ARTICLE | MANAGEMENT OF CYTOKINE RELEASE SYNDROME IN B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

ARTICLE | THE EFFECT OF EXERCISE ON FATIGUE, FITNESS, AND PHYSICAL FUNCTIONING IN GUILLAIN-BARRÉ SYNDROME PATIENTS

AMSj

Amsterdam Medical Student journal

EDITION 21 | DECEMBER 2020

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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

Dear readership,

As may have come to your attention, a remarkable number of students have enrolled for university in the Netherlands this year. This was most likely due to the global COVID-19 pandemic which continues to have a great impact on global health care and on studies in health care. In this edition of AMSj, we will also direct our attention to COVID-19 in the letters to the editor written by Dirk Hoogenkamp, a board member of the Dutch affiliate of the International Physicians for the Prevention of Nuclear War, and Salma Hamsa, a medical student from India. We hope that all of our readers are still in good health during this pandemic and manage to continue their medical studies as best as is currently possible.

Most students, especially those working on their Master’s degree, will have less exposure in the hospital than we were used to in the pre-COVID-19 era. Nevertheless, I am sure the students from the VU medical center will come across a familiar face this edition! Check out who this is in our new segment entitled ‘In Amsterdam UMC, I ran into…’

In our experience, many medical students are eager to explore far beyond the Dutch-Belgian or Dutch-German borders. In this edition, we will give you not one, but two examples of what it is like to do research Down Under. Read about the experiences of Niels van Mourik, including practical advice on how to arrange your own internship abroad, in our section Research Abroad, and read about how our staff reviewer Reinier Spek received funding to perform a clinical trial in Australia in Spotlight.

This is the last edition of 2020, and to kiss the year goodbye, we have awarded the prize for best publication of 2020 in AMSj! The author of this publication will receive a VGT Course, a Book and E-learnings by VGT Cursus. Do you want to know who wrote the best manuscript of 2020? Skip to page 6 to find out!

As many of students’ favorite activities are impossible now that bars in Amsterdam have been closed for quite some time, we hope that this edition of AMSj may provide you some distraction!

Please enjoy the 21st edition of AMSj,

Devica S. Umans
Editor-in-Chief
Amsterdam UMC, location AMC

NEWSNEWSNEWS

Smell recovery in COVID-19

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Loss of smell is a presenting symptom of COVID-19 but the recovery process remains unclear. Vaira et al performed the first prospective study where olfactory function was objectively tested. 138 participants diagnosed with SARS-CoV-2 infection were followed for 60 days. Four days after the diagnosis, 61% of the patients had loss of smell. The majority of the patients (71%) showed improvement of their olfactory function between 10- and 20-days follow-up. Loss of smell persisted in 6% of the patients at the end of the 60-day observation period. The results characterize loss of smell as an early, prevalent and quickly recovering feature of COVID-19. However, as SARS-CoV-2 continues to spread it can be expected that significant portions of the general population will experience persistent olfactory dysfunction. This is worrying because olfaction is a crucial alert system and disorders of olfaction have been linked with reduced quality of life, depression and cognitive decline.

Watchful waiting appears sufficient in most cases as the majority of patients recover olfactory function. Vaira et al suggest therapy for patients with loss of smell that persists for longer than 20 days. Although high quality evidence is lacking, olfactory training could benefit smell identification and discrimination. Oral steroids have also been shown to improve olfactory function but systemic steroids remain controversial in treating COVID-19. More trials on therapeutic strategies are needed to anticipate the potential increase of patients with persistent olfactory dysfunction after COVID-19.

1. Vaira LA, Hopkins C, Petrocelli M, et al. Smell and taste recovery in coronavirus disease 2019 patients: a 60-day objective and prospective study. J Laryngol Otol. 2020;134(8):703-709. doi:10.1017/S0022215120001826

Ileocaecal resection versus infliximab for ileitis in Crohn's Disease

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Research has shown that Crohn's disease has detrimental effects on patients' quality of life. Infliximab, an anti-tumor necrosis factor (TNF) drug, is the standard drug used for patients who respond poorly to conventional treatment. Ileocaecal resection is preferred when complications like terminal ileitis occur. However, selection and timing of different treatment options remains debated. Previously, Ponsioen et al.1 performed a randomized controlled study, the LIR!C trial, which showed that ileocaecal resection and infliximab had analogous effect in adult Crohn's disease patients with a median follow-up of one year. However, in the five-year follow-up study of the trial (median = 63.3 months), Stevens et al1 compared the long-term effects of the ileocaecal resection to infliximab. Data was collected from participants of the previous study (n = 134) with n = 69 for surgery and n = 65 for infliximab. Observations showed that 74% of patients with surgery did not need any additional (biological) treatment and 42% did not need a second resection. In the infliximab group, respectively 48% and 52% of patients did not require additional treatment or resection.

This therefore indicates an advantage for ileocaecal resection in comparison to infliximab. Additional treatment may not be required in the long run for patients who received surgery.

1. Stevens, T.W., Haasnoot, M.L., D'Haens G.R., et al., 2020. Laparoscopic Ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective long-term follow up of the LIR!C trial. The Lancet Gasteroenterol Hepatol 2020;5 , 900 – 907.

