination

Henriette S. Nielsen¹, Katarina Widgren², Kåre Mølbak², Betina Andresen¹, and Lars Peter Nielsen¹

¹*Department of Virology and* ²*Department of Epidemiology, Statens Serum Institut, Artillerivej 5, 2300 Kbh S*
Presenting author: Henriette S. Nielsen, e-mail: HCN@ssi.dk

A new influenza A H1N1 virus emerged in Mexico during spring 2009 and has since then been spreading throughout the world. On June 11th, 2009 the World Health Organization declared that this novel H1N1 virus (H1N1pdm) had reached pandemic properties.

Several studies have shown the presence of cross-reactive antibodies among the elderly (65 years or older) which likely provide protective immunity. In contrast, the younger age groups lack immunity.

From November 2009 a vaccination campaign was launched in Denmark as part of the national pandemic preparedness. The campaign included vaccination of high risk groups and healthcare workers. The majority of the vaccinated individuals received only one dose of the monovalent adjuvanted vaccine, Pandemrix (GlaxoSmithKline Biologicals).

We here present data from two independent studies performed to assess the level of H1N1pdm specific antibodies after a single dose of vaccine and in young adults after a H1N1pdm infection. In both studies the level of H1N1pdm specific antibodies were measured in the haemagglutination-inhibition assay against the H1N1pdm reference strain, A/California/07/09. A seroprotective immune response was defined as a HI titer of 40 or higher in the post-vaccination samples.

The purpose of the first study was to assess the immune response and to evaluate the disease severity in young adults after a H1N1pdm infection. In August 2009, an outbreak of influenza-like illness caused by H1N1pdm was reported on a boarding school in Sønderjylland. The students were 15-16 years of age and slept in bunk-beds that were placed head-to-head in two or six-bedded rooms divided over ten dormitory houses. To acquire an estimate of the disease to infection rate, a questionnaire was distributed to obtain clinical symptoms. Approximately three months after the outbreak, serum samples were taken and the level of H1N1pdm specific antibodies measured.

A total of 54 of 120 students (45%) had antibodies against H1N1pdm. The high number of infected is likely a consequence of close contact in the setting of this outbreak, i.e. staying in dormitory, many social and team building activities etc. Furthermore, 33 of the seropositive students had experienced clinical symptoms, resulting in a disease to infection ratio of 61%. As seen for previously circulating influenza A viruses, a high number of subclinical cases was detected. Despite these subclinical cases, a good correlation was observed between serology and clinical observations.

To assess the immunogenicity after a single dose of Pandemrix, the levels of H1N1pdm specific antibodies were measured in a group of adults, age 25 years or older.

Serum samples were obtained prior to vaccination (pre-vaccination) and approximately three weeks after vaccination (post-vaccination). While no H1N1pdm antibodies were detected in any of the pre-vaccination samples, a single dose of the adjuvanted influenza H1N1pdm vaccine induced an antibody response in more than 93% of the vaccinated individuals. This very high seroconversion rate correlates well with reports from other countries. Thus a single dose of the monovalent adjuvanted vaccine induces a robust immune response.

Lever cancer og Non-Hodgkin Lymfom blandt Hepatitis C Virus-inficerede patienter: Resultater fra DANVIR kohorten.

Lars Haukali Omland, Peter Jepsen, Henrik Krarup, Peer Brehm Christensen, Nina Weis, Lars Nielsen, Niels Obel, Henrik Toft Sørensen, Sherri Oliver Stuver; på vegne af DANVIR.

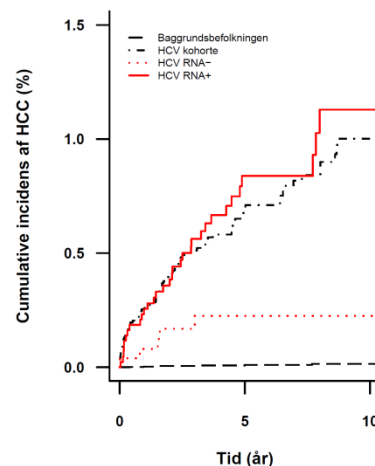
Præsenterende forfatter: Lars Haukali Omland, e-mail: omland@dadlnet.dk

Baggrund og formål: Hepatitis C virus (HCV)-infektion kan forårsage hepatocellular carcinom (HCC) og muligvis non-Hodgkin lymfom (NHL). Ingen studier har sammenlignet risikoen for disse cancer mellem patienter med kronisk og clearret HCV-infektion. Vi satte os for at estimere 10-års risikoen for HCC og NHL blandt HCV-inficerede patienter og at sammenligne risikoen for disse cancer mellem HCV-inficerede patienter og baggrundsbefolkningen i Danmark og mellem patienter med kronisk og clearret HCV-infektion, idet vi justerede for alkohol misbrug og HIV-infektion.

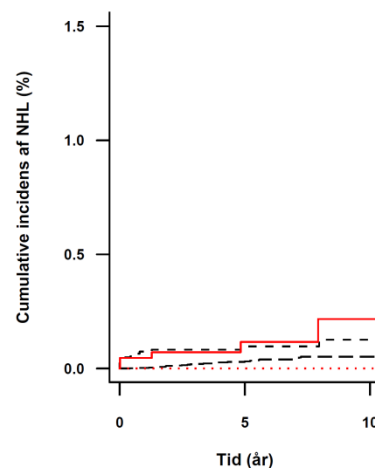
Metode: Landsdækkende kohorter blev benyttet: 12,262 HCV-inficerede patienter i DANVIR kohorten og 73,572 individer fra en alders- og kønsmatched baggrundsbefolkningskohorte; Vi undersøgte endvidere 4,331 patienter med kronisk HCV-infektion og 2,504 patienter med clearret HCV-infektion i DANVIR.

