

Exam Q8 Research

Research in Personalized Healthcare

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Module coördinatoren:

- Topics in Personalized Healthcare Research: dr Jan van den Brand
- Infectious Disease and Global Health: dr Foekje Stelma
- Alzheimer's Disease and Dementia: prof dr Marcel Olde-Rikkert
- Renal Disorders: prof dr Joost Hoenderop
- Nanomedicine: prof dr Alessandra Cambi

Aantal vragen: 25

Maximum score: 90

Vragen hebben deels betrekking op de abstracts en deels op de stof die tijdens de modules is behandeld. De abstracts worden een week van tevoren gedeeld via BrightSpace.

Infectious Disease and Global Health

HIV cascade of care in Greece: Useful insights from additional stages

Background

Aiming to eliminate HIV infection, UNAIDS has set a global “90-90-90” target by 2020. We sought to construct a 6-stages HIV Cascade of Care (CoC) in Greece, overall and by risk group, to assess risk-group and stage-specific progress in achieving the UNAIDS target.

Patients and methods

Combining data from the HIV/AIDS surveillance system and a population-based HIV cohort study, the CoC included: i) number of people living with HIV (PLHIV) by end of 2013; ii) proportion of PLHIV ever diagnosed; iii) proportion of diagnosed linked-to-care iv) proportion of linked-to-care ever initiating antiretroviral therapy (ART); v) proportion of treated who retained-in-care vi) proportion of those retained-in-care who were virally suppressed (<200 copies/mL) at their last visit (01/07/2012-31/12/2013).

Results

In 2013, 14147 PLHIV were in Greece. Overall, proportions of each stage in the cascade were: 78.4% diagnosed; 86% linked-to-care; 78.5% initiated ART; 86.4% retained-in-care, and 87.1% virally suppressed. Totally, 42.6% of all PLHIV were virally suppressed. The percentage diagnosed was lower among heterosexual men and women (heterosexuals) than in MSM (men who have sex with men) or PWID (people who inject drugs). Most MSM were linked to care (97.2% of diagnosed) while a substantial proportion of PWID were not (80.8% of diagnosed). Once treated, PWID remained in care in similar proportions to MSM. Unlike PWID, a high proportion of the retained in care MSM and heterosexuals achieved viral suppression.

Conclusions

At the end of 2013, we identified gaps in the HIV CoC in Greece, which differed across risk groups. Targeted interventions are critical in optimizing early diagnosis and timely linkage. A 6-stage CoC, stratified by risk group, can inform strategic public health planning in improving HIV treatment outcomes.

3. This paper studies HIV-care and HIV-related outcomes in HIV-infected individuals within Greece. HIV-infected individuals in western countries like the Netherlands or Greece can be categorized according certain risk groups: men who have sex with men, people who inject drugs, and heterosexuals. Which risk group that is important in sub Sahara Africa is not discussed in the paper? [2 points]
4. The paper describes six stages in the Cascade of Care (CoC) The third stage is defined by the proportion of those diagnosed who were linked-to-care. Individuals with at least one CD4 measurement reported, an AIDS diagnosis, or who initiated

cART were considered as linked to care. Explain why reporting CD4 counts is a good public health marker for HIV. [4 points]

5. In the abstract, there is a discrepancy between the number of people living with HIV and patients diagnosed with HIV. Explain, why there is a discrepancy between the two numbers.[4 points]

6. The proportion of *diagnosed* HIV infection among those living with HIV is higher among men who have sex with men and person who inject drugs compared to heterosexuals and migrants. Give three reasons for these differences arise.[6 points]

7. You aim to create a prevention program for men who have sex with men in order to reduce the number of new HIV infections. How can PrEP contribute to your preventive strategy? [4 points]

Alzheimer's Disease

Call for proposal in Personalized Medicine in the EU Joint programming for Alzheimer's disease and other dementias.

Introduction of the call

Neurodegenerative diseases are characterised by a large variability in their origins, mechanisms and clinical expression. When searching for a medical solution, e.g. a treatment or an optimised approach for care, this large variability constitutes a major hurdle if not controlled. Indeed a treatment addressing one disease pathway may not be useful for all patients experiencing the relevant symptoms. Thus, one of the greatest challenges for treating neurodegenerative diseases is the deciphering of this variability.

Personalised Medicine refers to a medical model using characterization of individuals' phenotypes and biomarkers (genotypes and molecular profiling) for tailoring the right (individual) therapeutic strategy, for determining the predisposition to disease and/or for delivering timely and targeted prevention.

Research Theme "Diagnosis"

Develop studies that validate use of biomarkers, noninvasive imaging, high throughput "omics" approaches and big data analyses, and thus improve diagnosis of Alzheimer's disease at all stages.

Research Theme "Care"

Propose a personalized medicine study that opens up new and important opportunities for optimising care outcomes, also in coping with cognitive decline and handling burdensome neuropsychiatric symptoms. Focus on better understanding of the large variability in the origins, mechanisms and clinical expression of dementia at the patient level.

