Minortrack Child Healthcare

CAT Current research in pediatrics, date 28 October 2016

This examination contains **9** open questions. Each question contains information about how many points can be earned. The maximum number of points to earn for the test is 70. The results of this test determine 50% of the final grade for this course. The other 50% is determined by the results from the writing assignment.

Only write down answers in logical sentences, no loose information with lack of structure. Your grade is not influenced by the number of words you use in your answers, unless this is specified otherwise at the question.
It is not permitted to give more answers than specified in the question (e.g. three criteria, four aspects). So don't write down six answers in hoping three of them are correct.

This examination takes two hours (+ 30 minutes for the students with extra time).

Practical matters

- Mobile phones have to be switched off and be put in your bag under your chair.
- Only necessities for this examination are allowed on the table.
- Questions about the content of the examination will not be answered.
- You can send your comments to the course representation (CVW) afterwards.
- Visiting the toilet is not permitted.
- Fraud will be punished.
- You are obliged to follow the instructions of the invigilator at all times.
- In the event of a technical malfunction, raise your hand so that your name can be written down by the invigilator. If your name is not written down, you have no right to complain afterwards.
- If you have not signed up for this examination, you will not receive a result.
    - You can object to the fact that you can no longer sign up for the examination after the subscription deadline.
    - Send in your appeal within one week after the examination. More information you will find on www.vu.nl/intekenen.

Good luck!

Fill in your details and save the document at regular intervals. (Ctrl+s)

When you have answered all the questions, please close the document and submit it through the 'Exam submission' link on your desktop. See the instructions on the last page.

Student number	
First name	
Prefix	
Surname	

Question 1a (3 points;1 point per criterium) Lectures Berkhout & vd Meij

Mention three important functions of the neonatal intestinal microbiome

- Retaining mucosal surface integrity
    - (→ by enhancement of tight junctions, stimulation of mucin production, downregulation of cytokine production)
- Maturation of a naïve immune system
- Metabolism/ nutrition

(→ Of essential vitamines, energy uptake)

Question 1b (2 points)

Explain what intestinal microbial dysbiosis means.

- Microbial dysbiosis is a term for a microbial imbalance or maladaptation leading to an abnormal gut flora

Question 1c (2 points)

How can intestinal microbial dysbiosis hypothetically provoke sepsis?

Presence of pathogenic bacteria may oppress healthy microbiota (commensals). Healthy, balanced microbiota is necessary for maintaining mucosal integrity. Dysbiosis may interrupt this mucosal integrity, leading to translocation of bacteria through the mucosal wall into the bloodstream, eventually leading to sepsis

Question 1d (3 points;1 point per criterium)

Several pediatric diseases are associated with microbial dysbiosis.
Name three factors of significant influence on the neonatal microbiome.

- Early administration of antibiotics
- Feeding pattern (for example the difference between breastmilk and formula)
- Way of birth (c-section of vaginal)

Ook goed gerekend:

- Center of birth of geologische plaats van geboorte heeft een significante invloed op microbioom
- Microbioom van de moeder (vagina), transmissie tijdens partus
- Omgevingsfactoren (bacteriën op speen, huid van ouders,etc)

Question 1e (4 points; 2 points per characteristic)

Over the past decade, an increasing number of studies demonstrated that microbiota has an important role in the etiology of pediatric inflammatory bowel disease (IBD). In addition, recent studies demonstrated an alteration in microbiota prior to an exacerbation of IBD, making microbiota analysis an interesting candidate as biomarker for predicting IBD exacerbations. You want to develop a device which allows for microbiota analysis which can be used in the outpatient clinic.
Mention two important characteristics the aforementioned device should possess, before it can be implemented in clinical practice.

- Results must be acquired quick , especially if a patient is suspected of an IBD exacerbation. You don't want to have any delay in starting the essential treatment.
- Results should be accurate and reliable (indien student benoemd dat het een hoge sensitiviteit en specificiteit nodig heeft, kan dit ook worden goed gerekend)
- Kosten, analyse zo goedkoopmogelijk

Question 1f (2 points; 1 point per reason)

You want to develop a device allowing for microbiota analysis which can be used in the outpatient clinic in order to detect IBD exacerbations. You have the option to use blood or feces as analytical medium for your new device. Assume that both feces and blood samples provide exactly the same results.
Mention a pro- (1point) and a contra reason (1point) for using blood instead of feces.