Resultater: 10-års risikoen for HCC og NHL blandt HCV-inficerede patienter var 1.0% (95% confidens interval (CI): 0.8 – 1.3%) og 0.1% (95% CI: 0.1 – 0.2%). Sammenlignet med baggrundsbefolkningen havde HCV-inficerede patienter en 64.1-fold øget risiko for HCC (95% CI: 29.6 – 139.1), en 8.5-fold øget risiko for NHL i de første 2 års follow-up (95% CI: 3.2 – 22.6), og en 1.3-fold øget risiko for NHL efter 2 års follow-up (95% CI: 0.3 – 5.9). Kronisk HCV-infektion var associeret med en 3.7-fold øget risiko for HCC (95% CI: 1.4 – 9.4) sammenlignet med clearret HCV-infektion. 5 og 0 tilfælde af NHL blev diagnosticeret hos patienter med henholdsvis kronisk og clearret HCV-infektion.

Konklusion: Risikoen for HCC er øget blandt HCV-inficerede patienter sammenlignet med baggrundsbefolkningen. Kronisk sammenlignet med clearret HCV-infektion øger risikoen for HCC og muligvis NHL.



Cumulative incidens i % (95% CI)			
Baggrundsbefolkningen	0	0.01 (0.00 – 0.02)	0.01 (0.00 – 0.03)
HCV kohorte	0	0.7 (0.5 – 0.9)	1.0 (0.8 – 1.3)
HCV RNA-	0	0.2 (0.1 – 0.5)	0.2 (0.1 – 0.5)
HCV RNA+	0	0.8 (0.6 – 1.2)	1.1 (0.7 – 1.7)



Cumulative incidens i % (95% CI)			
Baggrundsbefolkningen	0	0.03 (0.02 – 0.05)	0.05 (0.03 – 0.08)
HCV kohorte	0	0.1 (0.1 – 0.2)	0.1 (0.1 – 0.2)
HCV RNA-	0	0	0
HCV RNA+	0	0.1 (0.0 – 0.3)	0.2 (0.1 – 0.6)

Infektion med Humant Immundefekt Virus (HIV) – en tilstand med accelereret aldring?

Karin Kæreby Pedersen, Susanne Dam Poulsen

Epidemiklinikken M, Rigshospitalet.

Karin Kæreby Pedersen, e-mail: karin_kaerebypedersen@yahoo.dk

Formål: At undersøge hvorvidt infektion med HIV fører til en accelereret aldring.

Baggrund: Effektiv behandling af HIV har ændret fremtidsudsigterne for personer med HIV-infektion. Fra at være en sygdom med høj mortalitet, har HIV-infektion ændret sig til at være en kronisk sygdom med en estimeret overlevelse, der nærmer sig baggrundsbefolkningen. Den forventede livslængde for HIV-smittede er alligevel kortere end for HIV-negative, og dette er delvist på grund af sygdomme, der forbindes med høj alder så som hjerte-karsygdomme og cancer. Ligeledes har HIV-smittede kognitive og immunologiske forandringer, der ellers forbindes med høj alder.

Baggrunden for indeværende projekt er derfor en internationalt opstillet hypotese: Infektion med HIV medfører en accelereret aldringsproces.

I indeværende studie defineres aldring som tilstedeværelse af en eller flere af følgende: 1) fysisk/metabolisk fænotype med nedsat fysisk aktivitet og muskelstyrke, ændret fedtfordeling og insulinresistens, 2) kognitive dysfunktion og 3) immunologisk fænotype med nedsat thymus output, færre naive T celler, færre TRECs, nedsat telomerlængde og øget antal Tregs

Årsag til accelereret aldring hos HIV-smittede er ukendt. Hypotesen i dette studie er, at den accelererede aldring drives af 1) immundefekten, 2) kronisk inflammation muligvis drevet fra fedtvævet og/eller 3) co-infektion med cytomegatovirus (CMV).

Vi vil i indeværende projekt undersøge følgende:

-Sammenligne HIV-smittede med HIV-negative personer og belyse evt. forskelle i deres fysiske, kognitive og immunologiske funktion. (MR-scanning mhp. visceral fedt akkumulering, DXA-scanning mhp. kropssammensætning, fitness-test, OGTT, kognitiv test samt immunologisk undersøgelse: CD4/CD8 ratio, naive T celler, senescent T celler, Tregs, TRECs samt telomere længde).

-Belyse sammenhængen mellem accelereret aldring og funktionen af immunforsvaret målt ved CD4 tallet.

-Belyse sammenhængen mellem accelereret aldring og inflammation, og om denne inflammation kan stamme fra fedtvævet. (Fedt biopsier, hvoraf fedtcellernes evne til at differentiere samt graden af inflammation vil blive målt)

-Belyse sammenhængen mellem accelereret aldring og infektion med CMV. (CMV antistoffer, CMV PCR samt andelen af CD4 and CD8 celler der specifikt respondere på CMV)

Forsøgspersoner og design

70 HIV-smittede personer rekrutteres fra Epidemiklinikkens ambulatorium på Rigshospitalet. 35 med et CD4 tal > 500 og 35 med et CD4 tal < 500. Til sammenligning inkluderes HIV-negative personer matchet på alder, køn samt BMI, heraf 40 raske og 40 med type 2 diabetes.

The significance of neutralizing antibodies as predictor for achieving effect after treatment with pegylated interferon and ribavirin in patients with chronic hepatitis C.

