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The Amsterdam Medical Student journal (AMSj) is a scientific journal created and published by Amsterdam UMC staff members and students to promote research and to encourage other medical students to publish their clinical observations, research articles and case reports. Go to www.amsj.nl for publication options and to find out how you can contribute to AMSj as reviewer or member of the editorial board.

Editorial

First of all, on behalf of the editorial board, I hope that you and your loved ones are doing well. We are currently living in an extraordinary period that at times requires unorthodox and unusual measures. This demands a lot from us. But, as we know, measures remain necessary and are ultimately intended to protect everyone, and certainly vulnerable groups. Unfortunately, no-one has a crystal ball. Therefore, we will remain unable to predict what the future brings. Hopefully this pandemic and its effects will come to rest in the near future. We would like to wish you all the very best.

The previous AMSj edition, edition 19, was released on the 15th of June. Unfortunately, we have been unable to distribute the journal because of the measures in the context of COVID-19. Nevertheless, we now have excellent news: AMSj edition 19 is currently distributed and can be found in medical libraries and hospitals such as Amsterdam UMC. And do not forget to sign up for the Nicolaes Tulp Symposium which will take place on the 12th of November 2020. Hoping to see you there!

Having mentioned that, we can talk about the present situation; you are reading the latest edition of AMSj, edition 20! We are excited to share very diverse, new, inspiring and interesting content with you. In this edition a fruitful dialogue about COVID has been established in the column 'Letter to the editor', dr. Khalifeh will enrich us with an interesting overview of COVID-19 and the corresponding role and working mechanism of vaccines, and Checkrouni et al. discuss the potential of dexamethasone treatment in COVID-19 patients. Furthermore, you can find an inspiring interview with Trauma Surgeon and Orthopedic Trauma Surgeon L.M.G. Geeraedts Jr, MD, PhD, Msc and read an adventurous narrative about a trauma research project in rural Tanzania in the 'Research abroad' column. Are you excited yet? I most definitely am, but I will allude to some final content to make sure you are too. A fascinating systematic review from Abdelrahman et al. about lumbar puncture in children with acute lymphoblastic leukemia and a remarkable case report from Veltkamp et al. about a case of acute renal function deterioration in a patient with pulmonary arterial hypertension and decompensated right heart failure can also be found in this edition. Thank you to all the authors for your fantastic contribution to AMSj!

Eventually our goal is to enthuse medical students with a special interest in scientific research. We encourage medical students to find their inner 'scientist to be'; it is beautiful to see this process. VGT Cursus and AMSj have established a fruitful collaboration with new exciting ideas; so submit your manuscript to AMSj and stay posted for wonderful giveaways!

Lastly, I am extremely thrilled to be the incoming Editor-in-Chief VUmc next to Devica S. Umans. A special thank you to the very talented former Chief VUmc Zar Popal for all your hard work and enthusiasm with which you enriched AMSj!

Take a moment and enjoy the 20th edition of AMSj.

Yours sincerely,

Elise Beijer
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NEWSNEWSNEWS

Developments in prostate cancer screening

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Prostate-specific antigen (PSA)-based screening for prostate cancer is subject to considerable discussion. Because PSA often detects well-differentiated tumors, but frequently misses the poorly differentiated ones, an improved overall survival of individuals who have been followed with PSA-based prostate cancer screening may be influenced by length-time bias. Furthermore, screening with PSA causes substantial overdiagnosis which may lead to unnecessary burden of disease and even treatment-related mortality. The recent IP1-PROSTAGRAM study compared MRI-based screening with PSA-based screening, to investigate whether MRI can improve the screening accuracy. A PI-RADS score of 3-5 or 4-5 on MRI was considered as positive. The threshold value for PSA was 3 ng/ml. Positive MRI or PSA results were confirmed with prostate biopsies, in which a Gleason score of 3+4 or higher reflected clinically significant cancer. A PIRADS score of 4-5 detected 11 significant cancers and five insignificant ones, whereas PSA detected only seven significant cancers with six insignificant ones.

In conclusion, it remains debatable if screening for prostate cancer is effective. However, this study shows that using MRI may result in the detection of more significant cancers without a rise in false positives.

1. Eldred-Evans D. Population-based prostate cancer screening using a prospective, blinded, paired screen-positive comparison of PSA and fast MRI: The IP1-PROSTAGRAM study. J Clin Oncol 2020 May 20; 38: 5513-5513.

Dexamethasone as treatment in COVID-19

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The COVID-19 pandemic is currently overwhelming healthcare systems worldwide. Even though the majority of patients recover spontaneously, a significant proportion develops severe respiratory failure and needs hospital admission for supplemental oxygen therapy or invasive mechanical ventilation (IMV). In the latter patients, reducing mortality has been the main focus of many recent studies.
The RECOVERY trial is a randomized, open-label, controlled trial that randomized 6425 hospitalized patients with COVID-19 pneumonia in a 1:2 ratio to either the glucocorticoid dexamethasone 6 mg once daily or standard care.[1] The preliminary results have now been published only 98 days (!) after the first protocol was drafted.
The results show that dexamethasone significantly reduces 28-day mortality in patients requiring IMV (RR=0.65; 95%CI 0.51-0.82) and in those requiring oxygen therapy (RR=0.80; 95%CI 0.70-0.92). There was no benefit for patients that did not require oxygen, underlining that the greatest reduction in mortality was seen in the sickest patients. Furthermore, the effect appears to be stronger in patients with symptoms for >7 days compared to symptoms ≤7 days, suggesting that timing of dexamethasone might be an important factor.
Although the report has not yet undergone a formal peer-review process, we consider this a landmark trial in the current pandemic that is interesting for the readers of AMSj.

1. Horby, P. et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv 2020.06.22.20137273 (2020). doi:10.1101/2020.06.22.20137273

Peripheral perfusion-guided resuscitation as an alternative in septic shock

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Early recognition and management of septic shock is crucial to prevent mortality and multiple organ dysfunction. In current practice, resuscitation in patients with septic shock is guided by serum lactate levels. However, hyperlactatemia can be caused by different underlying pathophysiologies, and changes in serum lactate levels are relatively slow. For this reason, a peripheral perfusion-guided resuscitation strategy using the capillary refill time as an alternative strategy has been introduced. The ANDROMEDA-SHOCK randomized clinical trial by Hernández et al. showed that a peripheral perfusion-guided resuscitation strategy is associated with lower mortality and less organ dysfunction at 72 hours compared to a lactate-guided resuscitation strategy in patients with septic shock.[1] No significant difference was found for the 28-day mortality between the two strategies.
A recently published study by Zampieri et al. used the same cohort of patients, but different statistical techniques were performed to analyze the data. The results of Zampieri et al. support the findings of the ANDROMEDA-SHOCK trial, and even suggest that a peripheral perfusion-guided resuscitation strategy may result in a lower 28-day mortality in patients with septic shock.[2]
A peripheral perfusion-guided resuscitation strategy might be an easy-to-use, non-invasive and reliable alternative for a lactate-guided resuscitation strategy in patients with septic shock.

1. Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effects of a Resuscitation Strategy Targeting Peripheral Perfusion Status versus Serum Lactate Levels among Patients with Septic Shock A Bayesian Reanalysis: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA. 2019 Feb 19;321(7):654-64.
2. Zampieri FG, Damiani LP, Bakker J, et al. Effects of a Resuscitation Strategy Targeting Peripheral Perfusion Status versus Serum Lactate Levels among Patients with Septic Shock A Bayesian Reanalysis of the ANDROMEDA-SHOCK Trial. AM J Respor Crit Care Med. 2020 Feb 15;201(4):423-9.

Nonsurgical Rhinoplasty

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Nonsurgical rhinoplasty using filler injections has become increasingly popular in cosmetic practices, to correct deformities of the nasal sidewall, alter tip projection or rotation, augment the nasal dorsum, correct a deep radix, lengthen the nose, or alter the nasolabial angle. Although rhinoplasty remains the gold standard for changing nasal appearance, nonsurgical rhinoplasty can be offered to patients that prefer a temporary outcome (six months to one year) or would like to avoid general anesthesia.[1] Besides this, it can be used in post-rhinoplasty patients to correct nasal irregularities.

Hyaluronic acid and calcium hydroxyapatite tend to be the most commonly used materials; however, this procedure can also be performed using autologous fat or cartilage. The complication rate for calcium hydroxyapatite was shown to be almost ten times higher than the complication rate for hyaluronic acid, without significant differences in patient satisfaction. This may be because the majority of observed complications were minor (transient edema, erythema, and bruising). Major complications include vascular compromise. This can be caused by intra-arterial injection to the ophthalmic artery with filler emboli or by external vascular compression secondary to excessive volume injection or edema. An advantage of hyaluronic acid is that it can be rapidly dissolved with hyaluronidase in the case of vascular complications.

1. Williams, L. C., Kidwai, S. M., Mehta, K., Kamel, G., Tepper, O. M., & Rosenberg, J. D. (2020). Nonsurgical Rhinoplasty: A Systematic Review of Technique, Outcomes, and Complications. Plastic and Reconstructive Surgery, 146(1), 41-51.

Doctor Robot - Could and should doctors be replaced by Artificial Intelligence?

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Throughout the 21st century many jobs have been replaced by Artificial Intelligence (AI), which is a machine, computer or a piece of software that can solve complex problems. Many factory workers became unemployed as they were replaced by machines in the past century. This transition allowed humans to produce products in an exponentially more efficient way than ever before. One can even go as far as to say that most of the human population would not have survived if this transition had not happened.[1] Many believe that this is only the beginning and that most people will at some point lose their profession to AI. AI has already been shown to be more effective in the diagnosis of certain medical conditions than physicians.[2] This sparks the question if AI would be able to replace doctors.

AI works by learning from data sets by recognizing patterns. AI can compare patients to this data and diagnose their conditions. This method has proven to be more reliable than human physicians in cancer and dermatology diagnostics[2,3] There are constantly new developments in the potential of AI in the medical field. It could be used to predict treatment outcomes and therefore recommend the best treatment to a patient. AI could even be used as a medical device or as a form of treatment. According to recent studies, AI robots have the potential to become better surgeons than humans.[4,5] Because of the many developments, there is a good chance that at some point AI will be of higher quality than human physicians.

There are many financial benefits to replacing physicians with AI. Some predict that AI applications could save the United States healthcare economy up to $150 billion dollars by 2026.[6] These claims are based on the fact that the usage of AI could reduce the number of necessary healthcare workers by partially replacing them. They expect that AI will work more efficiently than a human doctor and require less time to diagnose and treat a patient. AI could also be able to predict what the best treatment is for patients and will avoid unnecessary expenses. Because of these factors, AI could potentially save the healthcare system billions of dollars. One American study showed that 24,1% of its participants, the majority being non-Hispanic white Americans (40% male), avoid healthcare because it is too expensive.[7] The implementation of AI could benefit these patients. Because AI works more cost-effectively, it allows care to be less expensive.

Additionally, AI could have many logistic benefits. Most healthcare systems are overloaded because of the constant, high influx of patients. Because of this overload, doctors simply do not have the time to properly tend to every patient. If AI were to replace certain medical professions, it would treat patients entirely on its own. AI does not require breaks and is able to operate 24 hours a day. This means that even in the most demanding situations, the healthcare system is less likely to overload.