Increased incidence of thrombotic events in hospitalized COVID-19 patients

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As the COVID-19 pandemic continues to hold the world in its grip, new revelations about the disease course of the novel coronavirus come to light. Insight into biomarkers that can predict the risk for deadly complications such as thrombosis is imperative in preventing more deaths. For this reason, Bilaloglu et al. screened a cohort of 3334 hospitalized COVID-19 patients for thrombotic events.[1] At least one thrombotic event occurred in 533 (16%) patients, of which 207 (6.2%) events were venous and 365 (11.1%) were arterial. These numbers may be underestimated due to limited imaging studies, myocardial infarction classification, and improved use of anticoagulants during the study period. Mortality was significantly higher in the group that underwent an arterial or venous thrombotic event (43.2%) compared to that without thrombosis (21.0%). The most important independent risk factor for overall thrombosis was the level of D-dimer (a fibrin degradation product indicative of fibrinolysis of a blood clot) at presentation. Moreover, this study reveals that the risk is clinical setting and thrombosis type dependent.
Explanations for the increased incidence of thrombosis in COVID-19 patients include cytokine storm and hypercoagulability. The data of this study suggest that a high D-dimer level is an indication for prophylaxis with anticoagulation in hospitalized COVID-19 patients. Further research is required to elucidate the precise pathogenesis of thrombosis in these patients to offer more targeted treatment.

1. Bilaloglu S, Aphinyanaphongs Y, Jones S, et al. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. JAMA. 2020;324(8):799-801.

Rivaroxaban for orthopaedic procedures

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Use of anticoagulants after nonmajor orthopedic surgery remains a topic of ongoing debate and evidence is lacking on which brand is most effective in preventing venous thromboembolic events. The PRONOMOS study is a double-blind, randomized controlled trial that compared rivaroxaban with enoxaparin in patients undergoing nonmajor orthopedic surgery in lower limbs and investigated if one of these anticoagulants would result in less major venous thromboembolic events. Within three years, 3604 patients were randomized to receive either oral rivaroxaban (n=1809) or enoxaparin subcutaneously (n=1795). In the rivaroxaban group, venous thromboembolism occurred in 0.2% of patients and in the enoxaparin group in 1.1% of patients (risk ratio, 0.25; 95% confidence interval, 0.09-0.75). Major bleeding events were reported in 0.6% of patients in the rivaroxaban group and 0.7% in the enoxaparin group (risk ratio, 0.81; 95% confidence interval, 0.35-1.88). Based on these data, one can conclude that patients on rivaroxaban have a lower risk of developing venous thromboembolism compared to enoxaparin and that there is no significant difference in major bleeding events.

This study emphasized the importance of using anticoagulants after nonmajor lower limb orthopedic surgery and has shown that rivaroxaban can reduce the incidence of venous thromboembolism without increasing the risk of major bleedings in comparison to enoxaparin. It is therefore recommended to incorporate these findings in current clinical guidelines.[1]

1. Samama CM, Laporte S, Rosencher N, et al. 2020. Rivaroxaban or Enoxaparin in Nonmajor Orthopedic Surgery: A Randomized Controlled Trail. New England Journal of Medicine. 2020:14;382(20):1916-1925.

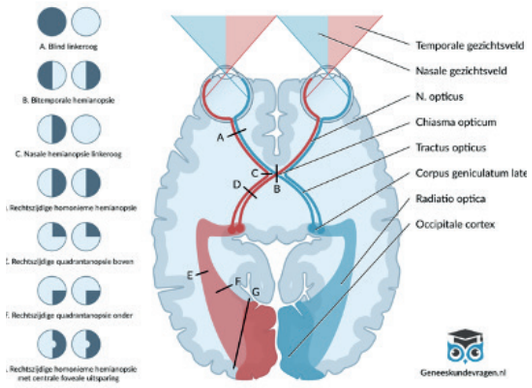
VGT Practice Questions

VGT Cursus

QUESTION 1

As a neurology intern you are being asked to neurologically examine a patient at the cardiology department. The patient was admitted because of heart failure and now presents with vision complaints. During confrontation visual field testing (*confrontatiemethode van Donders*) you notice that in both eyes the right visual field is impaired. How do you interpret this finding?

A. Bilateral hemianopsia
B. Right-sided homonymous hemianopsia
C. Left-sided homonymous hemianopsia



QUESTION 2

In the previous patient, where in the anatomical visual system is a lesion probably located?

A. Optic nerve
B. Optic chiasm
C. Left optic tract
D. Right optic tract
E. Occipital cortex

QUESTION 3

You see the following arterial blood gas results of a patient at the internal medicine department:

- pH = 7,34 [N 7,35-7,45];
- pCO2 = 4,4 pKa [N 4,5-6,1 pKa);
- HCO3- = 18 mmol/l [N 22-26 mmol/l]

What is your conclusion?

A. Metabolic acidosis, not respiratory compensated
B. Metabolic acidosis, partially respiratory compensated
C. Respiratory acidosis, not metabolically compensated
D. Respiratory acidosis, partially metaboli cally compensated
E. Mixed respiratory and metabolic acidosis

Q1: Answer: B

Q2: Answer: D

Q3: Answer: B

EXPLANATION Q3

This is a metabolic acidosis that is partially respiratory compensated. Use this step-by-step protocol to interpret an arterial blood gas:

1) pH: the pH in this case is below normal, which indicates an acidosis.
2) HCO3-: the bicarbonate is below normal, combined with a low pH this can only mean that it is the cause for the low pH; thus, a metabolic acidosis.
3) pCO2: the pCO2 is below normal, which indicates that respiratory compensation is in effect (because a low pCO2 increases the pH). However, since the pH has still not reached normal levels, the compensation is partial in this case.

For example, this could be the case in a patient with chronic kidney failure. There are less nephrons to reabsorb bicarbonate, which means that there is less bicarbonate available in the blood to convert H+ to CO2 that can be exhaled. To compensate, the patient will increase ventilation (in order to exhale more CO2). This will lead to pCO2 levels that are below normal. As mentioned, in this case the respiratory compensation is insufficient.