Jannie Pedersen¹, Henrik Krarup², Peer Brehm Christensen³, Axel Lund Laursen⁴, Kristian Schöning⁵, Jens Bukh¹, Nina Weis¹

1. Infektionsmedicinsk afdeling, Hvidovre Hospital. 2. FBE Klinisk biokemisk Syd, Aalborg Sygehus 3. Infektionsmedicinsk afdeling Q, Odense Universitetshospital 4. Infektionsmedicinsk Afdeling, Skejby Sygehus 5. Klinisk Mikrobiologisk Afdeling, Hvidovre Hospital

Presenting author: Jannie Pedersen, e-mail: Jannie.Pedersen@hvh.regionh.dk

Background: Worldwide approximately 170 million people are chronically infected with the hepatitis C virus. The current treatment is a combination therapy consisting of pegylated interferon α and ribavirin. The treatment contains a high risk for serious side effects and currently only 50-80 % responds with a sustained virologic response (SVR). The aim of this study was to clarify whether or not the neutralizing antibodies (nAb) in chronically hepatitis C infected patients could be used as a predictor for treatment outcome.

Methods: Patient cohorts: Through the Danish DANHEP database 80 patients were included using the following in- and exclusion criteria: Patients had to be infected with genotype (GT) 1 or 3, they could not have a HIV or HBV co-infection, the treatment period should be at least 12 weeks, the outcome should be known and categorized as either SVR or non-SVR and a treatment naive blood sample had to be available. They were grouped into 4 different groups according to GT and outcome. The samples were blinded according to genotype before use. nAb assay: The patient plasma was inactivated and mixed with different recombinant viruses according to GT: 1 GT3 (S52_JFH1), 3 GT1a (TN_JFH1, H77_JFH1, DH6_JFH1) and 3 GT1b (J4_JFH1, DH1_JFH1 and DH5_JFH1) and a GT6 (HK6a_JFH1) which has previous shown to be easier to cross-neutralize. Huh 7.5 cultures were infected with the plasma/virus mix and after 48 hours of infection the number of infected cells was counted. IP-10: Using an IP-10 ELISA kit the level of IP-10 was measured in all the samples.

Results: Baseline characteristics of the two groups (SVR-non-SVR) confirmed the groups were comparable. All samples except one showed a Nab titer > 200 against HK6a_JFH1 recombinant virus confirming the presents of Nab against HCV. The GT3a samples were run against S52_JFH1 and the GT1 samples against H77_JFH1, J4_JFH1, DH1_JFH1 and DH5_JFH1. Currently the GT1 samples are run against DH6_JFH1 and TN_JFH1. Since the samples are blinded any statistical calculations cannot be done yet. The measurements of IP-10 levels are also in progress.

Discussion: Up till today predictors for a SVR prior to treatment was limited to virus factors like GT and virus load and host factors like age giving only 50 % prediction rate. Recently the level of IP-10 and IL28B host genetics has shown to be very stabile predictors and can predict up to 80 %. However 20 % is still a considerable amount of patients, who will still suffer from ineffective treatment. If the neutralizing antibodies can be used as a predictor it will increase the prediction rate in correlation with the already existing predictors. From our preliminary data we see that the nAb titer varies from < 50 to > 400 in the samples. Whether these levels correlate with the outcome remains to be discovered.

Health care index score and outcome following TB diagnosis in HIV-infected patients

DN Podlekareva¹, A Mocroft², O Kirk¹, N Obel³, JD Lundgren^{1,3}, and the HIV/TB study group

- 1) *University of Copenhagen, Copenhagen HIV Programme, Denmark;*
- 2) *University College London Medical School, Royal Free Campus, London, UK;*
- 3) *Rigshospitalet, Copenhagen, Denmark*

Objectives: Previous research has shown that 1-year mortality among HIV/TB coinfecting patients varies from 7-11% in Western Europe and Argentina to 27% in Eastern Europe. Reasons for these differences may include access to and use of health care across Europe. Health care indices (HCI) were established and a HCI score was assessed and compared with clinical outcome for HIV/TB coinfecting patients.

Methods: 1075 consecutive HIV-patients with TB diagnosed between 01/2004 and 12/2006 at one of the 52 participating clinics were enrolled. The five HCIs (table) were included in the multivariable Cox model, and a weighted score was established based on natural logarithms of the relative hazards for each of the indices that were significantly associated with death in the Cox model. Zero was a negative or missing measure of a given HCI, and a maximum score for an individual patient was 5. HCIs were assessed according to the region of residence and mean HCI score was calculated for each region. Proportion of patients having successful treatment outcome of TB disease and proportion of patients being alive/dead at 12 months of TB diagnosis were compared with the HCI score value.

Results: There were profound regional differences in the HCIs, and the mean HCI score was lowest in regions with high mortality, in particular in Eastern Europe [2.3 (95%CI 2.2-2.4 vs. 4.0 (95% CI 3.8-4.4) in Central/Northern Europe)] ($p < 0.0001$).

When comparing TB treatment outcomes according to the HCI score value, patients with a higher HCI score were more likely to have successful outcome (46%, 41%, 62%, 60%, 75% for the score of 0, 1, 2, 3 and ≥ 4 respectively). The cumulative probability of death within the first 12 months after a TB diagnosis decreased from 38% (95% CI 29-46%) among patients with HCI score 0 to 10% (95% CI 6-14%) among those with a score of ≥ 4 . In an adjusted Cox model, 1 unit increase in HCI score was associated with a 24% reduced mortality (RH 0.76 (95% CI 0.66-0.84), $p < 0.0001$).

Conclusions: The proposed HCI score provides a tool for future research and monitoring TB-treatment in individual HIV-patients. The HCIs may serve as a benchmark to assess and improve HIV/TB coinfection management in Europe and elsewhere.

No increase in the detection of nontuberculous mycobacterial infections at the Copenhagen CF Centre over the last 19 years

Qvist T¹, Katzenstein TL², Hansen CR¹, Thomsen VØ³, Pressler T¹

¹CF Centre Copenhagen, Department of Pediatrics, RH. ² Department of Infectious Diseases, Rigshospitalet (RH), Copenhagen. ³ International Reference Laboratory of Mycobacteriology, Statens Serum Institut, Copenhagen, Denmark.