As mentioned, there are many benefits to applying AI to the current healthcare system. However, it can result in many new dilemmas. One dilemma is the liability of AI. When a fully automatic operating AI causes a medical error, it is unclear who is at fault. If a judge were to decide that AI itself is responsible for the error, without placing blame on humans, an ill-intentioned owner or programmer could use this to their advantage and purposefully perform medical misconducts. Currently there are no laws that define who is responsible if these kinds of scenarios were to occur. Similar discussions are held about other applications of AI, for example the liability of self-driving cars in case of traffic accidents.[8]

The medical decisions an AI program would make, would be based on 'big data'. Aside from privacy concerns, such a dataset would be incredibly hard to create. The data that the AI scans should be completely accurate. Many physicians make unclearly or incorrectly documented choices, implying that AI could make decisions based on incorrect data and thus treat patients incorrectly. When the dataset is smaller, AI will have to generalize data before applying it to a patient. Because every patient is different, one is never able to fully apply this generalization to one specific person. This means that the method of the AI inevitably causes bias to a certain extend. To avoid this bias, the dataset needs to be as extensive as possible, and consist of a sample that reflects society as closely as possible.

The qualities we value most about our physicians are the qualities that could not be replaced by AI, because they are human qualities. Being a good doctor does not mean that one is able to save as many lives as possible. Instead it means that one is able to make a difference in the lives of patients by paying attention to them and considering their desires. A good doctor allows patients to participate in the decision-making process while emotionally supporting them. It is unsure if robots will ever be able to connect with patients the way a fellow human is able to.[9]

AI has replaced many jobs in the past century, and it is predicted to continue replacing jobs. AI has been shown to be effective in diagnosing certain medical conditions, and there are many new developments in AI that show that it could function as well as a human doctor. AI can function for 24 hours a day and does not require breaks. If human physicians were to be replaced by AI the healthcare sector could achieve great financial benefits. It could also, however, result in dilemmas concerning the liability of AI. Additionally, it is nearly impossible to create a perfect data set for AI doctors to base their decisions on. The question also remains if AI is able to fully replace doctors. Based on what is valued most about doctors, the answer would be no. It is unavoidable that AI will have an increasing role in our healthcare system. I believe it could be very beneficial to apply AI in diagnostics and see great potential in its use in surgery. Some envision a future where doctors are completely replaced by AI, to the extent that the only function of a doctor is showing empathy. If this scenario were to occur, society should consider if it still wants to pay for a useless messenger. I fear this future, because I believe it takes a human to fully understand another human and that healthcare should not become transactional.

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A tearing abdominal pain

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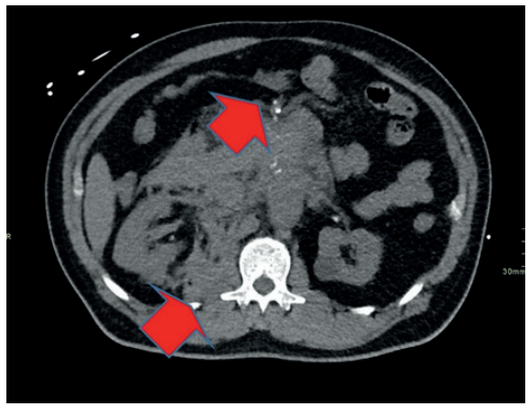
CASE

A 65-year-old male with a history of hypertension (treated with hydrochlorothiazide) was brought in by ambulance. He had started complaining of lower back pain a few days ago. The pain progressed this morning and he was feeling unwell. At presentation he was awake, however drowsy. Blood pressure was 60/30 mmHg on the right side and 110/60 mmHg on the left side. His heartrate was 70 BPM and pulsations of the femoral artery were more powerful on the left than on the right. An abdominal CT was performed.



QUESTION 1

The CT shows excessive tissue in the abdomen. What is this? Hint: what would you expect based on the physical examination?

A. Blood
B. Feces
C. Tumor
D. Urine

QUESTION 2

Which organ/structure is the source of the tissue? Hint: what complaints would you expect with each organ or structure?

A. Spleen
B. Ascending colon
C. Aorta
D. Mesenteric artery
E. Ileum
F. Liver
G. Bladder
H. Kidney

QUESTION 3

What is the anatomical relation to the peritoneum of the tissue? Hint: what is the anatomical relation of the organs mentioned above to the peritoneum?

A. Intraperitoneal
B. Primary retroperitoneal
C. Secondary retroperitoneal

QUESTION 4

What imaging modality would you use to confirm your diagnosis?

A. MRI
B. CTA
C. X-abdomen
D. PET-CT
E. Echo

Answer on page 41

IMPROVING ESSENTIAL HEALTH SERVICES IN LOW AND MIDDLE-INCOME COUNTRIES BY LOCAL CAPACITY BUILDING THROUGH FACILITATING MEDICAL VOCATIONAL TRAINING: A GLOBAL RESPONSIBILITY?

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Importance of tertiary education

Education is a fundamental resource and a valuable investment for individuals and communities. In most countries, education is considered a basic human right. In the last few centuries, education has expanded greatly across the world and global school life expectancy continues to increase.[1] Although the world is more educated than ever, low and middle-income countries (LMIC) are far behind (FIGURE 1).[1]

Education reduces poverty by stimulating economic growth and increases the chance of a healthy life.[2] Ensuring inclusive and equitable quality education, a sustainable development goal (SDG), is one of the most important investments that a country can make for the population and for the future.[3,4] Although the return on investments in tertiary education is the highest in the entire education system, less than 10% of the population in low income countries is enrolled in tertiary education (FIGURE 1).[5,6]

It is no surprise that 'improving the health and well-being of all world citizens' is another vital SDG.[4] According to the World Health Organization at least half of the world's population still lacks access to basic healthcare and many people are still pushed into extreme poverty due to their health expenditures.[7] An important contributing factor is the shortage of healthcare workers (HCW), especially in LMIC.[8,9]

Both tertiary education and basic healthcare remain out of reach of the most marginalized people in the world. Improving the accessibility of medical vocational training can tackle both challenges at the same time, which can be done most sustainably by supporting local infrastructures.[10]

Health systems in low resource settings already struggle to provide basic healthcare in non-pandemic times. The current COVID-19 pandemic shows the world more than ever that investments for weak health systems in LMIC are warranted. The health sector is in desperate need of(wo) manpower in LMIC. Is it a global responsibility to solve the discrepancy between the high motivation of many adolescents and their low chances to become a HCW?

Paul Kwofie - Medical student from Ghana

In 2017, Paul Kwofie and Lilian van Uhm (FIGURE 2) met in the the Egyam Children's Home in Ghana, where Lilian volunteered as a social worker. They became close friends and it became clear to Lilian that Paul was a really hardworking and serious young man with only one dream: to become a doctor. Paul had this dream since he was in primary school and saw many seriously ill people in his village. He witnessed (too) many deaths due to curable diseases, and wanted to help reduce these preventable numbers.

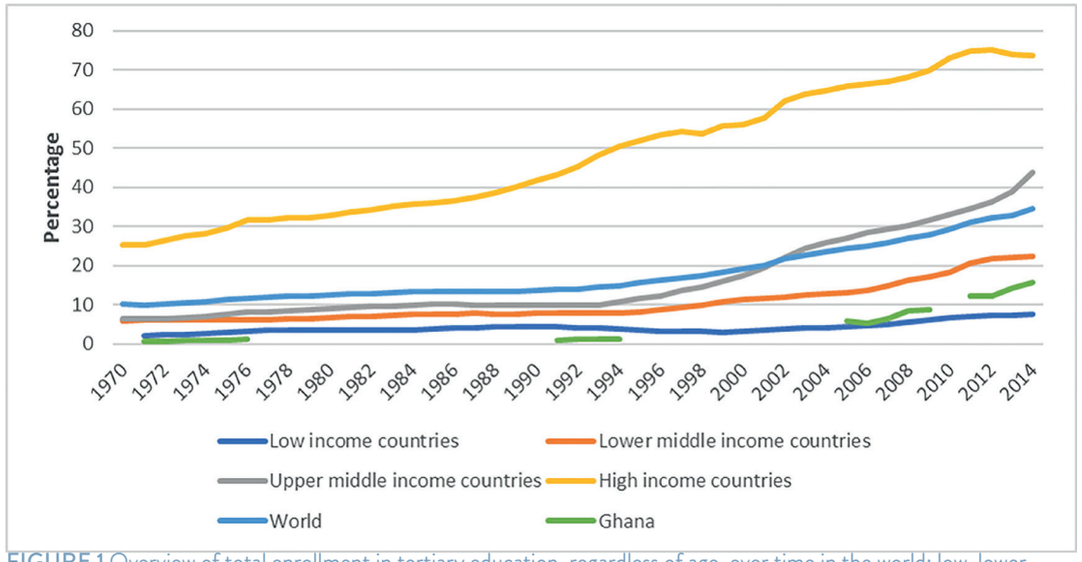

FIGURE 1 Overview of total enrollment in tertiary education, regardless of age, over time in the world; low, lower middle, upper middle, and high-income countries; and Ghana from 1970 – 2014.
Note. Data retrieved from UNESCO Institute for Statistics.[1] Total enrollment in tertiary education in the world visualized as well as categorized for four different income levels. In addition, Ghana (Country of Paul Kwofie) is visualized which had some missing data for some years.

Paul completed high school with good results, giving him access to medicine studies. However, neither he nor his orphanage could afford the tuition fee. Lilian was very keen to help Paul, as she believes it is a real pity to see talented young people like Paul who cannot attend tertiary education due to financial issues and will therefore not be able contribute to the development of their country. Lilian had heard about the iSTEPup foundation and introduced Paul to them. The board of the iSTEPup foundation carefully went through his application and decided to offer him a scholarship. Both Paul and Lilian were very grateful for this opportunity. Paul is now in his third year of medicine and achieves good results at the Kwame Nkrumah University of Science and Technology.

Through his personal webpage, Paul and his iSTEPup buddy Lilian update his study costs, results and progress for transparency purposes *(https://www.i-step-up.com/what-we-do/students/paul-kwofie/?lang=en)*. After finishing his medicine study in 2022-2023, Paul intends to work in his home country, Ghana, for as long as possible.

Scholarships for medical vocational training

iSTEPup* was founded in 2018 by three Dutch

FIGURE 2 Paul Kwofie [l] & Lilian van Uhm [r]

medical doctors to improve accessibility of medical vocational training in LMIC. Candidates with insufficient financial means can apply for a scholarship to follow medical vocational training to become a nurse, midwife, doctor or pharmacist. In a transparent and sustainable manner, iSTEPup facilitates local capacity building in basic healthcare through an existing educational infrastructure which supports local economy and self-reliance.
**International Sustainable Tertiary Education Programme*

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Bad habits

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CASE

A 30-year-old woman presents at the dermatology department with an asymptomatic purple discoloration of her left thigh, which is constantly present. She has not been sick. She does not have a medical history and is not using any medications. Due to the COVID-19 pandemic she has been working from home the last four months, which involved a lot of online work. We saw reticulated erythema and hyperpigmentation, similar to the photo.

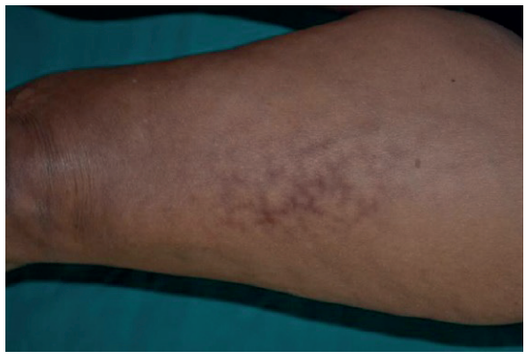

FIGURE Reticulated erythema on the left thigh.
Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5535666/figure/F1/

QUESTION

What is the diagnosis?

A. Erythema ab igne
B. Livedo reticularis
C. Post-inflammatory hyperpigmentation
D. Cutis marmorata

Correct answer: A

Explanation

A. Erythema ab igne, or hot bottle rash, is caused by repeated exposure of heat to the skin. Most often a certain habit is involved, like the use of heating pillows. Anamnesis is key; our patient seemed to work with her laptop on her thighs on the couch. Treatment involves avoiding the heat source. If hyperpigmentation occurs laser therapy could be considered.