For more in-depth information regarding the interpretation of arterial blood gas, check out the open access article 'Het arterieel bloedgas' at the website of VGT Cursus (in Dutch).

Winner of "Best manuscript 2020 - AMSj edition 17, 18, 19 & 20" and the VGT prize

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BEST MANUSCRIPT OF EDITION 19!

The winner of ''Best manuscript 2020 - AMSj edition 17, 18, 19 & 20'' and the corresponding VGT prize has been selected! We, AMSj & VGT Cursus, would like to congratulate ……*drum roll*, **Denise Veltkamp**! and the co-authors with their triumph. Thankyou very much for submitting your fascinating manuscript to AMSj!

In AMSj edition 20, Veltkamp et al. wrote an impressive and very interesting winning case report named ''*Acute renal function deterioration in a pulmonary arterial hypertension patient with decompensated right heart failure''*. Curious? Read the abstract below and read the captivating case report on page 19-21 in AMSj edition 20 (release September 15th 2020).

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.

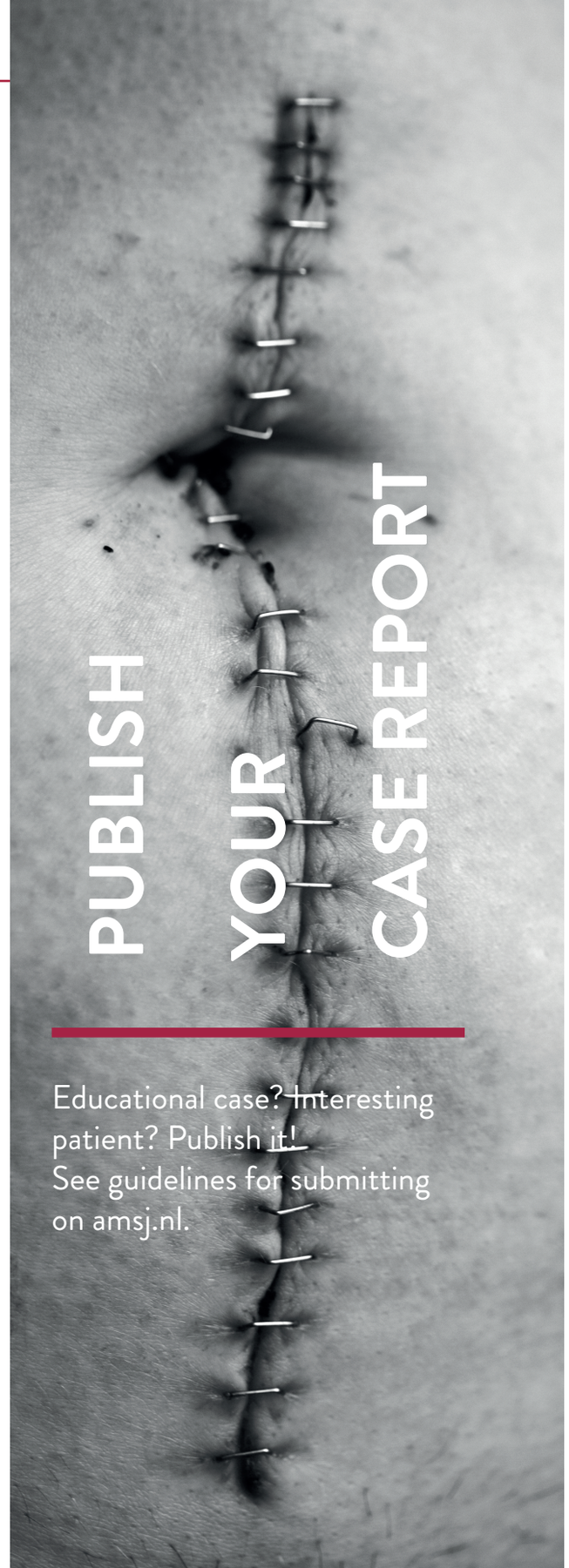
Denise Veltkamp: '' I feel very honoured that the case report '*Acute renal function deterioration in a pulmonary arterial hypertension patient with decompensated right heart failure'* that I wrote with Joanne Groeneveldt (MD PhD), prof. dr. Vervloet (nephrologist) and prof. dr. Vonk Noordegraaf (pulmonologist) has been elected as the best manuscript of the year 2020! The 'journey' of writing this case report started with a lot of curiosity; what had happened to this particular patient that had led to this acute renal 'shutdown'? Why did this patient react so differently? One day dr. Vervloet and I were thinking about this case. By drawing all the possible interactions the physiologic mechanism became clear. Multiple organs were involved: the lungs, the heart, and of course the kidneys. We might have solved the puzzle..! Indeed, 'might have'; of course more research is needed on this

subject, but this case report is a good first step. I would like to encourage other students to publish their manuscript in the AMSj, since the process of submitting and reviewing until the publication of the manuscript was professional, the provided feedback was useful, and the communication was pleasant. Board of the AMSj and the VGT student-course, thanks again for this prize of 'best manuscript'. Hopefully, it will motivate lots of others to publish their scientific work!''

If you are wondering how YOU could have a chance of winning 'Best manuscript of AMSj 2021': send in **your manuscript** to AMSj! This could be a case report, systematic review, thesis, meta analysis or your own original research; you could get published in one of our editions. Maybe your manuscript will even be announced best manuscript of 2021!

- Visit our website *https://amsj.nl/v3/authors/* to check our guidelines, edit your article and submit it to AMSj.
- If you have any **questions about guidelines and publishing** your research feel free to ask them by e-mailing: chief-editor@amsj.nl.

We are looking forward to reading your manuscript! Best of luck!