Presenting author: Tavs Qvist, e-mail: tavs.qvist@gmail.com

Background: Various CF centres from Europe and North America have reported increasing prevalences of nontuberculous mycobacterial colonisation/infection over the last years. The aim of the present study was to analyse the frequency of nontuberculous mycobacterial detection among patients at the Copenhagen CF Centre from 1991-2010.

Patients and methods: From the central mycobacterial laboratory at the Statens Serum Institut all samples positive for non-tuberculous mycobacteria from CF patients were retrospectively identified. Patient files were subsequently scrutinized for clinical manifestations and treatment regimes. During the study period sputum samples for mycobacterial culture were not routinely performed. Samples were collected when clinically indicated. Mycobacterial analyses were however performed on all bronchoalveolar lavages.

Results: Between 241 and 302 patients were seen annually at the Centre during the study period. A total of 34 patients had nontuberculous bacteria detected ≥ 1 time, mainly from sputum samples. The median age at the time of detection was 13 (range 3-30). 21 patients had chronic bacterial infection mainly *P. auroginosa* (52%). The rest were infected with *A. xylosoxidans* (19%), *S. maltophilia* (14%) and *S. aureus* (14%). *M. abscessus*, *M. avium* and *M. goodnae* were isolated from 21, 10 and one patient respectively. Ten patients had only one positive sample. The median number of positive samples was 3,5 (range 1-72). During the study period the number of samples analysed increased with a four-fold increase from 2001 to 2009. No increase in detection rate was found (Figure 1). Of the 24 patients with more than one positive sample 22 (92%) received antimycobacterial treatment in either oral or intravenous form. 13 (54%) patients received both intravenous and oral treatment as recommended by international guidelines. Two years after detection, median FEV1 had improved slightly.

Discussion: Unlike other CF centers we detected no increase in nontuberculous mycobacterial infection during the last 19 years. Adhering strictly to international treatment guidelines is challenging as patient compliance and drug tolerability varies and because delaying treatment is occasionally contraindicated. Close monitoring after nontuberculous mycobacterium detection probably explains the slight increase in FEV1 after two years.

Conclusion: Over a 19-year period the nontuberculous mycobacterias detection rate among CF patients at the Copenhagen CF centre was stable, with a predominance of *M. abscessus* infections.

HIV and risk of venous thromboembolism: A Danish nationwide population-based cohort study

Line Dahlerup Rasmussen¹ Merete Dybdal², Jan Gerstoft³, Gitte Kronborg⁴, Carsten Schade Larsen⁵, Court Pedersen⁶, Gitte Pedersen⁷, Janne Jensen⁸, Lars Pedersen⁹, Henrik Toft Sørensen^{9,10}, Niels Obel³

¹Department of Infectious Diseases, Odense University Hospital, Odense, ²Department of Clinical Epidemiology, Aarhus University Hospital, Skejby, ³Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, ⁴ Department of Infectious Diseases, Copenhagen University Hospital, ⁵ Department of Infectious Diseases, Aarhus University Hospital, Skejby, ⁶ Department of Infectious Diseases, Odense University Hospital, Odense, ⁷Department of Infectious Diseases, Aalborg University Hospital, Aalborg, ⁸Department of Infectious Diseases, Kolding Sygehus, Kolding, ⁹ Department of Clinical Epidemiology, Aarhus University Hospital, Skejby, ¹⁰Department of Epidemiology, Boston University, Boston, MA, USA

Presenting author: Line Dahlerup Rasmussen, e-mail: linedahlerup@hotmail.com

Objective: The association between HIV and risk of venous thromboembolism (VTE) is controversial. We examined the risk of VTE in HIV-infected individuals compared to the general population and estimated the impact of low CD4 count, highly active antiretroviral therapy (HAART) and IV drug abuse (IDU).

Methods: We identified 4,333 Danish HIV patients from the Danish HIV Cohort Study and a population-based age- and gender-matched comparison cohort of 43,330 individuals. VTE diagnoses were extracted from the Danish National Hospital Registry.

Cumulative incidence curves were constructed for time to first VTE. Incidence rate ratios (IRR) and impact of low CD4 count and HAART were estimated by Cox regression analyses. Analyses were stratified by IDU, adjusted for comorbidity and disaggregated by overall, provoked and unprovoked VTE.

Results: 5 years risk of VTE was 8.0% (95%CI: 5.78-10.74) in IDU HIV patients, 1.5% (95%CI: 1.14-1.95) in non-IDU HIV patients and 0.3% (95% CI: 0.29-0.41) in the population comparison cohort. In non-IDU HIV patients, adjusted IRRs for unprovoked and provoked VTE were 3.42 (95% CI: 2.58-4.54) and 5.51 (95% CI: 3.29-9.23), respectively, compared to the population comparison cohort. In IDU HIV patients the adjusted IRRs were 12.66 (95% CI: 6.03-26.59) for unprovoked VTE and 9.38 (95% CI: 1.61-54.50) for provoked VTE. Low CD4 count had minor impact on these risk estimates, while HAART increased the overall risk (adjusted IRR:1.93 ;95% CI: 1.00-3.72).

Conclusion: HIV patients are at increased risk of VTE especially in the IDU population. HAART and potentially low CD4 count further increase the risk.

Serum procalcitonin in pulmonary tuberculosis

TA Rasmussen¹, **OS Sogaard**¹, **C Camara**², **PL Andersen**¹ and **C Wejse**^{1,2}

¹*Department of Infectious Diseases, Aarhus University Hospital, Skejby, Denmark*

²*Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau, <http://www.bandim.org>, Statens Serum Institut, Copenhagen, Denmark*

Presenting author: Thomas Aagaard Rasmussen, e-mail; thomrasm@rm.dk

Background: We aimed to evaluate the level and prognostic value of procalcitonin (PCT) in a West-African out-patient cohort with pulmonary tuberculosis (TB).