B. Livedo reticularis is a reticulated cyanotic discoloration, mainly of the legs. It could be a physiological phenomenon (cutis marmorata) induced by cold but it may have and underlying cause, like vasculopathies or vasculitides. If there is no history of a heat source additional diagnostic tests are required.

C. Post-inflammatory hyperpigmentation can occur after any inflammatory reaction in the dermis or epidermis. Cytokines stimulate melanocytes to make melanin. In a way you could see some post-inflammatory hyperpigmentation in our case, but it does not explain the whole story.

D. Cutis marmorata is a physiologic response to cold, mainly in newborns and young women. When exposed to cold a red/blue reticulated pattern occurs which disappears with higher temperatures. Treatment is not necessary.

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2. www.huidziekten.nl

Is there a role for the BCG vaccine in protection against COVID-19?

Nouf Moh'd Khalifeh[1]

1. University of Jordan, Faculty of Medicine

ABSTRACT

After the first outbreak of corona virus disease (COVID-19) in China in December 2019, the World Health authorities have been working in collaboration with health organizations to enact counter-measures to minimize the catastrophic impact of this pandemic. Vaccine production is considered a very critical phase in controlling pandemics. At present, several stakeholders have suggested the possibility of using the BCG vaccine as a bridging intervention to reduce the morbidity caused by SARS-CoV-2 in the absence of a specific vaccine against the novel corona virus. The Bacillus Calmette-Guérin (BCG) vaccine is a live attenuated vaccine derived from an isolate of *Mycobacterium bovis* to provide immune protection against tuberculosis. Several studies demonstrated that BCG vaccine induces nonspecific immune protection against other unrelated pathogens which might be beneficial in protection against COVID-19. This response is attributed to lymphocyte mediated cross-reactivity and nonspecific innate immune response (trained immunity). However, in the absence of direct clinical evidence, the Word Health Organization does not recommend the use of BCG vaccine to protect against COVID-19. Therefore, large clinical randomized control trials are recommended to study the effects of the BCG vaccine in reducing morbidity and mortality associated with COVID-19.

In this article we will discuss the possible mechanism for the BCG vaccine nonspecific immune response, as well as the role of the BCG vaccine in the current COVID-19 pandemic.

INTRODUCTION

Since its first outbreak in China in December 2019, the novel corona virus has been responsible for more than 17 million confirmed infection cases with 675,000 deaths worldwide as of August 1, 2020.[1] COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with a reported case fatality rate of 2.3% with a higher mortality rate among elderly and patients with comorbidities.[2] Vaccine development is considered a very crucial step in controlling pandemics. By definition, a vaccine is a biological or synthetic stimulus that is introduced to the body in order to stimulate the immune system to produce immunity to a specific pathogen.[3] The Bacillus Calmette-Guérin (BCG) vaccine is a live attenuated vaccine derived from an isolate of *Mycobacterium bovis* to provide immune protection against tuberculosis.[4–6] Rivetingly, as soon as the BCG vaccine was first introduced in 1920, several observational studies denoted that the BCG vaccine significantly reduced infant mortality which cannot be explained solely by prevention of tuberculosis. Based on these observations, it was suggested that the BCG vaccine induces nonspecific immune protection against other unrelated pathogens.[4,7] Various studies were conducted all over the world to evaluate the nonspecific immune response of the BCG vaccine. A PubMed search was conducted using the following keywords: "BCG vaccine", "trained immunity", "nonspecific immunity" or "nonspecific effect". The related articles after filtering the titles and the abstracts were summarized in Table 1. Randomized control trials (RCTs) were also conducted and the majority were consistent with the previous observational studies (TABLE 1).[8–10]

The mechanism of nonspecific immune response induced by the BCG vaccine

Nonspecific immune response of vaccines is a beneficial response that protects against pathogens other than the targeted microorganism.[16]

Two possible mechanisms have been proposed to explicate the advantageous sequel of the nonspecific immune reaction of the BCG vaccine:

1. *Lymphocyte mediated cross-reactivity 'heterologous immunity'*

The vaccines in general work by establishing memory immunity to a certain pathogen. Nevertheless, vaccines can also give rise to T-cell cross-reactivity that may provide protection against non-related pathogens.[7,12,15] Several studies have shown that the BCG vaccine triggers heterologous lymphocyte response against non-related microorganisms.[5] For example, in healthy human volunteers, the BCG vaccine induced non-specific immune response of Th1 (IFN-Y) and Th17 (IL-17 and IL-22) to non-related pathogens that lasted for one year after vaccination.[17]

2. *Innate immune response 'trained immunity'*

Cumulative evidence has emerged, indicating that the defensive mechanisms during re-infection or cross-protection cannot be attributed exclusively to the adaptive immune response, which is acquired after the exposure to a specific pathogen by producing memory cells that eliminate the pathogen subsequently,[18] but also to an increased state of activation of the innate immune response. The concept of trained immunity was first proposed in 2011, which is defined as the non-specific immune reaction mediated by the innate immune system by monocytes/macrophages and natural killer cells (NK-cells) against the same or different pathogen.[19] The molecular mechanism that mediates the trained immune response induced by the BCG vaccine is proposed to be epigenetic reprogramming and histone modifications.[4,5] In humans, BCG vaccination enhanced the production of pro-inflammatory cytokines such as interleukins and tumor necrosis factor. This response is mediated by the monocytes upon in-vitro stimulation with an unrelated pathogen for up to three months after vaccination, which may provide a better outcome during secondary viral infections.[5,20] Moreover, recent studies have showed that monocytes and NK-cells can display memory characteristics.[13] In healthy volunteers, the BCG vaccine enhanced the response of NK cells to non-related microorganisms by increasing the production of cytokines for at least three months.[21]

Factors that may influence the heterologous immune activity of vaccines:

Several factors should be recognized upon considering the utilization of the BCG vaccine nonspecific immune response in clinical practice as these factors may enhance or suppress the beneficial effects of this response. These factors include: age, gender, sequence of vaccination, the dose of the vaccine used, the route of administration, and the vaccine strain used.[15,22,23] BCG strains are classified into early and late strains based on the timing of distribution of the original vaccine strain to different laboratories worldwide. Early strains (e.g., BCG Japan and BCG Russia) are associated with a distinctive immune response against non-related pathogens compared to the late strains (e.g., BCG Denmark). Thus, early strains may be associated with lower COVID-19 mortality compared with late strains as they are different genetically and phenotypically which can produce a significant immune response against non-related pathogens.[24]

BCG vaccine and COVID-19

The World Health authorities are working in conjugation with health organizations to set up protective measures to reduce the devastating effects of COVID-19. As there is no definitive treatment or successful disease control vaccine yet, the scientific community is putting every effort into finding treatment for the disease. At present, in the absence of a specific vaccine against the novel corona virus, several stakeholders have suggested the possibility of using the BCG vaccine as a bridging intervention to reduce the morbidity caused by COVID-19. In this context, several ecological studies (not peer reviewed) have claimed that countries with a national program of BCG vaccination appear to have a lower morbidity and mortality rate from COVID-19. However, a recent systematic review and meta-analysis of 13 ecological studies (12 of them are not peer reviewed) concluded that there is no clear evidence that the BCG vaccine can provide any protection against SARS-CoV-2 infection.[25] Therefore, we should be aware that the nonspecific immune response of the BCG vaccine might not provide protection against the novel corona virus. Clinical trials are needed to evaluate the beneficial role of BCG vaccine in protection against COVID-19. Currently, two clinical trials have been initiated in Australia and Germany to test if BCG vaccination reduces the incidence and severity of COVID-19 especially among healthcare workers.[32]

In conclusion, the accumulating evidence suggests that the BCG vaccine might provide protection against viral infections.[5] However, the World Health Organization does not recommend the use of BCG vaccination to protect against COVID-19 as there is no direct clinical evidence that the BCG vaccine can reduce the morbidity or mortality rate of COVID-19.[33]

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Näslund C.[34]	1932	Cohort study	Children who received BCG at birth had a mortality rate that was almost three times lower than the unvaccinated children.
Anderson et al.[26]	1974	Case series study	Reduction in the frequency of recurrent herpes simplex virus infection.
Niobey et al.[35]	1992	Case control study	Reduced the risk of death from pneumonia in children less than one year old by 50%.
Pönnighaus et al.[36]	1992	Cross-sectional study	Protection of more than 50% against leprosy.
Kristensen et al.[37]	2000	Follow up study	Reduced mortality rate among vaccinated infants compared with nonvaccinated.
Garly et al.[38]	2003	Cohort study	BCG scar and a positive tuberculin reaction are associated with better survival in BCG-vaccinated children.
Stensballe et al.[29]	2004	Case control study	May reduce the risk of developing acute lower respiratory tract infection caused by respiratory syncytial virus.
Roth et al.[39]	2005	Cohort study	Mortality was more than halved for children with a BCG scar compared with children without.
Ohrui et al.[40]	2005	Clinical trial	Decreased risk of developing pneumonia among elderly.
Wardhana et al.[41]	2011	Prospective study	Significantly reduced the amount of acute upper respiratory tract infection among elderly.
Aaby et al.[9]	2011	RCT	Significant reduction in neonatal mortality due to fewer cases of neonatal sepsis, respiratory infection, and fever.
Biering-Sørensen et al.[8]	2012	RCT	Early BCG vaccination in low birth weight infants may contribute to lower mortality rate.
Salem et al.[27]	2013	RCT	Topical BCG enhanced the resolution of common warts.
de Castro et al.[42]	2015	Retrospective study	Reduced hospitalization rates due to respiratory infections and sepsis not related to tuberculosis.
Leentjens et al.[28]	2015	RCT	Enhanced the production of antibodies against H1N1 influenza.
Biering-Sørensen et al.[10]	2017	RCT	Early administration of BCG-Denmark in low birth weight infants is associated with significant reductions in mortality rate.
Jayaraman et al.[11]	2018	RCT	BCG-Russia had no effect on neonatal mortality.
Arts et al.[14]	2018	RCT	Induced upregulation of IL-1β accompanied with reduction of yellow fever virus vaccine titers.

TABLE 1 Overview of non-specific effects of the BCG vaccine

VGT Practice Questions

VGT Cursus

QUESTION 1

A 51-year old woman visits an outpatient dermatology clinic with a skin problem that has persisted for a year. You see a sharply demarcated red, flaky patch of skin in the belly button (see photo below). You're considering a variant of psoriasis, despite it not being the typical skin site for psoriasis. Which variant of psoriasis do you see here?

A. Psoriasis guttata
B. Psoriasis inversa
C. Psoriasis unguium
D. Psoriasis vulgaris

QUESTION 2

A 5-year old boy from Congo presents with possible lactase deficiency. Which of the following statement(s) is/are correct?

I. The activity of the lactase enzyme increases at the age of 4 to 6 years
II. Lactase deficiency is more common in people of Asian or African origin
III. Lactose intolerance can be tested for through a hydrogen breath test

A. Only statement I is correct
B. Only statement II is correct
C. Only statement III is correct
D. Statement I and II are both correct
E. Statement I and III are both correct
F. Statement II and III are both correct

Q1: Answer: B

EXPLANATION

This is a case of psoriasis inversa.

Psoriasis inversa is a psoriasis that affects the body folds (which is the opposite of classical psoriasis, hence the name 'inversa'). Mostly it affects the belly button, groins, submammary fold and intergluteal cleft.

Psoriasis guttata (droplet-shaped psoriasis) is an acute eruption of psoriasis in the shape of papules (< 1 cm in size) that typically affects the trunk and proximal extremities. It is usually triggered by a streptococcal infection (pharyngitis, tonsillitis) or medication (NSAIDs, beta blockers). It usually resolves spontaneously, though a portion of patients may develop chronic psoriasis.

Psoriasis vulgaris is the classical presentation of psoriasis: sharply demarcated red, flaky patches of skin on the elbows and knees.