Letter to the editor

Dear Editors,

It was a pleasure for us to read the article titled "Is there a role for the BCG vaccine in protection against COVID- 19?" by Khalifeh NM[1], in your esteemed journal. It is a well written article and we would like to appreciate the author for her excellent effort. Adding on to the point made by the author, one of the main reasons to stick to WHO's recommendation to not use Bacillus Calmette-Guerin (BCG) vaccine is that there might be a bare possibility that upregulation of the immune system by BCG vaccination and its non-specific effects will aggravate COVID-19 in a minority of patients with severe ailments.[2] As BCG vaccine induces an upregulation of the immune system, which has been widely documented, recent studies have shown that the immune dysregulation in severe cases of COVID-19 in forms such as cytokine storms, may contribute to a more severe course in some patients with COVID-19. We would like to therefore mention a few other possible vaccines which may be considered in the treatment of COVID-19.

To begin with, Mumps Measles Rubella vaccine (MMR) can be a suitable vaccine candidate as it has been identified that there is a sequence homology between the fusion proteins of SARS-CoV-2 and measles and mumps viruses.[3] Moreover another similarity is the resemblance of 29% amino acid sequence between the macro domains of SARS-CoV-2 and rubella virus. However, studies conclude that that MMR will not prevent COVID-19 infection but could potentially reduce poor outcome.[4]

Alternatively, oral polio vaccine (OPV) may also be a beneficial vaccine. This is due to the fact that both poliovirus and SARS-CoV-2 are positive-strand RNA viruses which may induce and be affected by common innate immunity mechanisms.[5] Some of the benefits of using OPV over BCG are existence of more than one serotype that could be used sequentially to prolong protection, low cost, ease of administration, availability, and safety. As OPV is already a widely produced and distributed vaccine, it will be easier to conduct clinical trials over different demographic groups of the population. Moreover, compared to BCG, OPV has very low chances of developing complications.[6]

Lastly, Hepatitis A vaccine may help prevent lower respiratory tract involvement which is the leading cause of fatality in COVID-19 infections. This is due to a possible adaptive immune cross reaction which helps to keep the infection at mucosal colonization levels.[7] Until the development of a specific vaccine for SARS-CoV-2, the above-mentioned vaccines can play a vital role in stimulating the immune system of infected individuals and help reduce the fatality rate.

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The effect of exercise on fatigue, fitness, and physical functioning in Guillain-Barré syndrome patients

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ABSTRACT

BACKGROUND The effect of physical exercise in patients with Guillain-Barré syndrome (GBS), a rare progressive acute polyneuropathy caused by autoimmune induced neural damage, is discussed in this literature review. Although the risk of paresis due to vigorous physical exercise in GBS patients caused hesitance about the use of exercise, it is hypothesized to be of benefit in the rehabilitation of GBS patients.

METHODS PubMed was searched using the keywords 'Guillain-Barré syndrome', 'cardiovascular/aerobic exercise/training' and 'resistance exercise/training'. The effect of exercise is measured through improvements in either (severe) fatigue, physical fitness or (perceived) physical functioning.

RESULTS Five studies that apply cardiovascular exercise and two studies with resistance exercise were included in this review. All studies with cardiovascular exercise showed significant improvements in physical fitness. Fatigue and physical functioning due to cardiovascular exercise were both measured in three of the five studies, with all improving as a result. Resistance exercise is, partly due to limited available research, only found to have a positive effect on physical fitness and (perceived) physical functioning. (Severe) fatigue was not measured in the studies with resistance exercise.

CONCLUSIONS Cardiovascular exercise has a positive effect on fatigue, fitness, and physical functioning. Evidence is too limited to draw conclusions regarding the positive effect of resistance exercise in GBS patients. No conclusions could be drawn regarding the optimal exercise duration or intensity in either of these two types of exercise.

INTRODUCTION

Guillain-Barré syndrome (GBS), an acute polyneuropathy with an incidence of 0.8-1.9 per 100.000 in the Western world[1], can cause mild weakness in the limbs at the slightest, while approximately 20% of patients become tetraplegic and are bound to ventilation for weeks.[1,2] Mortality rates of 3-7% have been reported in the Western world while surviving patients often experience reduced functioning, fatigue, pain, and other complaints.[1]

Exercise in different forms has been found beneficial in the care and treatment of many diseases, especially metabolic and chronic disorders. Physical exercise has shown results not only in skeletal muscle but also in the associated neural system.[3]

In this review, cardiovascular exercise, like running and cycling, and resistance exercise, that is, weight training, are examined.

Since GBS is characterized by neuromuscular damage, exercise is hypothesized to improve fitness and functioning and reduce fatigue in GBS patients. (Severe) fatigue is a consequence of GBS reported to be independent of muscle weakness and present for years after the onset of GBS.[4] Physical fitness includes all physical performance results, while physical functioning covers the execution of the activities required for self-care and independence.[5] Due to widespread warnings on the risk of paresis as a result of high-load exercise in GBS rehabilitation, there has not been much research regarding the neuromuscular adaptations to exercise in GBS patients.[6] While the exact mechanisms are unclear, it is thought that when the intensity is too high or when too few motor units can be recruited, damage, sometimes irreversible, can take place.[7] In related autoimmune diseases like multiple sclerosis (MS), strenuous exercise could harm as well, by altering certain balances of antibodies and by reducing the lymphocyte concentration.[8] In MS, a decline of demyelination is found as an effect of exercise in animal studies.[9]

In brief, the role of (different forms of) exercise on GBS patients is discussed in this review, since it is questioned whether exercise reduces (long-term) fatigue and increases physical fitness and functioning in patients with GBS. The role of exercise in distinguished types of GBS is reported as well.