Method: Patients were clinically scored (TBScore), grouped into severity classes (SC) upon diagnosis and followed for 12 months. Patients were categorized after severity class (SCI+II or SCIII) and levels of PCT and CRP at diagnosis were compared. Fifty healthy volunteers from the study area were used as controls. Association with TBScore was explored using Spearman's rank correlation test. Survival curves stratified after baseline levels of PCT and CRP were graphed and compared using log rank test.

Results: We included 218 patients. Levels of PCT and CRP were low, but significantly higher in TB patients than controls ($p < 0.001$) and higher for patients in SCI+II compared to SCIII ($P = 0.021$ for PCT and $P < 0.001$ for CRP). HIV status did not influence results. We found positive correlations between both PCT and TBScore and CRP and TBScore. There was a significantly increased mortality risk with increasing baseline PCT ($P = 0.01$), whereas high CRP did not predict mortality rate ($p = 0.887$).

Conclusion: In West African pulmonary TB patients, levels of PCT were low but significantly increased with increasing severity of disease and predict mortality risk.

Changes in depression in a Cohort of Danish HIV-positive individuals: Time for routine screening

Rodkjaer L¹, Laursen T¹, Christensen NB², Lomborg K³, Ostergaard L¹, Sodemann M⁴

¹ Dept. of Infectious Diseases, Aarhus University Hospital, Skejby, ²The Research Clinic for Functional Disorders and Psychosomatic, Aarhus University Hospital, ³ Ass. Professor, PhD, Dept. of Nursing Science, School of Public Health, Aarhus University, DK-8000 Aarhus C, ⁴ Chief physician, PhD, Dept. of Infectious Diseases, Odense University Hospital, DK-5000 Odense.

Presenting author: Rodkjaer L, e-mail: Lottrodk@rm.dk

Background: The aim of this study was to follow a cohort of individuals positive for human immunodeficiency virus (HIV) for 3 years in order to assess changes in depression, adherence, emotional strains from living with HIV, and unsafe sex.

Methods: Participants were assessed for depression, adherence, emotional strain, and unsafe sex via a questionnaire. The Beck Depression Inventory II (BDI) was used to assess the prevalence and severity of depressive symptoms. Patients with a BDI score of 20 or above (moderate/major depression) were offered a clinical evaluation by a consultant psychiatrist.

Results: In 2005, 205 HIV-positive individuals participated in the study. Symptoms of depression (BDI>14) were observed in 77 (38%) and major depression (BDI ≥20) in 53 (26%) individuals. In 2008, 148 participants were retested (72% of original sample). Depression (BDI>14) was observed in 38 (26%) and symptoms of major depression (BDI ≥20) in 24 (16%) individuals. Patients at risk of moderate/major depression were more likely to be non-adherent to medications, practice unsafe sex, and suffer from emotional strains compared to patients not at risk of depression, both at baseline (2005) and follow-up (2008).

Conclusion: This study demonstrated a decline in depression scores over time and an association between the risk of depression and low medication adherence, stress, and unsafe sex. We recommend routine screening for depression to be conducted regularly to provide full evaluations and relevant psychiatric treatment.

Long-term Mortality in Patients Diagnosed with Pneumococcal Meningitis: A Danish Nationwide Cohort Study

Casper Roed, Frederik Neess Engsig, Lars Haukali Omland, Peter Skinhøj and Niels Obel

Epidemiklinikken, Rigshospitalet.

Presenting author: Casper Roed, e-mail: casperroed@hotmail.com

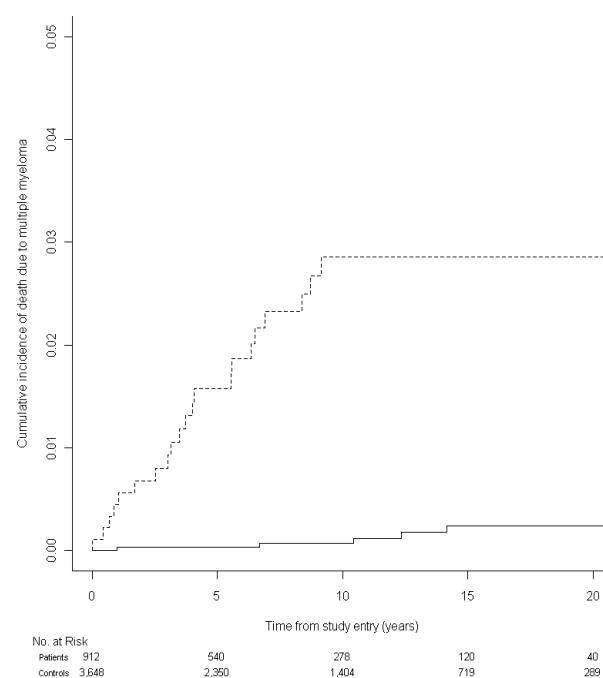
Objective: To determine the long-term mortality and the causes of death in patients diagnosed with pneumococcal meningitis.

Methods: We performed a nationwide, population-based cohort study including all Danish patients diagnosed with pneumococcal meningitis from 1977 through 2006 and alive 1 year after diagnosis. Data were retrieved from medical databases in Denmark. The absolute and relative risks of all-cause and cause-specific death were analyzed by using Kaplan-Meier survival curves, Poisson regression analysis, Cox regression analysis, and cumulative incidence functions.