Psoriasis unguium is the name for psoriasis that affects the nails ('psoriasis nails'). Typical are the small pits on the nails.

Q2: Answer: F

EXPLANATION

The activity of the lactase enzyme greatly diminishes at the age of 4 to 6 years, which is the cause of *primary lactase deficiency.* The hydrogen breath test can be used for diagnosing lactose intolerance; it measures the concentration of hydrogen in expired air after the intake of lactose (the hydrogen concentration will be increased in the case of lactase deficiency). Unlike the primary variant, a *secondary lactase deficiency* is temporary and is caused by underlying pathology.

The role of race in modern medicine

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In the past and present, race and ethnicity in medicine has received either too much or too little attention. In some countries, like the Netherlands, it is not allowed to document the race of patients in order to prevent privacy violations that could lead to racism.[1,2] The downside of this policy is missing potentially valuable epidemiological data, since racial and ethnic classifications reflect population genetics and could therefore be clinically useful.[1,2] For example, in the United Kingdom and the United States the mortality and morbidity of the COVID-19 pandemic were higher in people of color.[1,3] It is important to investigate the underlying cause in order to improve prevention and treatment strategies for each individual.

In addition, medical education and clinical research is mainly focused on a white man's perspective, which may lead to difficulties diagnosing and treating both females and people of color. For example, skin rashes present differently on various types of skin color. Yet, medical literature rarely shows these differences, making it more difficult to diagnose skin rashes in dark-skinned people.[4]

On the other hand, the documentation of race is potentially harmful when race is integrated as a correction in diagnostic tools and risk assessments. New insights have shown that these tools are mostly generalizations and based on empirical associations without biological explanations, making their value questionable and their use potentially harmful. For example, The Society of Thoracic Surgeon's risk calculator incorporates race based on observed differences in surgical outcome, while admitting they are unaware of the underlying mechanism. Changing the race to "black/African American" increases the risk of death, and could therefore lead to unjust withholding of surgery.

Recently, bias in medicine has received more attention (for example the atypical presentation of the female heart attack). However, these deviations from the white man's presentation are taught as 'extra' and have yet to become fully integrated in medical education.

In conclusion, the role of race in modern medicine is complicated but deserves our full attention. Ignoring or not documenting ethnicity and race deprives us of important data. At the same time, we should be cautious when implementing race-based medicine, since adjusting for race without a proper biological rationale could be harmful. In addition, medical training and clinical research should shift their focus from a white man's perspective to ensure equal quality of care for each individual.

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Acute renal function deterioration in a pulmonary arterial hypertension patient with decompensated right heart failure

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ABSTRACT

In an end-stage pulmonary arterial hypertension (PAH) patient with right-sided heart failure (RHF) and impaired responsiveness to a loop diuretic regimen, addition of a thiazide diuretic led to an acute renal function deterioration. Renal function recovered after discontinuation of the thiazide diuretic and addition of a vasopressor. This case demonstrates the challenges of treating end-stage RHF in PAH patients and underlines the need for research on optimal treatment strategies in these patients.

CASE DESCRIPTION

A 30-year-old female patient, diagnosed with pulmonary arterial hypertension (PAH) five years ago deteriorated gradually despite being on triple therapy (bosentan 125mg 2dd, sildenafil 20mg 3dd and treprostinil (10mg/ml) 94ml/24h) while awaiting lung transplantation. The patient presented at our emergency department with end-stage right heart failure (RHF), ankle edema and ascites despite chronic use of oral diuretic therapy consisting of 500 mg furosemide and 50 mg spironolactone. Vital signs upon admission were a blood pressure of 102/62 mmHg, a heart rate of 92 beats per minute and a body temperature of 35.9 °C.

Laboratory investigations indicated mildly impaired glomerular filtration (creatinine 78 umol/L, eGFR 75 mL/min/1.73m2, according to CKD-epi formula) and borderline low sodium levels (135 mmol/L). Latest right heart catheterization revealed severe pulmonary arterial hypertension (PAH) with mean right atrial pressure of 13 mmHg (2-6 mmHg), mean pulmonary arterial pressure of 94 mmHg (9-18 mmHg) and pulmonary vascular resistance of 1539 dynes·sec/cm5 (<250 dynes·sec/cm5). Cardiovascular magnetic resonance showed severe right ventricle dilatation with a cardiac index of 0.81 L/min/m2 (2.6–4.2 L/min/m2) and right ventricular ejection fraction of 24% (60-70%). Echography confirmed ascites and 2.5cm of fluid in the pericardial cavity.

To treat the severe venous congestion and ascites secondary to end-stage RHF, an intravenous loop diuretic, furosemide 500 mg/24h, was started after admission. Because of unsatisfying effect on the patients' bodyweight, hydrochlorothiazide (HCT) 12.5 mg was added. In response to the medication, the patient lost 1.6 kg of bodyweight in the next days (FIGURE 1A). Despite the positive effect on the patients' bodyweight, severe renal insufficiency developed after initiation of HCT (FIGURE 1A). Consequently, the thiazide diuretic was discontinued after five days. The next day, terlipressin was started in order to improve systemic blood pressure. The discontinuation of HCT and start of terlipressin resulted in improved kidney perfusion and glomerular filtration.

On terlipressin, kidney function recovered and the patient's body weight normalized within two days. With terlipressin, we were able to maintain a stable kidney function and bodyweight. The patient underwent successful lung transplantation two weeks later.

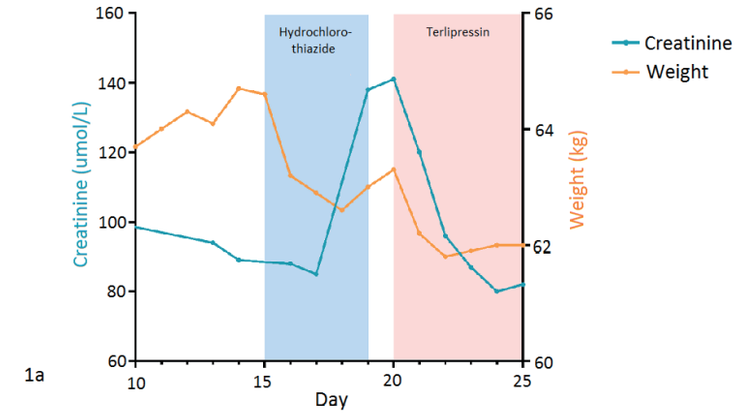
DISCUSSION

Kidney failure is a common complication of decompensated RHF, where both backward failure and forward failure occur. Backward failure causes central venous congestion, resulting in an increase in central venous pressure. Consequently, the pressure in renal veins is augmented.[1] This causes a compromise in kidney function by lowering renal perfusion.[2,3]

Numerous studies have described a combination of thiazide diuretics and loop diuretics as a treatment option for left-sided decompensated heart failure in patients with impaired diuretic responsiveness.4[5,6] In clinical practice a clear benefit is usually observed of diuretics in fluid overloaded PAH patients with RHF. However, in current scientific literature there are no randomized controlled trials present regarding diuretic regimens for PAH patients with RHF, let alone diuretic combination therapy.[7]

Both loop diuretics and thiazide diuretics augment the excretion of sodium (and to some extent also potassium), resulting in expanded volume excretion by preventing water reabsorption. In combination therapy, both drugs enhance one another, as sodium reabsorption is inhibited at subsequent segments of the nephron, thereby amplifying the total diuretic effect.[4]

In this case, we hypothesized that the acute renal shutdown was caused by several factors. First, as a consequence of furosemide, the renin–angiotensin–aldosterone system (RAAS) activation was increased, which induces vasoconstriction of the



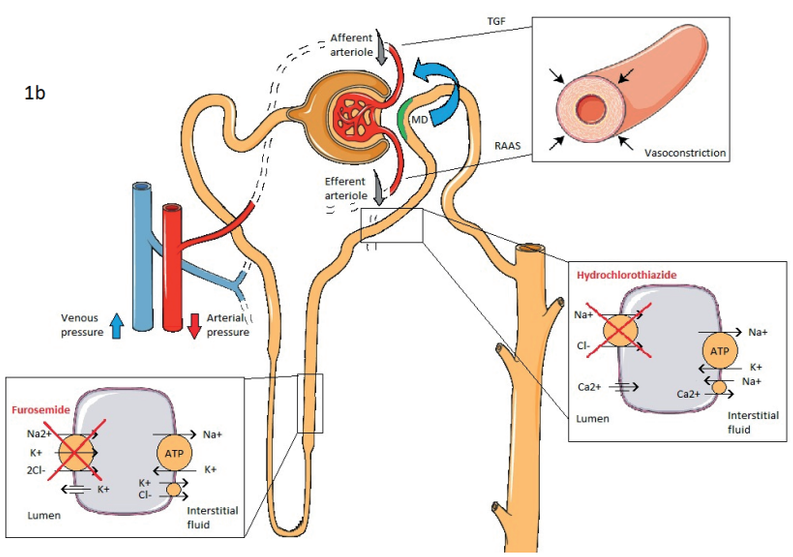


FIGURE 1a. Weight (kg) and creatinine (umol/L) levels shown from day 10 after admission. Intravenous infusion of furosemide 500 mg/24h was started at the time of admission.

FIGURE 1b. Schematic representation of a nephron and the factors that are involved in the acute renal shutdown. 1) Vasoconstriction of the afferent and efferent arteriole in response to the increased activated RAAS by furosemide; 2) Increased renal venous pressure as a consequence of amplified central venous pressure due to backward failure; 3) Vasoconstriction of the afferent arteriole as a result of TGF, induced by raised concentration of sodium passing the MD in the distal tubulus after addition of HCT to high-dose furosemide.
HCT, hydrochlorothiazide; MD, Macula densa (In the MD, symbolized by the green area, the urinary sodium content is sensed, and its paracrine factors, symbolized by the blue arrow, induce the tone of the afferent arteriole); TGF, Tubuloglomerular feedback; RAAS, renin-angiotensin-aldosteron-system.

efferent renal vessels. This diuretic induced activation of the RAAS escalated the activation by PAH itself, and may further lower total renal perfusion.[8] Secondly, the renal venous pressure was enlarged as a consequence of backward failure. Thirdly, by adding HCT, the amount of sodium that passed the macula densa was amplified. This led to vasoconstriction of the afferent renal artery induced by tubuloglomerular feedback (FIGURE 1B).[9] These three factors together resulted in high renal vascular resistance and impaired glomerular filtration, leading to an acute renal function deterioration. The kidney function recovered presumably as a result of restored renal blood flow. This was accomplished by attenuated tubuloglomerular feedback and thereby reduced afferent vasoconstriction after discontinuation of HCT, and increased systemic vascular resistance by addition of terlipressin (FIGURE 1A).

Terlipressin is an analogue of vasopressin, which induces systemic vasoconstriction. Our hypothesis is that in this case, in response to terlipressin, the systemic blood pressure increased. This augmented glomerular perfusion pressure, resulting in an improvement of renal filtration, diuresis and consequently loss of peritoneal fluid. This case underlines the potential benefit of vasopressive drugs in the treatment of severe fluid retention in end-stage RHF.[10] Since the discontinuation of HCT was followed quickly by addition of terlipressin, we cannot conclude with certainty if terlipressin contributed to the recovery of the kidney function.

CONCLUSION

In this case we demonstrated the challenges of treating end-stage RHF. Combination therapy of furosemide and HCT can cause acute renal shutdown in a patient with end-stage RHF and addition of terlipressin might be effective in the treatment of end-stage PAH patients with RHF. Research regarding diuretic regimens and the use of vasopressors in the setting of treatment for PAH patients with RHF is needed. For now, in clinical practice treatment should be individualized, taking into account the potential risk of acute kidney function deterioration in these vulnerable patients with RHF.