METHODS

In this literature review, searches in PubMed have been conducted to select relevant studies. Search terms of GBS (*Guillain-Barré syndrome, GBS*) were combined with exercise-related terms (*cardiovascular/aerobic and resistance/weight training/exercise*). Relevant articles were selected after reading the titles and/or abstracts. Subsequently, studies were included after full-text analysis if the inclusion criteria were met. First of all, the participants in the studies had to be diagnosed patients of GBS in rehabilitation at the time of the study. Then, exercise had to be the main intervention examined and be distinguishable as either cardiovascular and/or resistance exercise. Also, the measured outcomes of exercise were a component of either (severe) fatigue, physical fitness or physical functioning, as is presented in the tables. Lastly, the articles had to be in English or Dutch. Relevant articles were only excluded when the full text was not available. Finally, seven studies were selected, regardless of study design. No statistical analysis was performed.

RESULTS

The effect of cardiovascular exercise in GBS on fatigue, fitness, and physical functioning

In SUPPLEMENTARY TABLE 1, all studies included in this review that investigated the effect of cardiovascular exercise in GBS patients are displayed.[10,11,12,13,14] These studies measured the effects on one or more scales of fatigue, fitness or physical functioning.

The results are unambiguous. All studies showed significant improvements in physical fitness, measures of cardiovascular performance (cardiac output, VO2-max, etc.) and exercise performance (PO-max, walking/cycling performance). All of the four studies that measured muscle strength reported improvements. Fatigue was taken into account in three of the five studies, which all showed significant improvements and even one that showed a 20% reduction after training compared to baseline.[11]

Physical functioning also improved significantly (post-training vs baseline), according to the several questionnaires used in the three studies included.

The studies that applied cardiovascular exercise are characterized by the long duration (12-25 weeks) but low frequency (3 p/w) compared to the resistance studies (3-12 weeks, 1 p/d).

The effect of resistance exercise in GBS on fatigue, fitness, and physical functioning

SUPPLEMENTARY TABLE 2 shows the studies that evaluated the effects of resistance exercise in GBS on one or more scales of fatigue, fitness or physical functioning.[15,16] Only two case reports were found that could be included.

In both studies, muscle strength improved, even though in one study, the exercise was directed at (daily life) activities instead of muscle strength.[15]

Physical functioning also improved, with a focus on functional mobility[16] and daily living activities.[15] Fatigue was not measured in these studies, but in a similar study with patients of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), often considered as a chronic form of GBS,[10] the fatigue severity was not significantly reduced after a 12-week training program.[17]

DISCUSSION

Even though cardiovascular exercise is not always linked to muscle strength improvements,[18] this was reported by all four studies that were measured.

The reduction of (severe) fatigue could be caused by improved feelings of energy[19] and limited inflammation through exercise.[20] For application in practice, cycling or ergometer training or addition of resistance exercise is advised to equally improve (upper body) strength in cardiovascular exercise.

It is hard to draw conclusions regarding the effect of resistance exercise in GBS patients due to limited research, which might be caused by the fear of a recurrence of symptoms after excessive muscle overworking.[6,7] Often, cardiovascular exercise is chosen over resistance training due to its low intensity character.[13] Additionally, in a training setting it can be hard to measure overwork in an objective way.[15] More research is necessary to define the effects of resistance exercise in GBS, possibly in combination with cardiovascular exercise. No conclusions could be drawn regarding the optimal

exercise duration or intensity in both types of exercise due to limited research.

In conclusion, cardiovascular exercise has a positive effect on fatigue, fitness, and physical functioning. Evidence is too limited to draw conclusions regarding the positive effect of resistance exercise in GBS patients. Therefore, it is difficult to favor either for rehabilitation in GBS.

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An ill female with yellow skin color

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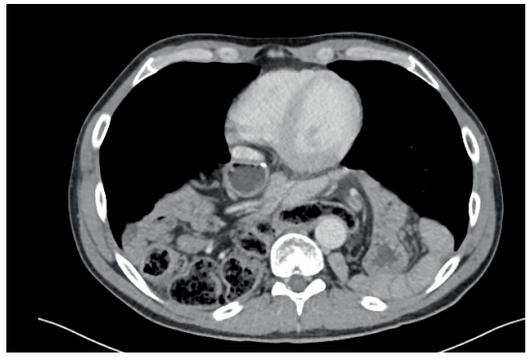
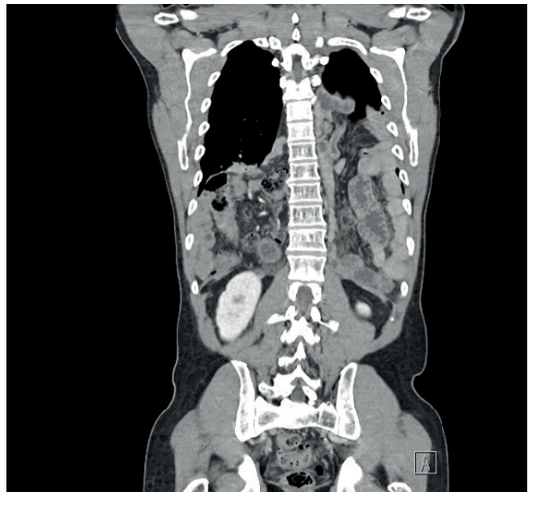
CASE

A 57-year old Chinese female presented with moderate cramping chest pain and progressive jaundice for one week. Her medical history shows an esophagectomy with partial gastrectomy with gastric tube (McKeown), because of a distal esophageal carcinoma. At physical examination reduced abdominal bowel sounds are audible. She has no abdominal pain. Blood results show elevated total bilirubin level. A CT-scan of the thorax and abdomen was performed. Pictures of the following laparoscopy are also included.