Suppose you can choose out of the biomarkers below in personalizing the care for a patient with dementia:

- Advanced glycation end products concentration in blood
- Angiotensin Converting Enzyme concentration in plasma
- Beta 42 amyloid concentration in plasma
- Beta 42 amyloid concentration in liquor
- Beta 40 amyloid concentration in liquor
- KAT8 genotype
- Phosphorylated tau in liquor
- Phosphorylated tau in plasma
- Tau concentration in liquor
- Tau concentration in plasma
- Total cholesterol

8. Which two biomarkers would help you most in assessing whether the patient is suffering from Alzheimer's disease? [2 points]

9. Does applying these two biomarkers as the core of your research proposal make it fulfill the definition of Personalized Medicine as stated in the call for proposals (see abstract)? Explain your answer (in max 20 words). [3 points]
10. Consider the following three etiologic mechanisms relevant in AD etiology: 1) genetic predisposition; 2) aging related damage accumulation; 3) Amyloid-beta aggregation. Which of these three is becoming least relevant in Alzheimer at high age? Briefly explain why. [3 points]
11. Suppose you want to propose a diagnostic research project in the call described in the abstract. Your study would focus on validating the diagnostic value of a new plasma biomarker for early recognizing AD patients with depressive symptoms. For the inclusion of patients in your study you can use different criteria: a) diagnostic criteria strictly based on biomarkers (e.g. the ATN classification); and b) functional performance, physical examination, and neuropsychological test results, added to exclusion criteria based on presence of comorbidity. What inclusion criteria fit best with the study aim? Explain your answer with two arguments. [6 points]
12. You want to propose a study for the research theme "Care". Often the burden of dementia care for family members is increased by the family members' notion that patients underperform, or that they intentionally show behavioral problems. Your idea is to give patients and family personalized explanation of the patient's MRI scan and explain symptoms by describing the consequences of the brain lesions visible on the MRI. Explain how describing the impact of a lesion in the occipital region of the brain (visible on a MRI scan) can result in paranoid delusions, and how that information can help family members provide better informal care. [6 points]

Renal Disorders

Enhanced passive Ca^{2+} reabsorption and reduced Mg^{2+} channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia.

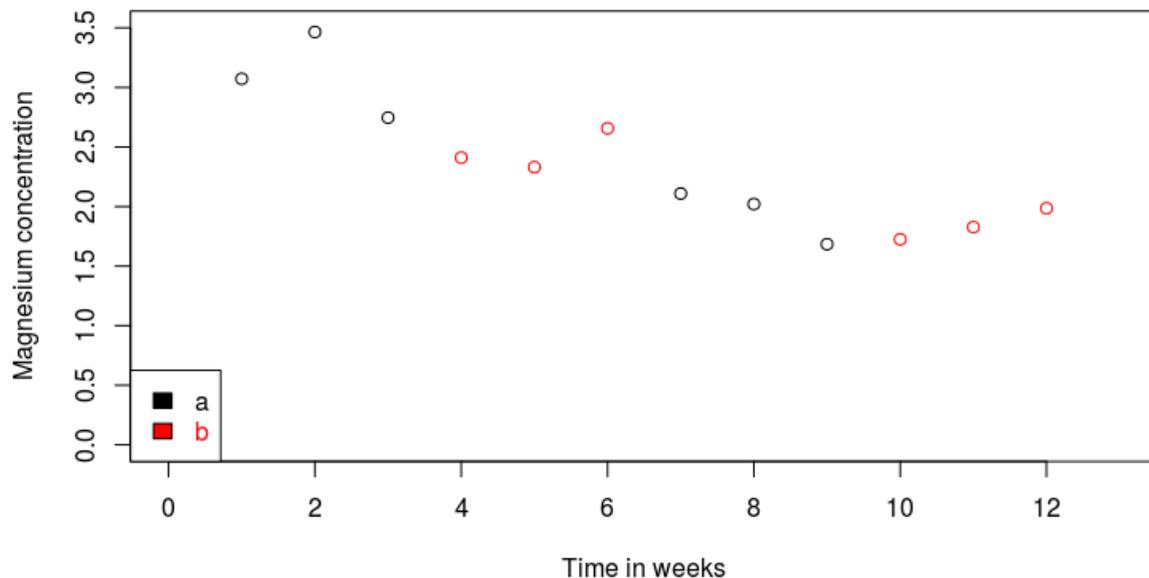
Thiazide diuretics enhance renal Na^+ excretion by blocking the $\text{Na}^+\text{-Cl}^-$ cotransporter (NCC), and mutations in NCC result in Gitelman syndrome. The mechanisms underlying the accompanying hypocalciuria and hypomagnesemia remain debated. Here, we show that enhanced passive Ca^{2+} transport in the proximal tubule rather than active Ca^{2+} transport in distal convolution explains thiazide-induced hypocalciuria. First, micropuncture experiments in mice demonstrated increased reabsorption of Na^+ and Ca^{2+} in the proximal tubule during chronic hydrochlorothiazide (HCTZ) treatment, whereas Ca^{2+} reabsorption in distal convolution appeared unaffected. Second, HCTZ administration still induced hypocalciuria in transient receptor potential channel subfamily V, member 5-knockout (Trpv5-knockout) mice, in which active distal Ca^{2+} reabsorption is abolished due to inactivation of the epithelial Ca^{2+} channel Trpv5. Third, HCTZ upregulated the Na^+/H^+ exchanger, responsible for the majority of Na^+ and, consequently, Ca^{2+} reabsorption in the proximal tubule, while the expression of proteins involved in active Ca^{2+} transport was unaltered. Fourth, experiments addressing the time-dependent effect of a single dose of HCTZ showed that the development of hypocalciuria parallels a compensatory increase in Na^+ reabsorption secondary to an initial natriuresis. Hypomagnesemia developed during chronic HCTZ administration and in NCC-knockout mice, an animal model of Gitelman syndrome, accompanied by down regulation of the epithelial Mg^{2+} channel transient receptor potential channel subfamily M, member 6 (Trpm6). Thus, Trpm6 downregulation may represent a general mechanism involved in the pathogenesis of hypomagnesemia accompanying NCC inhibition or inactivation.