Learning objectives

- Diuretic combination therapy of furo semide and HCT can, based on this case, cause acute renal shutdown.
- In clinical practice diuretic treatment may need to be individualized, taking into account the potential risk of acute kidney function decline in vulnerable patients with RHF.
- A vasopressor, such as terlipressin, might be an effective medicine in the treatment of end-stage PAH patients with RHF and diuretic resistance.
- Additional research is needed regarding diuretic regimens and the use of a vasopressor in the setting of treatment for PAH patients with RHF.

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Era of connection: The value of cultural diversity in the healthcare system

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With special thanks to Dr. Gem Kramer and Dr. Wessel Fuijkschot

Nowadays, Dutch society is more culturally diverse compared to 25 years ago, with non-native Dutch citizens making up 25% of the inhabitants. Due to the surge in migrants, a multicultural society has been formed. As a result, the patient population of hospitals is becoming increasingly culturally diverse.[1] But what is the actual definition of culture, and why is it important? How should we deal with this shift in patient population? I believe that there should be more cultural diversity among medical specialists in order to reduce healthcare disparities.

Culture is defined as the shared patterns of a group that are learned through the process of socialization. It contains everything that a group of people feels, does and experiences— its processes, behaviors, and feelings. These patterns can be used to identify and distinguish members of different cultural groups.[2]

Without proper knowledge about these patterns and their meaning to patients, one is not able to provide optimal care. The elements of culture influence belief systems regarding wellbeing, illness and health. Comprehension of the influence of culture on health perception positively affects delivery of care.[3] In modern healthcare, we find it vital to provide care that is respectful and responsive to the needs of patients. However, in the Netherlands cultural diversity among medical specialists is sparse. In fact, only two to four percent of all the medical specialists has a culturally diverse background, contrary to 20 to 30 percent among medical students.[4]
Culturally competent care integrates cultural intelligence into the delivery of healthcare.[5] This cultural competence is crucial when providing care due to a number of reasons.

Firstly, the importance of cultural competence is underlined by reason of medical errors being the third leading cause of death in western countries such as the US. It is reported that communication issues are one of the main causes of medical errors.[6] Due to language barriers, patients from different cultural backgrounds have a harder time expressing their needs and are accordingly more likely to suffer, for instance, during the final stages of their life.[5,7] It is reported that the quality of care and safety is diminished for minority patient groups.[8,9]

Avoidable suffering and healthcare disparities are unacceptable in any healthcare system that strives for respectful and responsive care.

Secondly, doctor awareness of the influence of culture on help-seeking behavior and utilization of health services is essential for the relationship between doctor and patient. To build a relationship based on trust, a patient has to have a feeling of being heard and understood, which cultural awareness could contribute to.[10] One of the effects of a poor doctor-patient relationship is loss of therapy adherence. It has been proven that migrants and refugees are particularly vulnerable when it comes to therapy adherence. When combined with an inadequate treatment relationship these groups are more likely not to adhere to prescribed therapies.[11]

Furthermore, when treating mental health problems an approach backed by cultural competence is of the utmost importance. The stances on mental health differ substantially between various cultures. A doctor who has no knowledge about these differences and how the patient perceives the concept of mental health might not give the ideal treatment, or might even choose an approach that is more harmful than beneficial for the patient. Understanding one another in terms of health perspectives and values is unquestionably valuable in providing optimal care.[12]

Battling healthcare disparities requires cultural competency. Research shows behaviors of healthcare providers contribute to health disparities. Education on how to deliver culturally competent care is valuable, but the intracultural diversity calls for more than education.[13] This is mainly due to the dynamic concept of culture. Diversity within one cultural group can be substantial, it is unfeasible for someone outside of the culture to be aware of all the variances of cultural elements in a certain sub-population. When the doctor has the same cultural background as the patient, optimal care is more easily provided. For this reason, it is necessary to have cultural diversity among medical specialists.

In conclusion, I believe that there should be more cultural diversity among medical specialists in order to reduce health disparities. Culture has an extensive influence on the quality and efficacy of healthcare and to optimize care, a culturally diverse team of medical specialists is needed. A possible way to improve diversity within a medical team is to take cultural background into account during application rounds for specialties that are less diverse. Another solution could be showcasing established diversity, in order to motivate medical students with a diverse background to apply for a specialty.

Over the recent years, the Dutch patient population has transformed into a multicultural group and now it is time to reflect that change among our medical specialists. Our hospital staff has always been a representation of our society, so why is it not now?

Cultural differences have major impact on the quality of Health Care. To deliver optimal Health Care and promote a speak-up culture between doctors and patients, we must aim to analyse and improve these differences. However, structural changes take years to take place. We encourage our readers to help us think! Please contact us if you have ideas, visions or if you just want to participate in the discussion. We are looking forward to it! We design the future of Health Care.

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Cluster Randomized Controlled Trials

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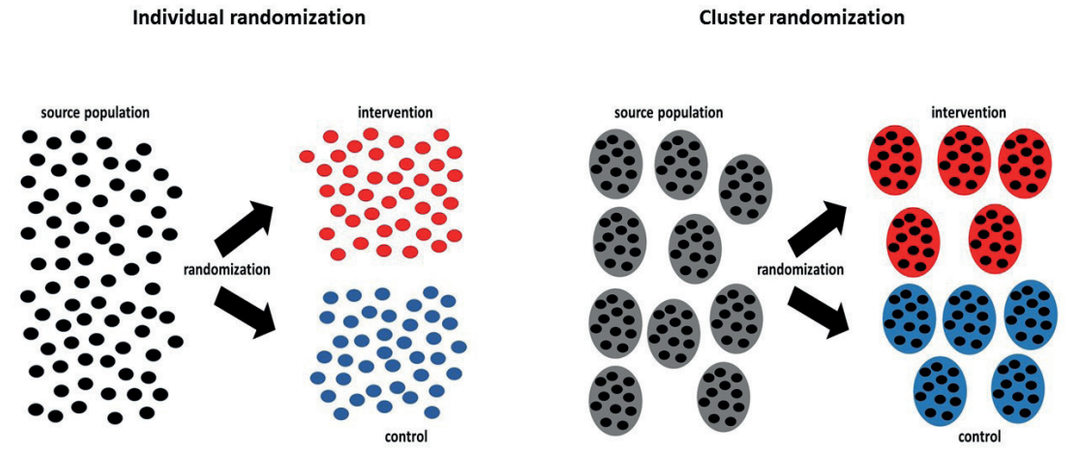
For the last 30 years, the randomized controlled trial (RCT) has been the gold standard to investigate the efficacy of new drugs, new treatments or new interventions. The general idea behind an RCT is that a group of patients is randomized into a treatment group and a control or placebo group. Normally this randomization is performed for individual patients. However, in some situations it is not possible to randomize the individual patients, but the randomization has to be performed on a higher level. For instance, the randomization can be performed on the hospital level (i.e. intervention hospitals versus control hospitals), nursery home level or on the medical doctor level. When the randomization is performed on a higher level, the RCT becomes a cluster RCT. When the data of a clustered RCT is analyzed, the statistical methods are slightly more complicated than the methods used for analyzing the data from an RCT with individual randomization. The problem with the analysis of data from a clustered RCT is the fact that the observations of patients belonging to the same cluster (i.e. hospital, nursery home, medical doctor) are not independent of each other. Independency of observations is one of the key assumptions in regular statistical analysis. So, when data of a clustered RCT is analyzed this dependency of the observations must be taken into account. The most simple way of dealing with that dependency is to adjust for the cluster variable, i.e. adjust for the hospital, the nursery home or the medical doctor. That adjustment works well when the number of clusters is relatively low in comparison to the total number of patients. When the number of clusters becomes large, the standard adjustment for the cluster variable is not possible anymore. It should be realized that in regular regression analysis the adjustment for a cluster variable is performed by adding dummy variables to the regression model. Because the number of dummy variables equals the number of clusters minus 1, it is obvious that



the more clusters there are, the less efficient the estimates of the regression model will be. To deal with this problem a statistical method named multilevel analysis (also known as mixed model analysis) can be used. The general idea behind a multilevel analysis is that the adjustment for the cluster variable is performed in a very efficient way, by estimating only one parameter irrespective of the number of clusters. To understand the basic principles of a multilevel analysis, we have to go back to a regular regression analysis to analyze the efficacy of a new treatment. That regression model includes an intercept and the treatment variable (and the baseline variable of the outcome, but that's not important for this discussion). Suppose we want to adjust this model for sex. This adjustment is performed by adding the variable sex to the model, but it actually means that for males and females, two different intercepts are estimated. The adjustment for the cluster variable in a clustered RCT is basically the same, i.e. for each cluster a separate intercept is estimated. Again, when the number of clusters is large in comparison to the number of patients, the regular adjustment with the dummy is not efficient and therefore not possible. How is this adjustment performed in a multilevel analysis? Well, basically the method contains three steps: 1) for each cluster a separate intercept is estimated (as in a regular adjustment), 2) a normal distribution is drawn over all the intercepts, and 3) from that normal distribution the variance is estimated and that variance is added to the regression model to adjust for the clustering. Although the method is mathematically complex, the general idea is relatively simple. Multilevel analysis is, therefore, a very efficient way to deal with clustering in the data.

Read a paper, but question the statistical analyses? Let us know via AMSj.nl or our Facebook page!

Lumbar puncture in children with newly diagnosed acute lymphoblastic leukemia: at diagnosis or delayed? A systematic review

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ABSTRACT

BACKGROUND Diagnosing patients with acute lymphoblastic leukemia (ALL) involves performing a lumbar puncture (LP). Traumatic lumbar puncture with blasts (TLP+) at diagnosis is associated with poor overall survival (OS) and event free survival (EFS). The objective of this systematic review was to analyze and determine the best timing of initial LP to reduce CNS-relapse and improve OS and EFS.

METHODS Two databases (PubMed and Web of Science) were searched using the keywords 'Acute Lymphoblastic Leukemia', 'Lumbar Puncture', and 'Central Nervous System'. Clinical trials, prospective- and retrospective studies were included, whereas meta-analysis and systematic reviews were excluded.

RESULTS Ten relevant articles were selected, four of which performed a delayed LP, five performed the LP at diagnosis and one study performed it at both intervals. Initially, studies that performed a delayed diagnostic LP reported lower incidence of TLP+, compared to studies that performed the LP at diagnosis. However, when LP is performed at diagnosis, early intensification and risk-adjusted therapy can prevent CNS-relapse and increase EFS and OS. Risk of TLP+ can be reduced by use of deep sedation or general aesthesia, correction of thrombocytopenia, and an experienced clinician performing the LP.

CONCLUSION Delayed intrathecal therapy (IT) seemed to reduce rates of TLP+ at diagnosis. Studies that performed the LP at diagnosis, stratified their patients according to risk of relapse and central nervous system (CNS) status, reported increased EFS and OS, along with reduction of CNS-relapse. Even though risk of TLP+ is highest at diagnosis, adequate precautions can eliminate this risk. Prospective and randomized clinical trials are needed to confirm the best timing of LP.

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) accounts for 25.4% of childhood tumours, making it the most common cancer type among children.[1-9] Lumbar puncture (LP) is often performed for diagnostic and therapeutic purposes. Studies have examined the impact of delaying the diagnostic lumbar puncture along with the first dose of intrathecal therapy (IT), until the clearance of circulating blasts in the blood (after seven and no later than 10 days). The reason for the delay, as provided by several studies, involved the theory that leukemic cells can be introduced into the central nervous system (CNS) due to traumatic lumbar puncture with blasts (TLP+). Mainly at diagnosis, when patients have the highest number of blasts in their peripheral blood (PB), TLP+ can lead to iatrogenic introduction of blasts into the cerebrospinal fluid (CSF).[13,14] LP is a routine procedure to determine the stage of ALL, but different timings for initial lumbar puncture have been applied by clinicians.[5,9,10] In the Netherlands, LP in children is often performed at diagnosis, along with the first dose of IT therapy, after which patients can be stratified according to CNS involvement and risk of relapse12. The hypothesis is that performing the initial LP at diagnosis might result in better overall outcome, firstly because adequate precautions can prevent TLP+ and secondly because early risk stratification yields risk-based treatment and hence higher event free survival (EFS) and overall survival (OS). The aim of this systematic review is to assess the available literature regarding the advantages and disadvantages of either performing the LP at day one of diagnosis versus delaying the initial diagnostic LP in children with newly diagnosed ALL.