Results: We identified 2,131 pneumococcal meningitis patients and an age- and gender-matched, population-based cohort of 8,524 individuals. Compared with the background population, the pneumococcal meningitis patients had an increased long-term mortality varying from an 8-fold increased mortality in the age category 0–<20 years to a 1.5-fold increased mortality in those aged 60–<80 years. The increased risk of death stemmed from neoplasms, liver diseases, and nervous system diseases. The excess mortality due to neoplasms stemmed mainly from a 5-fold increased risk of death due to hematologic neoplasms. The 10-year risk of death due to multiple myeloma was 2.9% (95% confidence interval (CI): 1.4%, 5.3%) in patients diagnosed with pneumococcal meningitis after the age of 50 years compared with 0.1% (95% CI: 0.0%, 0.2%) in population controls.

Conclusions: To improve survival in patients surviving the acute phase of pneumococcal meningitis, physicians should meticulously screen this patient population for neurologic sequelae and comorbidity predisposing to the disease.

Age	Follow-up	Adjusted	MRR	95% CI
0 - <20	0 - <10	No	8.04	3.02, 21.42
	Yes	6.04	2.06, 17.67	
10 - <30	No	8.05	0.73, 88.82	
	Yes	6.36	0.51, 78.83	
20 - <40	0 - <10	No	4.60	1.67, 12.68
	Yes	2.38	0.70, 8.12	
40 - <60	0 - <10	No	1.90	0.82, 4.40
	Yes	1.99	0.83, 4.77	
60 - <80	0 - <10	No	3.83	2.78, 5.27
	Yes	3.25	2.33, 4.54	
80+	0 - <10	No	2.35	1.44, 3.85
	Yes	2.20	1.28, 3.78	
0 - <20	0 - <10	No	1.58	1.34, 1.86
	Yes	1.45	1.23, 1.71	
10 - <30	No	1.50	1.18, 1.91	
	Yes	1.45	1.13, 1.85	
40 - <60	0 - <10	No	1.33	1.08, 1.64
	Yes	1.32	1.06, 1.63	
60 - <80	0 - <10	No	1.20	0.91, 1.58
	Yes	1.20	0.90, 1.59	



Regulatoriske T celler ved akut inflammation: en endotoksinmodel

Ronit A¹, Plovsing R², Madsen H³, Ullum H⁴, Andersen AB⁵, Hartling HJ¹, Iversen M⁶, Gaardbo J¹, Poulsen SD¹

1. Epidemiklinikken 5132, Rigshospitalet. 2. ITA 4131, Rigshospitalet 3. Vævstype Laboratoriet, Rigshospitalet 4. Klinisk Immunologisk, Rigshospitalet. 5. Medicinsk Afdeling C, Infektionsmedicin, Odense Universitetshospital. 6. Medicinsk Afdeling B, Rigshospitalet.

Præsenterende forfatter: Andreas Ronit, e-mail: roniten@hotmail.com

Baggrund

Indgift af lipopolysakkarid (*LPS*) til raske individer inducerer et akut inflammatorisk respons, som i en vis grad efterligner det inflammatoriske respons set hos patienter med fx gram negativ sepsis. Lymfopeni efter i.v. *LPS* stimulation kan observeres med nadir efter 4 timer. Efterfølgende normalisering ses efter 10-12 timer. Effekten af *LPS* på lymfocytære subpopulationer er endnu uafklaret. Fokus i dette studie er således effekten på lymfocytpopulationer med særlig fokus på regulatoriske T celler (Tregs). Tregs er unikt vist at udtrykke Toll Like 4 receptoren (TLR 4), hvortil *LPS* er ligand. In vitro er det desuden vist, at *LPS* stimulering fører til proliferation af Tregs samt øger Tregs evne til hæmning af CD 4 celler. Om denne proliferation samt øget evne til suppression også gør sig gældende in vivo, eller hvorvidt *LPS* evt. fører til en op- eller nedregulering af TLR4 på Tregs er ukendt.

Formål

- a) At undersøge virkningen af *LPS* stimulering i blod og lunger på forekomst af lymfocytære subpopulationer i hhv. blod og lunger, herunder særligt Tregs.
- b) At undersøge Tregs suppressive evner over for CD4 før og efter *LPS* stimulation i blodet.
- c) At undersøge virkningen af *LPS* stimulering i blodet på TLR4 ekspressionen hos Tregs.

Metoder

Interventionen består af a) Intravenøs injektion af *LPS* (4 ng/kg) og endobronchial instillation af placebo (NaCl) eller b) intravenøs injektion af placebo (NaCl) og endobronchial instillation af *LPS* (4 ng/kg). Forsøgspersonerne (n=15) indgår i begge interventioner med minimum to uger i mellem. Bronkoskopi med BAL samt blodprøver foretages ved t= 0 foruden ved t =2,4,6,8 eller 24 timer begge forsøgsdage. Ovennævnte metode er opstillet af Ronni Plovsing i forbindelse med et andet studie og foregår på ITA, Rigshospitalet.

Til kvantitativ analyse af Tregs og immunologiske subpopulationer (aktiverede, naive og aldrende lymfocytter) anvendes flowcytometry. Magnetisk isolation af regulatoriske Tceller samt mRNA oprensning fra Tregs bruges til rtPCR bestemmelse af TLR-4. Suppresionsassay vil blive forsøgt opsat og anvendt til kvalitativt at undersøge Tregs. Luminex bruges til bestemmelse af cytokinerne (TNF α , IL-1, IL-6 og IFN γ) på stimuleret og ustimuleret fuldblod.

Resultater

Patientinklusion og intervention med *LPS* er færdiggjort og analysearbejdet er netop påbegyndt, hvorfor de første flowcytometri data forhåbentligt kan præsenteres.