13. Thiazides are frequently prescribed to lower an increased blood pressure.

Thiazides block the $\text{Na}^+\text{-Cl}^-$ cotransporter (NCC) and are often used to lower the calcium concentration in the urine, a positive side effect of the drug. Explain how thiazides affect the calcium balance and provide a schematic diagram about the mechanism. [2 points]

14. Explain how a mutation in the gene that encodes the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter (NKCC2) in the limb of Henle results in tubular magnesium wasting. [2 points]

A physician and patient with Gitelman Syndrome have decided to try magnesium supplementation to treat magnesium wasting. In order to find the optimal treatment, they have performed an N-of-one study to compare two possible therapies. The therapies have been labeled 'a' and 'b' and were administered over four treatment periods of 3 weeks each. The figure below shows the magnesium concentration in plasma at the end of each week.



15. What kind of bias can be observed from this figure? [2 points]

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16. What could have been done in the design of the study to alleviate this bias? [2 points]

17. The epidermal growth factor (EGF) hormone stimulates the EGFR in the renal distal convoluted tubular cell. As a consequence renal transepithelial magnesium transport is enhanced. Patients with mutations in EGF suffer from hypomagnesemia. Design 2 approaches which activate a renal molecular target to normalize the hypomagnesemia. Illustrate these approaches with a renal cell model showing the molecular transporters/targets.[6 points]

18. Patients with Gitelman Syndrome that suffer potassium wasting via urine have low levels of potassium in serum. Therefore, these patients require potassium supplementation or treatment with spirolactone, or a combination of both. Schematically draw a timeline for a N-of-one trial to study a drug treatment for the treatment of Gitelman Syndrome that includes these 3 possible regimens.[6 points]

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8RNM Nanomedicine

Chemically activatable viral capsid functionalized for cancer targeting

Aim

To design a theranostic capsule using the virus-like nanoparticle of the hepatitis E virus modified to display breast cancer cell targeting functional group (LXY30).

Methods

Five surface-exposed residues were mutated to cysteine to allow conjugation to maleimide-linked chemical groups via thiol-selective linkages. Engineered virus-like nanoparticles were then covalently conjugated to a breast cancer recognized ligand, LXY30 and an amine-coupled near-infrared fluorescence dye.

Results

LXY30-HEV VLP was checked for its binding and entry to a breast cancer cell line and for tumor targeting in vivo to breast cancer tissue in mice. The engineered virus-like nanoparticle not only targeted cancer cells, but also appeared immune silent to native hepatitis E virus antibodies due to epitope disruption at the antibody-binding site.

Conclusion

These results demonstrate the production of a theranostic capsule suitable for cancer diagnostics and therapeutics based on surface modification of a highly stable virus-like nanoparticle.

19. Briefly describe, in a few sentences, what Chen et al. mean with the term “theranostic”. [2 points]
20. The authors’ ultimate plan is to generate theranostic capsules in cancer Please mention one possible payload (*i.e.* the capsule cargo) that could serve in anticancer therapeutics. [2 points]
21. Explain why it is important that the engineered virus-like nanoparticles (VLPs) appeared immune silent to native hepatitis E virus antibodies. [4 points]
22. What molecular characteristic of the hepatitis virus E major capsid protein allows its use for building (theranostic) **capsules** ? [6 points]

23. What is the most important criterion that should be fulfilled before these VLPs can be used in the clinic? Briefly motivate your answer. [6 points]