Pro: Always obtainable

- Ook goed gerekend als student schrijft dat feces is afhankelijk van of een patiënt toevallig op dat moment moet defeceren.

Contra: invasive procedure

- Ook goed gerekend als student schrijft dat feces op een noninvasieve manier verkregen kan worden

Question 2a (3 points; 1 point per example) lectures Tutu vd Furth & vd Kuip

One of the features of encephalitis is encephalopathy.
Give three examples of encephalopathy that have NO direct infectious origin.

Antwoord: het gaat hier om de **niet** infectieuze differentiaal diagnose van encefalopathie:

1. Anatomisch: b.v bloeding of tumor:
2. Metabool: b.v ureumcyclusdefect:
3. Toxisch: b.v alcohol: directe toxiciteit
4. Para-infectieus/immunologisch: b.v. ADEM of chorea

Question 2b (2 points)

Which form of viral meningo-encephalitis is the most common in the Netherlands?

enterovirus-meningo-encefalitis

Question 2c (2 points; ½ point per item)

Name 4 characteristics of a normal clinical course of viral meningo-encephalitis (1/2 point per item, 2 points total).

prikkelbaarheid, koorts, malaise, jonge kinderen moeten meestal enkele dagen (3-7) worden opgenomen

Question 2d (2 points)

What is the long term prognosis for this disease?

over het algemeen herstel zonder restverschijnselen

Question 2e (2 points; 1 point per cause)

Name two other viral causes for meningo-encephalitis. (1 point per cause)

O.a.: Herpes simplex, herpes zoster, HIV, bofvirus

Question 2f (2 points; 1 point per cause)

Name two viral causes for congenital encephalopathy. (1 point per cause)

CMV
Zika

CASE 1 (3 points) lecture vd Kuip, Bakker

Case vignette
A 15-year-old girl presents to the emergency department (ED) with confusion and a seizure. Her parents note that she has been more forgetful and irritable for the past 10 days. Her behavior has also become bizarre, and at one point she thought the television was talking to her. The pediatrician ordered basic blood work and a urine toxicology, which were normal. On the morning of presentation, she had a generalized tonic-clonic seizure while eating breakfast. On arrival to the ED, she is alert and oriented to place and person but not time. She has poor short-term memory and decreased attention span. She exhibits a postural tremor in her upper extremity.

Question 3a (1 point)

What is the most probable diagnosis in this girl?

Viral encephalitis

Question 3b (2 points)

Cerebrospinal fluid demonstrates 12 cells/2L with normal protein and glucose levels. Intravenous acyclovir and phenytoin are started. MRI of the brain and EEG are normal. After 3 days, her clinical status does not improve and the CSF PCR testing is negative for herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6.

Which autoantibodies are most likely to be responsible for her presentation? Name the type.

Anti-NMDA receptor antibodies.

Question 4 (7 points; 1 point for each correct answer)

Below you find an abstract from Pubmed.

Neurology. 2005 Apr 26;64(8):1461-4.

Leukoencephalopathy with ataxia, hypodontia, and hypomyelination.

Wolf NI[1], Harting I, Boltshauser E, Wiegand G, Koch MJ, Schmitt-Mechelke T, Martin E, Zschocke J, Uhlenberg B, Hoffmann GF, Weber L, Ebinger F, Rating D.

Author information

Abstract

The authors describe four unrelated girls with a distinctive neurologic disorder with early-onset progressive ataxia and hypodontia with a characteristic pattern of delayed dentition. Cerebral MRI shows hypomyelinated white matter and cerebellar atrophy; 1H-MRS of white matter reveals a marked elevation of myo-inositol.

The authors of this article describe 4H syndrome.
Which of the following symptoms are typically found in hypomyelinating disease?
Please fill in 'yes' or 'no' for each symptom.

Symptom	Yes	No
Ataxia	X	
Nystagmus	X	
Spasticity	X	
Hypodontia		X
Low visus	X	
Epilepsy		X
Dystonia	X	

1 point for each right answer

Question 5a (1 point).