QUESTION 1

What is the diagnosis based on the imagery?

A. Gastric perforation
B. Diaphragmatic hernia
C. Paralytic ileus
D. Ectopic tapeworm

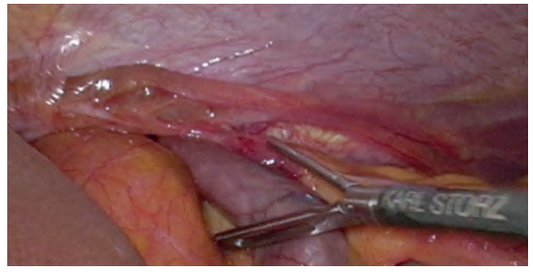
Hint: Imagine the human anatomy

QUESTION 2

What is the most probable cause of the diagnosis in this case?

A. Her female gender
B. Her age >50
C. Her origin
D. Her medical history of abdominal surgery

Hint: Find out about the given information



QUESTION 3

What is usually the treatment for a condition of this severity?

A. Surgery
B. Wait and see
C. Anti-inflammatory drugs
D. Proton pomp inhibitors

Hint: Consider the patient's symptoms

Answer on page 36

The implementation of genome editing in clinical settings

Cathy Hu[1]
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With the emergence of the CRISPR/Cas9 system, genome editing is more viable than ever and poses as a likely reality in the near future. This method allows for site-specific genomic targeting with unprecedented ease of use and efficiency.[1] However, as biomedical technology continues to advance, ethical debates will inevitably arise to question the morality and social implications of the newfound techniques. The possibility of genome editing is no exception: although this revolutionary discovery holds the potential to serve as a curative therapy for many hereditary diseases that plague the world today, it is accompanied by significant ethical concerns that may provide sufficient reason to intercept clinical adoption. This paper will address these concerns and elucidate the merits of implementing genome editing in clinical settings, proposing that the drawbacks may not be equivalent to the benefits of this technique.

Prenatal screening[2] and carrier testing[3] have greatly contributed to increased insight on the embryo's genetic makeup in the recent years, offering prospective parents valuable information that could play a vital role in their decisions moving forward. Typically, the detection of a genetic defect presents the parents with two grim options: to face the anticipated hardships of raising the diseased child or to terminate the pregnancy. However, by implementing genome editing, the parents can be spared the emotional burden of these dire circumstances by simply removing the issue at its root: extracting the causal gene and therefore ridding the child of their disease.[4] The employment of this technique dismisses the potential need for pregnancy termination and can dramatically enhance the quality of life for both the parents and the child by eliminating certain health complications. Additionally, undergoing genome editing would prevent future generations from being affected by the defective gene. In this manner, genome editing can act as the key to eradicating taxing hereditary diseases (such as sickle cell disease) from a bloodline, thus alleviating suffering for countless individuals.

However, some medical ethicists argue that widespread implementation of genome editing may start us on a slippery slope to utilizing the method with the intent to enhance traits, ultimately resulting in the normalization of the controversial "designer babies".[5] While this is a valid concern, application of rigorous surveillance and strict regulations should drastically lessen the chances of a genetically enhanced generation coming to fruition. Furthermore, implementation of this technique would unquestionably warrant careful deliberation across multiple disciplines (including other non-medical stakeholders) in reaching a clear verdict on which specific diseases and corresponding genes call for genome editing, therefore leaving few opportunities to misinterpret and unintentionally misuse this procedure. Similar to regulations surrounding euthanasia, genome editing would be meticulously guarded and exclusively practiced in cases where all criteria have been met. Unfortunately, it is inevitable that gray areas and heated debates will arise regarding this verdict, seeing as it is impossible to reach a general consensus when involving ethical matters. Many factors will need to be taken into careful consideration. An additional argument is that parents will feel pressured to adhere to the new norm of correcting their child's defective gene when genome editing is widely implemented in clinical settings. Although there is no doubt that genome editing will cause a shift in social standards and expectations, many people may deem the prospect of providing a plethora of families with a simple solution to their great misfortune to outweigh the societal pressure some parents may consequently be confronted with.

Another line of reasoning opposing genome editing involves the principles of informed consent: the procedure is performed on the child, which makes true informed consent unattainable given that it is beyond the bounds of possibility to communicate with embryos. There are some individuals in today's society that view their disability as an integral part of their identity and would not choose to have it removed.[6] However, parents should be deemed appropriate representatives of their child's medical decisions at such early stages in their life, including the choice of altering their child's genome. Absolute parental authority in medical decisions is not a foreign concept, as consent to treatment often requires the patient to be of a certain age to ensure that they are making an informed and calculated decision. Neglecting the benefits of genome editing due to the argument of incomplete informed consent would rob numerous individuals of a monumental cure for their disease.

In conclusion, the ethical considerations of implementing genome editing in clinical settings should not undermine the considerable contribution it can make to improving quality of life. Genome editing may become the driving force behind the eradication of many hereditary diseases worldwide and can serve as a true curative therapy as opposed to mere palliative care. This revolutionary technology wields the power to bring exceptionally positive change to the world of healthcare and should therefore not be shunned, but embraced.

"This revolutionary technology wields the power to bring exceptionally positive change to the world of healthcare and should therefore not be shunned, but embraced"

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Clinical trial on non-operative treatment of surgical neck fractures of the shoulder

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In the column 'Spotlight' we shine a light on students who already published their research in other journals or started their PhD course before graduation, or PhD students who have achieved a special accomplishment in the course of their PhD.

Last year, Reinier Spek received funding from the OLVG to carry out a clinical trial on non-operative treatment of surgical neck fractures of the shoulder: Congratulations! We have invited him to tell us more about this project and what is required to write a successful grant application.