METHODS

Search strategy

The search was performed using two databases, PubMed and Web of Science, between January 2000 and January 15th, 2020. The PICO model was used (SUPPLEMENTARY TABLE 1). Search terms included 'Acute Lymphoblastic Leukemia', 'Lumbar Puncture' and 'Central Nervous Neoplasia'.

Inclusion criteria and data-extraction

All articles were screened on title and abstract by one author (SA).

The inclusion criteria were: newly diagnosed acute lymphoblastic leukemia, use of (diagnostic) lumbar puncture, full text in English or Dutch and age of patients between 0 and 18 years. Prospective and retrospective clinical trials were included. Studies in the form of (systematic) reviews, meta-analyses and non-human studies were excluded. Subsequently, all articles were read in full text and assessed by one author on quality (according to PRISMA guidelines), eligibility and relevance.

An overview of the study characteristics that were extracted from the included studies is listed in SUPPLEMENTARY TABLE 2.

RESULTS

Study selection

Initially, the search resulted in 95 hits in PubMed and 84 hits in Web of Science. After removing duplicates, 10 articles were selected (FIGURE 1). The detailed study characteristics are presented in SUPPLEMENTARY TABLE 2.

Main study characteristics

Clinical trials, prospective- and retrospective studies were included. All studies used the CNS classification:

- CNS-1: non-TLP (<10RBC/ml) and no detectable blasts
- CNS-2: non-TLP (<10RBC/ml), <5WBC/ml + blasts
- CNS-3: non-TLP (<10RBC/ml), >5WBC/ml +blasts
- TLP-: traumatic LP (>10RBC/ml), no blasts
- TLP+: traumatic LP (>10RBC/ml), with blasts

Study outcomes

Six studies that performed the LP at diagnosis found prolonged EFS and decreased CNS-relapse, when the LP was followed by intensified treatment.[5-10] The EFS was between the ranges of 54%-85.6% and their OS between 69,5%-93,5% (SUPPLEMENTARY TABLE 3). The studies that performed the LP at diagnosis reported EFS between the ranges of 79.6%-85,6%.

Five studies performed the initial diagnostic LP on day 8 or 10 (delayed).[1-5] The studies with delayed LP, reported an incidence of TLP ranging from 0-0.8%, whereas those with LP at diagnosis reported a range from 0-38%. The stratified groups received treatment according to their CNS involvement and risk of relapse, which resulted in high intensity treatment for high risk patients, and low intensity treatment for low risk patients (SUPPLEMENTARY TABLE 4).

DISCUSSION

Delayed initial lumbar puncture in childhood ALL: advantages and disadvantages

In four studies, delaying initial LP seemed to reduce CNS relapse and TLP+ in children with newly diagnosed ALL.[1-4] However, concern remains regarding the CNS-2 and CNS-3 status, because administration of systemic therapy masks CNS involvement due to elimination of blasts in CSF, yielding false-negative results and unfair risk stratification when initial diagnostic LP is delayed.[1,2,3,4] Not performing the LP at diagnosis could potentially underestimate the patients at high risk for CNS relapse and therefore undertreat them.[2,3,7]

Diagnostic LP at diagnosis: advantages and disadvantages

Early intensified treatment or reduction of treatment according to CNS status and risk of relapse can increase EFS and prevent treatment related toxicity.[4,7-10]

Nonetheless, LP at diagnosis can lead to TLP+ and is therefore associated with poor OS and increased risk of CNS relapse in high risk (HR) groups. However, use of deep sedation, an experienced clinician performing the LP and correction for thrombocytopenia, along with the immediate ad-

ministration of IT treatment seemed to reduce risk of TLP+.[5,9] This can mainly be seen in two studies that reported 0 TLP's, even though different timings for the LP were used.[1,7]

Limitations

Studies about (timing of) LP and risk factors for TLP and its impact on CNS outcome are controversial and comparison of these studies is complex. The 10 studies differed in sample size, in- and exclusion criteria, institution in which LP was performed, experience of clinicians performing the LP, study population and design. Not all studies differentiated between TLP and non-TLP, and some of them did not include OS. In addition, only articles between 2000 and 2020 were included. Moreover, the articles were selected and screened by one author.

CONCLUSION

The initial diagnostic LP can be safely performed at diagnosis, if it is followed by early intensified treatment according to risk-group and/or CNS-status. Even though the probability of TLP+ is highest at diagnosis, creating the right conditions can reduce, if not eliminate this risk.[7] Risk of TLP+ can be reduced by use of deep sedation or general anaesthesia, correction of thrombocytopenia, and an experienced clinician performing the LP.
Nonetheless, more controlled clinical trials are needed to further investigate the impact of performing the initial LP at diagnosis versus performing a delayed LP.

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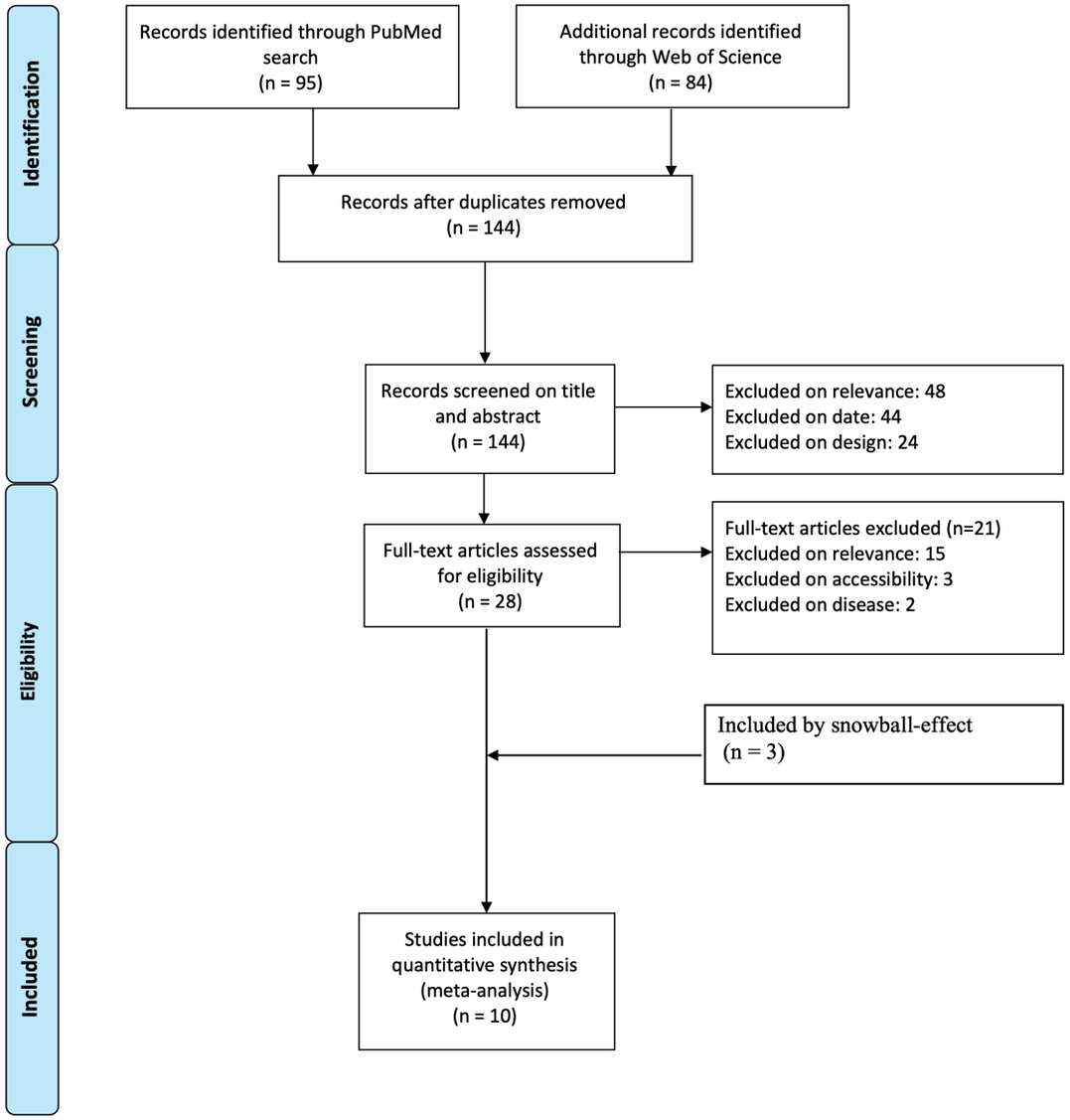

FIGURE 1 PRISMA Flowchart

L.M.G. Geeraedts Jr, MD, PhD, Msc

Interviewed by Stefan van Wonderen[1]
1. Faculty of Medicine, Amsterdam UMC, location VUmc

Area of expertise: Trauma Surgery, Orthopedic Trauma Surgery, Hemorrhagic Shock, Trauma Resuscitation, Prehospital Trauma Care, Pelvic & Acetabular Fracture Surgery, Trauma Education.

Function as specialist: Trauma Surgeon and Orthopedic Trauma Surgeon, Amsterdam UMC, Location VUmc.

What are your research interests?
Multiple trauma-related topics are of interest, but the most intriguing topic is trauma-related hemorrhagic shock. Life-threatening hemorrhage is the most important preventable cause of death in trauma. During trauma resuscitation, disturbed vital functions such as airway and breathing are often quite easily restored, even in the prehospital arena. The disturbance of the circulation in trauma is much more challenging and it requires in-depth knowledge, skills, resources and teamwork to stop the bleed, restore blood volume and prevent traumatic coagulopathy throughout the Trauma Chain of Survival from the field to the ICU. As a trauma surgeon and team leader one can really make the difference in these cases.

How did you become involved in trauma-related hemorrhagic shock and research?
I became involved in this topic during my medical studies. I knocked on the door of Prof. dr. R.J.A. Goris, Trauma Surgeon and Head of the Surgical Department of the Radboud UMC at that time. He was very inspiring and I participated in his research on the immune consequences of trauma, shock and sepsis as a voluntary student researcher. Actually, at the end of the 1980s, he was one of the pioneers who discovered 'sepsis without bacteria' in severely injured trauma patients on ICU and called it 'whole body inflammation'. Nowadays this state is recognized as the Systemic Inflammatory Response Syndrome (SIRS)! Finally, I was able to do my own project as a scientific research internship at the Institute for Surgical Research of the Ludwig-Maximillian University of Munich, as a student.

You introduced 'Stop the bleed, save a life' in the Netherlands. How did you come up with the idea and what is your future perspective of the course?
'Stop the bleed, save a life' was already invented and introduced in the United States because of the high incidence of mass shootings and after the Boston Marathon Bombing incident. Concepts from military prehospital care were translated to civilian bystander care. In 2016, after the Brussel Bombings, we felt the urge to teach this knowledge and these skills in the Netherlands and started a campaign and a first-aid course. Over 10.000 Dutch citizens have followed the course already. The public is taught how to stop a bleed, following some easy steps: apply direct pressure while using a t-shirt, for example, pack the wound using hemostatic gauze or apply a tourniquet if possible. Since bystander care has improved survival from cardiac arrest, it is expected that with early care from bystanders, victims with life-threatening hemorrhage will have a better chance of reaching the hospital alive and/or in a better condition.