What is the cause of Alexander disease?

Mutations in the GFAP gene.

Reference
I.D.Duncan et al. Experimental Neurology (2016)

Question 5b (4 points; 1 point per right answer).

Mutations in genes can lead to protein changes in different celltypes of the brain, which in turn lead to a whitematter disorder.
In which four cell-types are these protein changes seen?

Oligodendrocytes, astrocytes, microglia, neurons

Reference
I.D.Duncan et al. Experimental Neurology (2016)

Question 6 (4 points; 2 points per right answer).

Professor Van der Knaap collected 5 patients with similar MRI abnormalities consistent with a leukodystrophy with a pattern of white matter abnormalities that were never identified in the described diseases. All these patients have consanguine parents and Van der Knaap expects an autosomal recessive genetic disorder. In order to find the genetic mutations responsible for the condition she considers whole exome sequencing (WES).

There is the possibility of secondary or incidental findings. Describe how incidental findings can have consequences for patients and their relatives and therefore should be addressed during counseling.

Incidental findings in treatable conditions: will be reported
Incidental findings of disease with adult onset: not reported to minors
Incidental findings with implications for the family: reported in treatable conditions

Source: lecture medical ethical debate, ethical cases

CASE 2

A five-year old girl is presented to the pediatric oncology department with a history of fever for two weeks, pallor and bruises. On physical examination you see an apathetic girl, with some bruises, petechiae and hepatosplenomegaly; otherwise normal. Her blood sample provides the following results: hemoglobin 4.6 mmol/L (norm values: 8.5-11.0 mmol/L), thrombocytes: $18x10^9$/L (norm values: 150-$400x10^9$/L), leucocytes: $200x10^9$ (4-$10x10^9$/L), differentiation of peripheral white blood cells: 81% lymphoblasts. You work as a resident of the department and you suspect an acute childhood leukemia.

Question 7a (3 points; 1 point per right answer)

You are meeting this patient at the emergency ward of your hospital and inform her and the parents about your suspicion and the diagnostic tests that should take place now.

Which 3 diagnostic tests on blood and/or bone marrow do you explain to the patients and the parents that should be performed to differentiate between acute lymphoblastic leukemia and an acute myeloid leukemia in this patient?

Morphology, flow cytometry/immunophenotyping, cytogenetics and molecular analyses

(lecture vd Velde)

Question 7b (2 points)
Since the early 1960's the focus of pediatric acute lymphoblastic leukemia research has been to improve survival. Over the last decade there has been a shift in the research focus of acute lymphoblastic leukemia.

What is nowadays the focuspoint of acute lymphoblastic leukemia research instead of survival (1 point) and what was the reason of this shift in focus (1 point)?

Survival rates have increased from a deadly disease in the 1960's to a disease with an overall survival rate of more than 80% Therefore, the focus of pediatric research in acute leukemia has shifted from increasing survival to quality of life and reducing late effects of treatment
PS: percentages don't have to be mentioned exactly. Mentioning the increase in overall survival and therefore the shift to quality of life research is sufficient.

(lecture vd Velde)

Question 7c (2 points)

The overall survival and event free survival of children with acute lymphoblastic leukemia is superior to that of pediatric acute myeloid leukemia.

Name 2 reasons for these differences.

- The relapse rate of acute myeloid leukemia is higher than that of acute lymphoblastic leukemia leukemia.
- The treatment of acute myeloid leukemia is more intense and therefore more toxic than that of acute lymphoblastic leukemia. This leads to more treatment related toxic deaths.

Lecture vd Velde

CASE 3

A fifteen year old post-puberal girl underwent biopsy for a swollen lymph node in her neck. Diagnosis: a stage II Hodgkin lymphoma. The girl and her parents have come to the hospital to discuss the test results. After the initial news some questions arise.

The girl and her parents had anticipated this diagnosis and did some online research concerning the disease and its treatment. During this search they questions raised about possible late effects of childhood cancer and its treatment.

One of the potential late effects of childhood cancer and its treatment, that may significantly impair quality of life, is infertility. When at risk for this particular side-effect of treatment, several fertility preservation techniques can be offered to a female cancer patient before treatment starts.