I want to thank AMSj for the congratulations and acknowledgement in this edition. I am pleased to explain more about this project and the process of a grant application and to provide tips for all readers who are planning to apply for research funding in the future.

I am Reinier Spek, 26 years old, and my ambition is to become an orthopedic surgeon. I am currently doing a PhD at Flinders Medical Centre (Adelaide, Australia) in collaboration with OLVG Amsterdam and University Medical Centre Groningen. My PhD is on shoulder fractures and in our thesis we want to evaluate outcomes of current clinical practice and assess the added value of upcoming innovations in orthopedic surgery such as deep learning to detect shoulder fractures on radiographs, 3D models to improve diagnostic work-up and virtual planning to reduce intra-articular screw penetration after surgery.

My last internship as a medical student was my elective in the department of Orthopedic Surgery in the OLVG. During this elective, we started to set up the first project for my PhD: a clinical study on outcomes of non-operative treatment of surgical neck fractures of the shoulder. In this cross-sectional study we invite patients to undergo shoulder function measurements, radiographs and to fill out several questionnaires. We aim to strengthen the statement that these patients respond well to non-operative treatment and that surgery is only required in few carefully selected patients. Back then we had written out the project, but we did not have the financial resources to cover study costs, such as radiographs and transport for patients. When we received the grant, we were incredibly happy as it was not only a big boost for my PhD, but it also meant that we could start with the study.

Writing a clear, concise, and well-thought-out funding application is a time-consuming process and requires a timely start. I want to advise everyone to involve a motivated expert panel, including a statistician, and to create a transparent overview of expected costs. Having a dedicated research-minded team is one of the key aspects to writing a successful grant application. Brainstorm together, send the draft around multiple times and ask for feedback pro-actively. I also want to emphasize to read the grant guidelines thoroughly as, in general, grants have specific aims and eligibility criteria. In this grant, for example, the focus was on interdepartmental collaboration, so we involved as many departments as we could. That was a great way to get to know new colleagues and it improved the application substantially.

We included the first participant at the end of February, but the study is currently on hold due to COVID-19. We are all looking forward to resuming the study and I genuinely want to thank all involved investigators and in particular Professor M.P.J. van den Bekerom for his valuable feedback and guidance throughout this application.

"Having a dedicated research-minded team is one of the key aspects to writing a successful grant application."

H. F. M. Rhodius-Meester, MD, PhD

Interviewed by Marit Jonker[1] en Arenda Mank[1]
1. Faculty of Medicine, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands
2 Department of Neurology, Alzheimer center Amsterdam, Amsterdam UMC, location VUmc, the Netherlands

Current position: Clinical geriatrician and post-doc researcher, section Internal Geriatric Medicine and Alzheimer Center, Amsterdam UMC, location VUmc.

Introduction

As our supervisor, we know Hanneke as a very intelligent, hard-working woman with an inexhaustible enthusiasm for her profession.

When did you know you wanted to specialize as a geriatrician? How did you make that choice?

During my internships I enjoyed working with older patients. It feels like an honor to support them in the last part of their life. I started working in geriatrics at the Slotervaart Hospital, where I experienced how to treat the whole patient and not just one illness or disorder. To list all the problems, while continuously asking yourself: what is important and what is desirable for this patient? It seems like Tropical Medicine in the Netherlands: not everything is needed, or possible. For example, you cannot force people to have a brain scan. This pragmatic work suits me; not just following guidelines, but consciously deviating from them to find the best treatment.

What is your area of expertise?

I work as a geriatrician and my fields of expertise are neurodegeneration and artificial intelligence. In my clinical work as a geriatrician I treat patients with dementia. Seeing these patients inspires me to do research.

Can you tell us something more about artificial intelligence?

With artificial intelligence more and more is possible in our field. In the Alzheimer Centre, where I do most of my research, we developed a computer tool that helps to analyze MRI-scans, thereby improving the diagnostics of dementia and other neurodegenerative disorders.

What do you like most about your job and what don't you like?

As researchers, we face a great delay in the implementation of developments, especially in artificial intelligence. It always costs a lot of money, time and paperwork to get something new implemented. The impossibilities of electronic patient records and promises that are made, which are in the end hard to realize, make the work difficult. However, the most frustrating is that I have so little to offer to my patients in terms of curation. Patients have many questions: when does my dementia get worse, how much time is left, for how long will I be able to drive my car? It frustrates me that I cannot answer those questions with full certainty.

If you had to make a choice between clinical practice or doing research, what would it be?

That is a very difficult question, as one cannot exist without the other and I prefer the combination. [Hanneke sighs]. I think I would choose research, as it aims to contribute to a larger group. The field of neurodegeneration is still in its infancy in terms of diagnostics, treatment and communication. It requires a lot of creativity and carefulness.

> "Do what feels best and talk with your peers about what you want to achieve and what makes you happy"

H. F. M. Rhodius-Meester, MD, PhD

CURRICULUM VITAE

1981	Year of birth
2000	Gymnasium (cum laude), Alberdingk Thijm College, Hilversum
2006	Master of Science (MSc), Medicine (cum laude), Vrije Universiteit, Amsterdam Internship Tropical medicine, AIM Hospital, Kijabe, Kenya
2014	Specialty training in Geriatric Medicine, Slotervaart Hospital, Amsterdam and Kennemer Gasthuis, Haarlem
2017	Course "Practical Neuroanatomy and Neuroradiology", course "Regression Techniques" and course "Clinical Prediction Models"; VU Medical Centre, Amsterdam
2018	PhD Alzheimer Centre, VU Medical Centre
2018	Dissertation 'Optimizing use of diagnostic tests in memory clinics: the next step', VU University, Amsterdam

What helps you to continue your work, what is your motivation?