Title Chronic kidney disease in HIV patients with normal eGFR at baseline- results from EuroSIDA

Ryom L.; *CHIP, Faculty of Health Science, Univ of Cph, DK*, Mocroft A.; *Univ College London Medical School Royal Free UK*, Reiss P.; *Academisch Ziekenhuis bij de Univ van Amsterdam NHL*, Ledergerber B.; *Univ Hosp Zurich, Div of Infect Diseases CH*, De Wit S.; *CHU Saint-Pierre, Dept of Infect Diseases BG*, Duiculescu D.; *Dr. Victor Babes Hosp, Spitalul de Boli Infectioase si Tropical RM*, Monforte A.D.; *Ospedale San Paulo, Clinica delle Malattie Infettive e Tropicali, I*, Murphy M.; *Royal London hosp, Grahame Hayton unit, Ambrose King center UK*, Lundgren J.D and Kirk O.; *CHIP, Faculty of Health Science, Univ of Cph/ Dept. of infect diseases RH , DK*- for the EuroSIDA study group. Only Ryom L. will be participating in the meeting: lrn@cphiv.dk

Background Chronic kidney disease (CKD) is an emerging co-morbidity among HIV patients. Recent EuroSIDA analyses have identified CKD risk factors in HIV patients including hypertension, diabetes, hepatitis C, age>50, low CD4 count, prior AIDS events and cumulative exposure to certain antiretrovirals (ARVs; tenofovir, indinavir atazanavir and probably lopinavir/ritonavir).

Objectives We aimed to extend our previous findings by estimating the CKD incidence among patients with normal kidney function at baseline with and without other risk factors, in order to disentangle if ARVs also pose a risk to patients with normal kidney function, and not only to those with pre-existing impairment.

Methods Cockcroft-Gault equation standardised for body surface was used to estimate Glomerular filtration rate (eGFR, ml/min/1.73m²). Patients with baseline eGFR> 90 were included. Baseline was defined as the first eGFR assessment after 01.01.2004. CKD was defined as 2 consecutive eGFR<60 (≥ 3 months apart). Follow-up was from baseline until CKD or last eGFR. Unadjusted incidence rates (IR) are presented per 100 PYFU and stratified by cumulative ARV exposure.

Results 4824 patients had baseline eGFR>90. They were predominantly white (86.4%), male (74.4%) infected via homosexual contact (41.4%). At baseline 17.6% had hypertension, 3.7% diabetes and 24.1% hepatitis C. Median age was 40 (IQR: 34.6-45.1) years, and median CD4 count 446 (300-640) cells/mm³. During 15391 PYFU and a median follow-up of 41 (IQR 21-56) months, 34 (0,7%) developed CKD (IR 0.22, 95%CI 0.15-0.30). Among patients without traditional risk factors, 7 patients developed CKD during 8076 PYFU (IR 0.09 95%CI 0.04-1.18). In unadjusted analyses CKD incidences increased with increasing cumulative ARV exposure for the ARVs tested (test for trend significant for all drugs investigated), table.

Conclusions This study of almost 5000 patients and a median follow-up >3 years demonstrates that CKD development from normal kidney function was infrequent. The IR was higher in patients with renal risk factors and those cumulative exposed to the ARVs investigated in unadjusted models. This suggests that ARVs might also pose a risk in patients with normal kidney function. Adjusted analyses were not possible due to low IR. Future studies with substantially larger size and longer follow up are needed to reproduce the findings in adjusted models, determine the role of cumulative exposure to individual ARVs and investigate the clinical implications.

Short-term gentamicin therapy and risk of renal toxicity in medical patients with bacteraemia

Marianne H. Spanggaard, Bo L. Hønge, Henrik C. Schönheyder, and Henrik Nielsen

Departments of Infectious Diseases and Clinical Microbiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark

Objectives: Since renal safety has been questioned for gentamicin therapy even when dosed once-daily, we assessed plasma creatinine levels after gentamicin treatment in bacteraemic patients in medical wards at a Danish hospital.

Materials and Methods: Patients >18 years with community-acquired bacteraemia were candidates for this retrospective study if they did not have chronic renal disease or malignancy. We obtained information on antibiotic treatment from a microbiological bacteraemia database and a detailed chart review comprising patients treated with gentamicin once-daily for ≤ 5 days and a balanced sample of patients not receiving gentamicin. Data were analysed in a cohort design with gentamicin being the exposure and the primary end-point being elevation of plasma creatinine $>40 \mu\text{mol/L}$ from baseline; mortality within 30 days was the secondary end-point.

Results: We identified 165 patients treated empirically with gentamicin and 150 patients treated with antibiotics that did not include gentamicin. Increase in plasma creatinine was equally common in patients exposed to gentamicin (13/165, 7.9%) and not exposed (13/150, 8.7%) ($p=0.80$). Concerning the 26 patients with the renal end-point, creatinine levels within normal range were reached in 8/12 (67%) evaluable patients among the exposed and 7/9 (78%) evaluable patients among the non-exposed ($p=0.66$). Thirty-day mortality was 7.9% among exposed vs. 7.3% among non-exposed ($p=0.86$).

Conclusion: We did observe renal impairment among patients with bacteraemia but independently of short-term gentamicin use. For most patients with renal impairment during hospitalization plasma creatinine reached a normal level during one year of follow-up. We suggest that renal toxicity should not be considered a barrier to short-term gentamicin therapy in combination with a β -lactam for the septic medical patient.

Searching for studies on bacteremia, bloodstream infection, septicemia, or whatever the best term is: a note of caution

Mette Søgaard^{1,2}, Jens Peter Andersen³, Henrik C. Schönheyder¹

¹*Department of Clinical Microbiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark*

²*Department of Clinical Epidemiology, Clinical Institute, Aarhus University Hospital, Aarhus, Denmark*

³*Medical Library, Aalborg Hospital, Aarhus University Hospital*

Correspondence: Mette Søgaard, email: mette.soegaard@rn.dk

Objective: Several terms are used for bacteremia. To demonstrate that inconsistent terminology hamper retrieval of relevant information, we compared the yield of articles from PubMed/MEDLINE using the terms bacteremia, bloodstream infection, and septicemia, respectively.