Question 8a (2 points; 1 point per right answer)

Name 2 types of fertility sparing techniques that can be offered to this particular girl before treatment starts.

Ovarian shielding/ ovarium transposition
GnRH analogues (leading to suppression of LH and FSH production) (effectivity is doubtful)
Cryopreservation of oocytes
Cryopreservation of ovarian tissue (still experimental)

Puntenverdeling vraag 2:
1 punt per goed gegeven behandeling. Totaal te verkrijgen punten vraag 2: 2.

Literature of question 2:
Metzger ML1, Meacham LR, Patterson B, Casillas JS, Constine LS, Hijiya N, Kenney LB, Leonard M, Lockart BA, Likes W, Green DM. Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol. 2013 Mar 20;31(9):1239-47.
doi: 10.1200/JCO.2012.43.5511.
Fulltext link: http://jco.ascopubs.org/content/31/9/1239.long

Question 8b (2 points; 1 point per right answer)

Name 2 ethical dilemmas which we face when we try to preserve female fertility before the start of treatment

Possible answers:
Fertility sparing techniques commonly take time leading to a delay in treatment.
Re-implantation of cryopreserved ovarian tissue has the risk of re-implantation of cancer cells.

Question 8c (4 points; 1 point per right answer)

Name four other common late effects than infertility that survivors may develop as a consequence of their pediatric oncology treatment.

- Cardiovascular dysfunction
- Hypertension
- A premature menopause
- Pulmonary dysfunction
- Neuro-cognitive dysfunction
- Neuro-sensory dysfunction (hearing difficulties, neuropathy, …)

- Secondary malignancies
- Endocrinological dysfunction (hypothalamic-pituitary-adrenal disturbances, diabetes mellitus, ...)
- Metabolic disorders (hepatic abnormalities, renal insufficiency, ….)

Literature of question 1:
Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, Green DM, Armstrong GT, Nottage KA, Jones KE, Sklar CA, Srivastava DK, Robison LL. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA. 2013 Jun 12;309(22):2371-81.
doi: 10.1001/jama.2013.6296.
Fulltext link: http://jama.jamanetwork.com/article.aspx?articleid=1696100

Question 9

Your department performs a trial concerning a new test for diagnosing meningitis in children. The trial is titled 'meningitis trial'. The participants will be asked to give two extra blood samples. A 4 year old girl is admitted to your department and she would be a good candidate for the trial. You decide to ask the parents for informed consent. The parents are married and thereby they have both the guardianship over this child.

Question 9a (3 points; 1 point per item)

Name 3 mandatory components of a patient information form according to the CCMO (Central Committee on Research Involving Human Subjects).

- Background of the trial
- Possible side effects/complications for the patient
- Possible advantages for the patient
- Usage and storage of data and bodily material
- Insurance information
- Contact information of the independent investigator
- Procedure in case of complaints

Question 9b (4 points; 1 point per right answer)

Below you find a part of the informed consent form.

I give informed consent to store my child's blood for 15 years after the end of this trial.

☐ yes ☐ no

I give informed consent to let my child participate in the 'meningitis trial', about a new test in diagnosing meningitis in children.

Name parent/~~legal guardian~~** P. Smith

Signature: Smith

Date (DD/MM/YYYY): __/__/__

Name parent/legal guardian** _____

Signature: _____

Date (DD/MM/YYYY): __/__/__

I declare that I fully informed the above-mentioned person(s) about the 'meningitis trial'.

If during the study new information is available , which might influence the consent of the parents or legal guardians, I will inform the parents or legal guardian forehanded.

Name investigator _____

Signature: _____

Date (DD/MM/YYYY): 26/10/16

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*) cross out what is not applicable.

Name 4 elements which are not correctly filled in. (1 point for each element).

- The box yes/no is not checked
- No date after signature 1
- Only signed by one parent
- Name of the investigator is not written

SUBMITTING YOUR EXAM:

1. Save this document with your student number as the file name (e.g. 1234567.pdf) and close it.

2. Submit the document via the 'Exam Submission' link on the desktop. You will need to log in using your VUnetID on the submission website.

3. If a green tick appears, your exam has been successfully submitted. Please leave the computer switched on and exit the hall in silence.