What kind of student were you during medical school?
Mainly, a student who was very busy with sidelines. I was in a competitive rowing team (national level) for four years, was a coach for two years and chairman of the student rowing club (NSRV Phocas). In addition, in 1990 we set up a foundation called 'Stichting Hippocrates College Noviomagensis'. This foundation focused on reducing the distance between clinical specialists and medical students. Once a month, medical specialists (led by a professor) from let's say surgery or cardiology (and so on) were asked to introduce themselves and their specialty during an informal meeting. Nowadays, the foundation still functions! At that time (30 years ago now) we also founded a new student union (NSV Ovum Novum) that currently happens to be the largest formal student union in Nijmegen.

L.M.G. Geeraedts Jr, MD, PhD, Msc

CURRICULUM VITAE

1967	Born in Nijmegen
1995	MD, Radboud University, Nijmegen
1996	Surgical Resident VUmc, Amsterdam
1997	Start Surgical Residency Training, CWZ-Hospital and Radboud UMC, Nijmegen
2002	HEMS Physician, Lifeliner 3, Nijmegen
2003	Board Certified Surgeon
2004	Board Certified Trauma Surgeon
2005	David Sloane Clinical Trauma Fellow, Sydney, Australia
2006	Consultant Trauma Surgery, Radboud UMC, Nijmegen
2010	Consultant Trauma Surgery and Orthopedic Trauma Surgery, VUmc, Amsterdam
2010	HEMS Physician, Lifeliner 3, Nijmegen
2013	PhD, VU, Amsterdam https://research.vu.nl/en/publications/management-of-trauma-patients-with-life-threatening-hemorrhage
2014	MSc Clinical Epidemiology, VU, Amsterdam https://doi.org/10.1016/j.injury.2014.08.001
2016	Initiator and Program Director of 'Stop the bleed, save a life' The Netherlands www.stopdebloedingredeenleven.nl
2018	Board member and Course Director Definitive Surgical/Anesthetic Trauma Care, The Netherlands

What would you advise students (during their surgery internship)?
Medicine is solving the problem of the patient. If it is not your expertise, it is still your responsibility to refer the patient to one of your colleagues who can solve the problem. If you want to be a good doctor, take responsibility and be accountable. Also, try to learn and think in concepts. Nowadays a lot of information is gathered as bits and pieces from the internet and one will not get the big picture. My advice is to read books and chapters on topics and broaden your horizon. This will make deduction easier when solving problems. Conceptual thinking is needed for successful clinical reasoning. Also, spend as much time as possible watching how experienced doctors solve problems (or not) and learn from their good and bad habits. You will learn yourself by doing it, but don't be disappointed how much time it may cost to become an expert: it is a marathon, not a sprint.

Geeraedts is not a common name in the Amsterdam area. Where does the name come from and how did you end up in Amsterdam?
My family roots stem from the south of Limburg and I was born and raised in Nijmegen and surroundings. After my propaedeutic year in Biology I started with Medical School at the Radboud University Medical Center. After graduation in 1995, I started working as a surgical resident (ANIOS) at the VU medical center (VUmc) in 1996. In 1997, I started formal surgical residency training (AIOS) at the Canisius-Wilhelmina Hospital and Radboud University Medical Center. During this period, I was also trained as a Helicopter Emergency Medical Services physician and became a member of the Lifeliner 3 Mobile Medical Team. My surgical training was completed in 2003 and my formal training as a trauma surgeon in 2004. After that I became the David Sloane Clinical Trauma Fellow

in the Liverpool Hospital in Australia. Then, after some years as a trauma consultant at the level I trauma center of Nijmegen, I returned to the VUmc as a consultant in trauma surgery and HEMS-physician in 2010.

Multiple publications are attached to your name. Is there one in particular that you are most proud of?
I am proud of 'Exsanguination in trauma: A review of diagnostics and treatment options', published in Injury (2009). It attempts to approach trauma-related hemorrhage as a challenging, time-critical disease starting from the point of injury and ending in the ICU when (coagulopathic) bleeding has stopped. And I must mention another paper published in Injury (2015) called: 'Prehospital fluid resuscitation in hypotensive trauma patients: do we need a tailored approach?' This is my Master of Science graduation thesis in Clinical Epidemiology!

Do you have other interests in trauma surgery beside trauma-related hemorrhage?
Yes, besides performing epidemiological studies with very motivated medical students and with trauma databases, I have gained experience in treating trauma patients with pelvic ring fractures and/or acetabular fractures. These fractures are very challenging. By using 3D–print fracture models and a developed concept, I continuously try to do my best to perform better due to meticulous preparation and tenacity during these long-lasting operations, in order to have the best outcome for the patient.

Letter to the editor

Dear Editors,

We have read the response to our letter regarding the high fatality rate in developed countries. We enjoyed reading it and would like to emphasize the vaccines under study for COVID-19.

The Bacille Calmette-Guérin (BCG) vaccine is currently being researched in a phase-III study (NCT04328441). The hypothesis is that "BCG vaccination induces (partial) protection against susceptibility to and/or severity of COVID-19 infection".[1] No definitive relation between BCG and COVID-19 infection can be drawn yet, because the study is still incomplete. There are some other vaccines which are being tested in phase-I studies. These include mRNA-1273(encapsulated mRNA vaccine), Ad5-nCoV (an Adenovirus type 5 vector), and INO-4800 (a DNA plasmid).[2,3]

Thus, from the discussion on the possible reasons for high COVID-19 deaths in developed countries, we can speculate the following:

1. Certain preventive vaccines like BCG are not administered routinely.
2. There is better hygiene in developed countries. The immune system is not challenged as much as it is in developing countries. This leads to a greater susceptibility to diseases.
3. High fraction of old age group due to the health facilities provided in developed countries.

Other than vaccines, new therapies for COVID-19 have been finalized:

- Ozone Therapy (NCT04400006): It is considered useful for prevention of COVID-19 because it causes stimulation of phagocytic cells and restoration of the immune system due to the oxidative stress of ozone.
- Convalescent Plasma Therapy (NCT04346446): Convalescent plasma contains antibodies against COVID-19 which can be given to the infected patients to boost their immune system.

For the future, I hope that we are better prepared for pandemics so that social, psychological and economic crises can be avoided. Telemedicine should be taught in colleges. Education regarding hygiene measures must be spread.

With kind regards,

Haleema Anwar
Dr. Qudsia Umaira Khan
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Updated guideline for diagnosis and initial management of miscarriage*

*Disclaimer; this guideline has not been authorized yet

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BACKGROUND

A miscarriage is a pregnancy that ends spontaneously before the 20th week of pregnancy.[1,2] The majority of miscarriages takes place in the first trimester before 12 weeks of pregnancy. Approximately 15-20% of pregnancies end in a miscarriage.[4,5] Therefore, miscarriage is the most frequent complication of pregnancy. It is estimated that every year about 20,000 women suffer from a miscarriage in the Netherlands.

Currently there is a wide variation in the management of first trimester miscarriages in the Netherlands. Despite several quality documents for first line care, a guideline for medical specialized care is still missing. Because of the extensive and time-consuming character of conducting a new guideline, the British NICE guideline 'Ectopic pregnancy and miscarriage: diagnosis and initial treatment'[6] served as the basis for the present Dutch guideline. Where possible, recommendations were adjusted and updated according to the latest evidence.

The present guideline covers diagnosis and management in women who have symptoms such as abdominal pain and/or blood loss in the first 20 weeks of pregnancy that may indicate a miscarriage or a non-vital pregnancy.

AIM

The aim of the guideline is to reduce the number of complications after treatment of miscarriage, to make treatment across health care professionals more uniform, to increase the efficiency of medical care by reducing the costs and to increase patient satisfaction.

Recommendations on diagnostic management

An ultrasound scan, preferably transvaginal, is considered the golden standard in the assessment of viability and localization of an early intrauterine pregnancy. See figure 1 for diagnosing an early non-vital pregnancy.

- Offer every woman a transvaginal ultrasound scan 6w4d from gestation if the patient has concerns about the viability of the pregnancy.
- Conduct a second ultrasound scan 7-14 days after the initial ultrasound scan in case of uncertainty about the viability of the embryo.[6]

Recommendations on treatment

For women with a confirmed non-vital pregnancy there are several treatment options. These include expectant management, treatment with medication or surgical removal of embryotic tissue by curettage. Discuss all treatment options with the patient to allow her to make an informed choice.

- Women should be offered expectant management and medical treatment above surgical treatment.
- Despite the high effectiveness of curettage there are indications that curettage may have negative influence on the future fertility and pregnancy outcome.[7,8]
- Medical treatment should consist of a combination of mifepristone and misoprostol.
- Consider cervical priming with misoprostol prior to curettage because this leads to easier surgical procedures and less complications.[9] Administer 400mcg misoprostol transvaginal three hours before the procedure.
- Standard prophylactic antibiotic therapy in surgical treatment for miscarriage is not recommended.

Other recommendations

- Routine ultrasound scan after medical treatment is not recommended.
- Transvaginal ultrasound scan is indicated in case of hardly any or no blood loss at all after medical treatment.
- Offer anti-D rhesus prophylaxis to all rhesus-negative women with > 10 weeks pregnancy and CRL > 33mm with spontaneous miscarriage or with medical treatment of miscarriage.
- After an early pregnancy loss, all women should be offered the option of a follow-up appointment.

The following criteria seen with transvaginal ultrasound scan may indicate an early non-vital pregnancy:

- Crown-rump length ≥ 7mm without visible fetal heartbeat
- Mean gestational sac diameter ≥ 25mm (preferably measured in three dimensions) without embryonal parts
- Absence of an embryo with fetal heart beat ≥ 2 weeks after initial ultrasound scan which demonstrated amniotic sac without yolk sac
- Absence of an embryo with visible fetal heartbeat ≥ 11 days after initial ultrasound scan which demonstrated amniotic sac with yolk sac

FIGURE 1 Criteria for diagnosing an early non-vital pregnancy

Curettage should be considered if the patient has one of the following criteria:

- High bleeding risk
- Doesn't have 24/7 urgent medical access
- Has an infected miscarriage
- Has large blood loss and hemodynamic instability
- Has traumatic experience with miscarriage, stillbirth or post-partum hemorrhage
- For any other reason can't or doesn't want expectant management or medical treatment

FIGURE 1 Criteria for considering curettage as treatment for miscarriage

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Trauma research project in rural Tanzania

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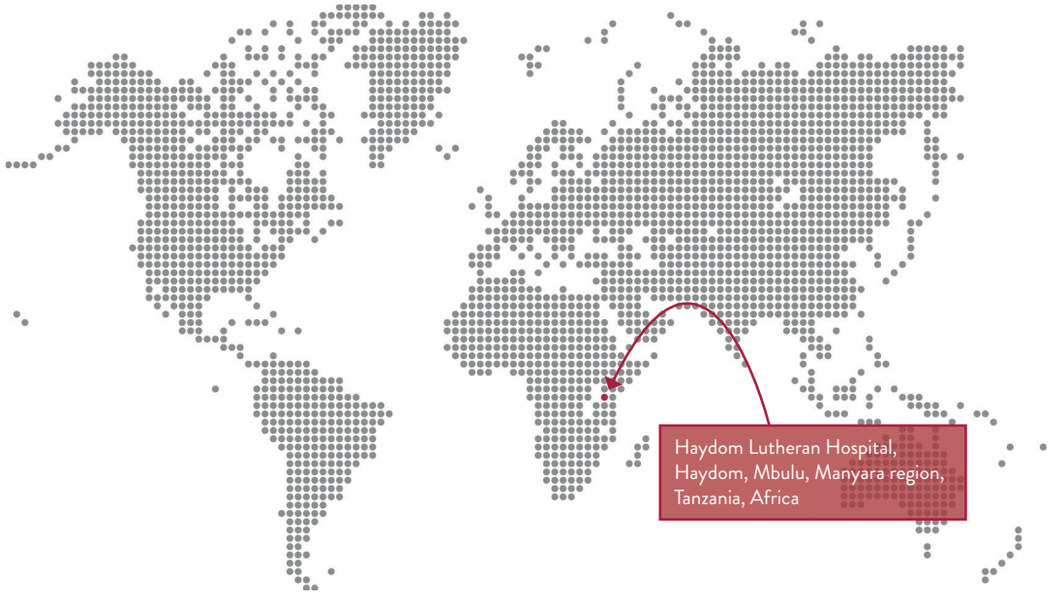

Waking up after a night of wild camping in rural sub-Saharan Africa drs. Anneloes Eleveld, drs. Grayson Mtui and we were ready for another day of follow-up. Unfortunately, we started the day with some bad luck; our car was completely stuck in the mud. Luckily, in no time, over twenty people came to help us, pushing the Land Cruiser out of the dirt. By chance, one of those people happened to be a relative of our patient. This was a fortunate coincidence, since you have no street names or functioning Google Maps in Tanzania to find the patients' homes. On top of that, almost all roads are dirt roads with quickly changing conditions, as we experienced ourselves this morning. The family member joined us in the car, and together we drove to our patient's home. The patient was a 42-year-old man who sustained an open tibial fracture from a motorcycle accident three months ago. He had been treated in the hospital and it was time for his three months follow-up. The patient and his family were incredibly hospitable and he explained to us how he had been since the accident. Shocked to see the enormous impact of the open fracture on his life and his family, we realized how incredibly important this research is and how grateful we are that we were able to help.