Methods: We searched for articles published between 1966 and 2009. The relation between articles recovered by different queries was depicted using a Venn diagram. To examine the content of the retrieved articles, we extracted all MeSH terms in each query set and compared the topics using a cosine similarity measure.

Results: The number of recovered articles differed greatly by term; as little as 53 articles were captured by all three terms. The query for bacteremia was most successful; of the articles retrieved, 21438 (84.1%) were specific for this query. Only 2243 (19%) of the 11796 articles recovered by the free-text query for bloodstream infection, was retrieved by the bacteremia query. When entering bloodstream infection as a phrase, 46.1% of the records were shared with the bacteremia query. Similarity measures ranged from 0.52 when comparing bloodstream infection as phrase and septicemia to 0.78 for bloodstream infection as phrase and bacteremia.

Conclusion: Inconsistent terminology has a major impact on the yield of articles with regard to both numbers and contents. The best remedy will be to agree on the terminology and clearly communicate this to the scientific community. A partial, but not sufficient solution is for the National Library of Medicine to add bloodstream infection to the MeSH vocabulary.

Diabetes, Glycemic Control and Risk of Bacteremia with Hemolytic Streptococci group A, B and G in Adults: A 15-year Population-based Case-control Study

Reimar W. Thomsen¹, Anders Riis¹, Sia Kjeldsen², Henrik T. Sørensen¹, Henrik C. Schönheyder²

¹*Department of Clinical Epidemiology, Clinical Institute, Aarhus University Hospital, Aarhus, Denmark;*

²*Department of Clinical Microbiology, Aarhus University Hospital, Aalborg*

Corresponding author: Reimar W. Thomsen (E-mail: r.thomsen@rn.dk)

Objective: To examine the association between diabetes, glycemic control and group A, B and G hemolytic streptococcal bacteremia in adults.

Methods: In this population-based case-control study we identified all adult patients with first-time microbiologically documented bacteremia with hemolytic streptococci between 1992 and 2006, using health care databases in Northern Denmark. For each case, ten sex- and age-matched population controls were selected from Denmark's Civil Registration System. We used conditional logistic regression to compute the odds ratio (OR) for streptococcal bacteremia among persons with and without diabetes, controlling for potential confounding factors.

Results: We identified 397 adult patients with bacteremia with hemolytic streptococci (median age 67 years, 51% women), of which 63 (17%) had diabetes. Persons with diabetes had a 2.1-fold increased risk of streptococcal bacteremia compared with population controls (adjusted odds ratio (OR) = 2.1; 95% confidence interval (CI) 1.5-2.9). For persons with type 1 diabetes, the adjusted OR was 14.8 (95% CI: 2.4-91.2). The risk of streptococcal bacteremia increased with longer diabetes duration, and poor glycemic control conferred higher risk estimates: adjusted OR = 1.5 (95% CI: 0.8-3.0) for HbA_{1c} level <7%, and OR = 3.6 (95% CI: 1.6-8.1) for HbA_{1c} level ≥9%. The risk increase associated with diabetes was high for group B streptococcal bacteremia (OR 3.5, 95% CI 1.8-7.0) and for group G streptococcal bacteremia (OR 2.6 (1.6-4.4), whereas there was no clear risk increase for group A streptococcal bacteremia (OR 1.2, 95% CI 0.7-2.2). These diabetes-serogroup-specific associations were observed consistently regardless of underlying foci of infection.

Conclusions: Diabetes is a strong risk factor for group B and G but not group A hemolytic streptococcal bacteremia. The risk of streptococcal bacteremia increases with diabetes duration and poor long-term glycemic control.

Decreasing treatment delay in Tuberculosis in Guinea Bissau, West Africa: a longitudinal cohort study

Virenfeldt J^{1,2}, Rudolf F^{1,2}, Gomes V¹, Aaby P^{1,3}, Rabna P¹, Camara C¹, Petersen E², Wejse C^{1,2}.

¹ *Bandim Health Project, INDEPTH network, Apartado 861, Bissau, Guinea-Bissau*

² *Dept. of Infectious Diseases, Aarhus University Hospital, Skejby, Denmark;*

³ *Danish Epidemiology Science Center, Statens Serum Institut, Copenhagen, Denmark*

Contact e-mail: javirenberg@gmail.com

Aims: To describe the time dependent changes in patient treatment delay and the importance of delay for the outcome of tuberculosis (TB) infection.

Background: Previous studies have found that a treatment delay in tuberculosis is associated with both individual patient prognosis and transmission rate in society. Change in delay over time is rarely reported.

Materials and Methods: The data were collected from a cohort at the Bandim Health Project in Guinea Bissau. Cases were included upon diagnosis at the three local TB clinics and the national TB reference hospital. TB diagnosis was made according to WHO criteria and clinical severity was described using the Bandim TBscore calculated from clinical variables. Delay was assessed by patient questionnaires.

Results: 1424 cases were diagnosed with active TB-disease, of which 973 cases were included in the study. The median treatment delay was 12.1 weeks. TB treatment delay decreased with a factor 10% per year during the study period, equivalent to a median delay of 14.6 weeks in 2003 and a median delay of 8.6 weeks in 2010. The total treatment delay was not influenced by HIV-status, but median TBscore at inclusion was significantly influenced by total treatment delay.

Conclusion: Treatment delay in tuberculosis cases in Guinea Bissau is decreasing. Delay is associated with clinical severity at treatment start but not with HIV status.