Road traffic injuries (RTIs) cause 1.3 million deaths annually.1,2 Africa has the highest mortality for RTIs. In addition, open tibial fractures are a common result of RTIs and have serious socio-economic effects.3–5 More current than ever

is the theme of inequality between different races and continents. Unfortunately, this inequality also occurs within medical research and healthcare. A '10/90 gap' has been reported, where only 10% of the global investment in medical research refers to 90% of the population worldwide, who mainly live in low- and middle-income countries (LMICs). The widely varying range of health care facilities, resources and demographic data between LMICs and high-income countries (HICs) often makes western research unsuitable for developing countries, revealing the necessity for these countries to conduct their own research locally 6,7. This illustrates the importance of research regarding surgical care in LMICs.

Being interested in the specialization 'Global Health and Tropical Medicine' from the beginning of our masters, we knew we wanted to go to a LMIC for a longer period of time instead of only reading about this topic. How to gain this experience was an easy choice: a six-month research and tropical medicine internship in a LMIC. Through Global Surgery Amsterdam we got in contact with drs. Anneloes Eleveld. From September 2019 until March 2020 we collaborated on a prospective research project focused on trauma care in a rural referral hospital, Haydom Lutheran Hospital in Tanzania. During our six-month stay, we participated in the project for open fractures and hip fractures, assisting the research team to investigate access to surgical care, treatment provided and complications encountered for both conditions. Follow-up of the outcomes is performed at three months, six months and one year after inclusion. Our tasks consisted of inclusion of patients, extracting data from hand-written patient files, in-hospital follow-up of patients, observing and assisting in the operation room, and, as mentioned above, participating in follow-up weekends. Eventually, Fleurance Smit wrote her master thesis on the topic of treatment and in-hospital outcomes of open tibial fractures, while Anna Keetelaar evaluated barriers in access to care for patients with open tibial fractures. Both research projects were performed under supervision of drs. Anneloes Eleveld (global health doctor), drs. Matthijs Botman (plastic surgeon and global health doctor) and prof. dr. Frank W. Bloemers (trauma surgeon). However, even with good supervision, performing research in such a setting is certainly not easy, due to poor Wi-Fi, language and cultural barriers, patient records being illegible or lost for weeks and destroyed X-rays after a lightning strike. In addition, we were constantly confronted with the fact that patients are not able to afford simple healthcare, which we take for granted in the Netherlands. And even when they were able to collect enough money, the best

possible treatment is very basic compared with the standards in HICs. On top of this, this research project has taught us how extremely important it is to conduct research locally in collaboration with local doctors. Besides this, we've learned to open up to other cultures and other perspectives instead of sticking rigidly to Western medical thinking. We can only recommend other students to follow your interests and broaden your view by taking part in such a research project. In these times, we strongly hope that in addition to the trend of posting a black-colored square on Instagram, there will also be a significant improvement in access to surgical care in LMICs and performing research about this topic.

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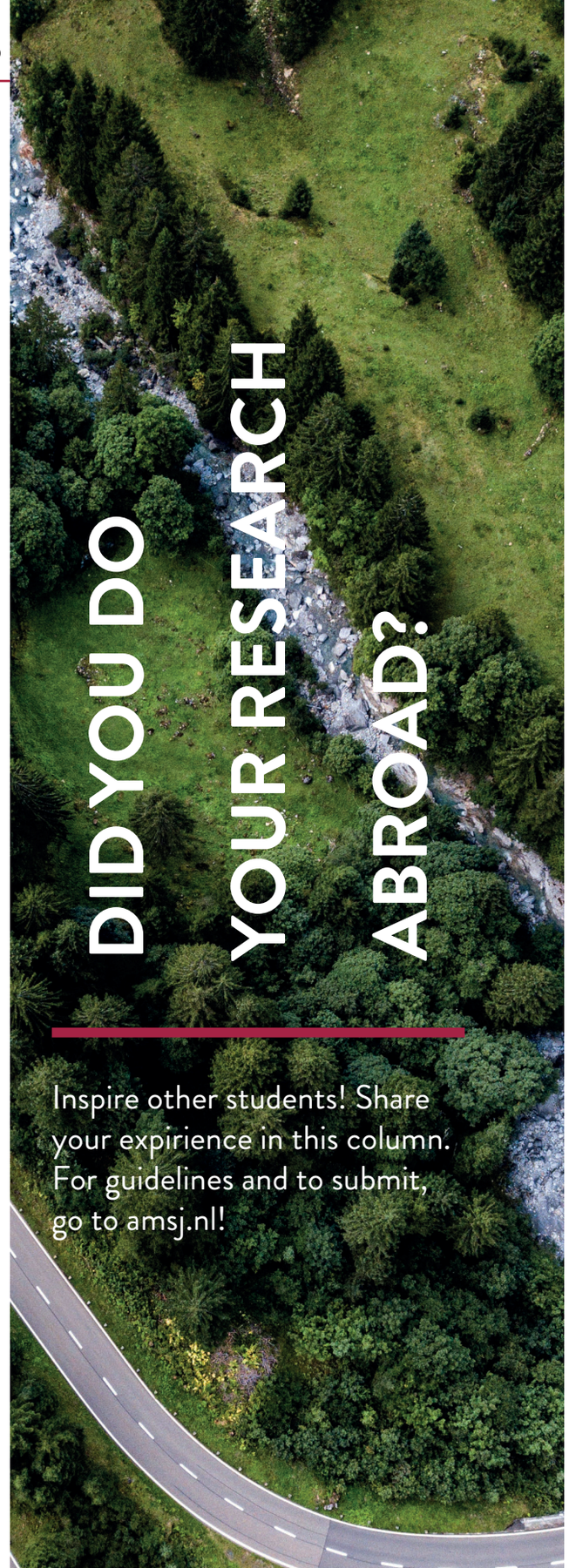

Five years later

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It has been five years since I published in the AMSj1. The case I described was a case I had seen as an intern during my pediatric rotation years before publication. During the time of publication, I was busy finishing my thesis while I also just started working as a resident in Internal Medicine. Research was something I have always been interested in, and, as a matter of fact, almost made me choose to study Biomedical Sciences instead of Medicine after graduating high school. Looking back though, I am glad to have chosen this path; the opportunity to be able to work as a clinician as well as the possibility to do research turned out to be the ideal combination.

Ever since the early years as a medical student, I have wanted to become a specialist in Internal Medicine and Infectious Diseases. My PhD thesis was entitled “Cell-specific Innate Immunity in Lung Infection and Inflammation”, and after finishing in 2017, I chose to focus on my career as a clinician specializing in Internal Medicine and Infectious Diseases, and did not engage in any research. This is something I will definitely try and pursue later on. And even though the case I published in the first issue of the AMSj did not involve an infectious disease, I believe any interesting case can be worthwhile to share with colleagues and young doctors, whether it involves your preferred area of expertise or is something completely out of your comfort zone.

Before choosing your career path, it is wise to try and imagine your future self. Early in your career, ask yourself regularly: “What kind of doctor do I want to be?”, “Do I want to work in a hospital?”, “In what hospital do I want to be working later on?” and “What do I need to do to be able to achieve this?”. Speak to people involved in your area of interest, it will help you make that decision, especially young specialists like me who have to actively think about these questions to decide their next move in their career. Don’t forget: one of the great things about becoming a physician is the opportunity to form your own career and become the doctor you want.

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Answers 'A tearing abdominal pain'

Sanne van Beem and Mario Maas

Correct answers: 1A, 2C, 3B, 4B

EXPLANATION

The patient suffered a rupture of an aneurysm of the abdominal aorta. The excessive tissue on the CT is thus blood. An abdominal aortic aneurysm (AAA) occurs when the diameter of the aorta is larger than three centimeters or 1.5 times the diameter of the rest of the aorta. There are several risk factors for an AAA, including: smoking, ***age (older than 60), male gender***, a family history of AAA, ***hypertension*** and peripheral vascular disease. Our patient has three of these risk factors. AAA is often asymptomatic, however in slim patients a pulsating mass might be noticed in the abdomen during physical examination. If an AAA becomes symptomatic, it often presents with back or abdominal pain caused by the development of fistulas or thromboembolization. Management of AAA focuses on treating risk factors such as smoking cessation and controlling blood pressure.[1]

The two phases CT scanning, one without and one with contrast-enhancement (in the arterial phase) were performed in our patient. The non-contrast-enhanced scan shows an increase in soft tissue posterior (the iliopsoas muscle on the right is ill-defined compared to left). This is in the retroperitoneal cavity. When searching for the origin of this extra tissue the focus should be on the organs in the retroperitoneal cavity. The large vessels are ill-defined as well. Vessels are more visible with contrast enhancement: image two shows an aneurysmatic enlarged abdominal aorta (the calcified wall shows the outer contour, contrast shows the real lumen). On the anterior part a leakage of contrast in the retroperitoneal cavity is visible. The peritoneum is an epithelial tissue that covers the abdominal cavity. Abdominal structures can be classified by their anatomical relation to the peritoneum. Organs that lie intraperitoneal are entirely surrounded by the peritoneum, such as the ileum, spleen and stomach. For example, in case of a bowel perforation you would expect that the excessive tissue (feces) would be located intraperitoneal. Structures that lie primary retroperitoneal are entirely outside the peritoneum, e.g. the kidneys and aorta. Organs outside the peritoneum with an inflammatory process do not cause peritonitis, whereas structures within the peritoneum do. Secondary retroperitoneal structures were originally located in the peritoneum but moved retroperitoneal during the embryological development, e.g. the pancreas and parts of the duodenum.[2]

An AAA might rupture. Risk factors for rupturing include female gender, COPD and a diameter larger than 5.5 cm or rapid growth (>0.5 cm/ 6 months). Patients often complain of tearing back pain and may present with signs of hypovolemic shock. The diagnosis of a ruptured AAA can be confirmed based on a CTA (the CT below shows the CTA of this patient, the arrow indicates the blood flowing out of the aorta), but can also be seen using echo or MRI. A ruptured AAA needs to be treated with emergency surgery. This can be either done via EVAR (endovascular aneurysm repair) or open repair surgery. In both cases a graft is placed. The type of surgery depends on several factors, such as shape of the aneurysm, anatomy and perioperative mortality risk (EVAR carries a lower risk of mortality than open surgery). Our patient received an aortic bifurcation prosthesis during open surgery.[3]

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