The frustration I just mentioned is my biggest motivation. It motivates me to do my clinical work and research better. That is also one of the best parts of my job; the combination of clinical work and doing research for the same patient group, so that I can advise and convince my patients with the results of my research.

You have achieved a lot in your career, do you have further ambitions?

If I would have more time and money, I would put more effort in research and PhD students. I want to grow and learn in research and leadership, in a relaxed way. Though, what is most important is to enjoy my current life and to be thankful for what we have achieved.

Are there people you look up to?

My promotor Wiesje van der Flier (professor and doctor in Neurology and Epidemiology). She is very smart, stays on track and makes people grow. She gives people their responsibilities, with a supportive 'kick in the butt'. She is able to support you in a constructive way to make a next step in your career.

Do you have any advice for young medical students?

If you really want something, then don't hesitate to approach people, create your own chances. That professor of that particular department you are interested in, is also just a person. So invite yourself for a cup of coffee and try to relax. Do what feels best and talk with your peers about what you want to achieve and what makes you happy. Use each other's connections.

> "If you really want something, then don't hesitate to approach people, create your own chances"

Management of cytokine release syndrome in children and young adults with B-ALL undergoing CAR T-cell therapy

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1. Faculty of Medicine
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ABSTRACT

BACKGROUND Refractory or relapsed B-cell acute lymphoblastic leukemia (B-ALL) is an important cause of death in pediatric cancer. A relatively new and promising treatment is chimeric antigen receptor (CAR) T-cell therapy. Cytokine release syndrome (CRS) is a common adverse event of CAR T-cell therapy that is potentially life threatening if left untreated. Little is known about specific treatment for CRS and its potential interference with the CAR T-cells. Therefore, the aim of this review is to analyze different management strategies used to reverse CRS in children and young adults undergoing CAR T-cell therapy.

METHODS A systematic literature search was conducted in PubMed.

RESULTS 10 articles were included with a total of 269 patients, of whom 227 (84%) patients developed CRS and in 226 patients this was reversible. Different types of treatment were described, which were categorized into two groups: tocilizumab, corticosteroids and chemotherapy as therapy targeting the developmental mechanism of the syndrome and supportive care for symptom distress relief.

CONCLUSIONS Treatment with tocilizumab seems to be the most effective in reversing CRS without interfering with the CAR T-cell efficacy. Corticosteroids can be used as a second-line therapy. Chemotherapy prior to CAR T-cell infusion may decrease the risk of developing CRS. An adequate tool for relieving the symptom distress is supportive care. More meaningful research needs to be done to allow one international, standardized treatment guideline for the optimal regimen.

INTRODUCTION

B-cell acute lymphoblastic leukemia (B-ALL) is the most common type of pediatric leukemia, with chemotherapy as baseline therapy.[1] Unfortunately, some cases of B-ALL tend to relapse or are refractory to chemotherapy or allogeneic stem cell transplantation. A promising treatment option for these patients is chimeric antigen receptor (CAR) T-cell therapy.[2] T-cells that are isolated from the patients' blood are genetically modified with an inactive virus, which causes them to express a CAR. After re-infusion, the CAR T-cells activate an immune response against B-cells through recognition of the CD19 receptor.

A frequently noticed side effect of CAR-T cell therapy is cytokine release syndrome (CRS), a systemic inflammatory response.[2,4] The infusion of CAR T-cells causes the release of cytokines and activates macrophages and monocytes.[5] This can eventually lead to a so-called 'cytokine storm'. Symptoms range from fever and nausea to hypotension, vascular leakage and coagulation leading to multi-organ failure, usually presented with a delayed onset of 1 to 14 days.[6,7] Severity of symptoms is suggested to be dependent on disease burden and degree of lymphocyte depletion.[8]

There is no standardized treatment or management guideline for this adverse event. It is hypothesized that symptoms will be treated with supportive care, for example fluids and antipyretics. Recent literature shows the possibility of using tocilizumab. This is a monoclonal anti-interleukine-6 antibody[12], which binds to an IL-6 receptor and blocks it, disabling IL-6 so it cannot connect itself to cause inflammation.[19]

This review will analyze different treatment strategies for CRS in children and young adults with relapsed or refractory B-ALL after CAR T-cell therapy, to reveal better insight in the best treatment options.

METHOD

A systematic search was conducted in the database PubMed. Keywords used were: "car t cell therapy", "cytokine release syndrome" and "b-all". These terms were converted into [MeSH] terms (appendix 1). Afterwards, a title and abstract ([tiab]) search was performed, using ("car t cell therapy"[tiab] AND "cytokine release syndrome"[tiab]). Inclusion criteria for filtering were English language and age <25 years.

The objective was defined as reviewing the therapies used for CRS and to which extent these therapies induced recovery from the CRS.
Inclusion criteria for eligibility were: 1) CD19 CAR T-cell therapy, 2) studies describing B-ALL, 3) studies reporting CRS as an adverse event, 4) studies based on humans and 5) original studies.

RESULTS

In total, 10 clinical trials or case studies were included, published between 2013 and 2019. The total study population consists of 269 patients aged between 1 and 25 years. 227 out of 269 patients (84%) developed CRS.

All of these patients survived except for two (0,74%). One patient died from cerebral hemorrhage17 and one patient died of septic shock, not caused by CRS.[11] The symptoms were very diverse throughout all the studies, as were the described therapies. In SUPPLEMENTARY TABLE 1 AND 2, an overview of these therapies can be found.

CRS management

The following treatment options for CRS are mentioned in the trials: tocilizumab (anti-IL6R), chemotherapy (mainly cyclophosphamide and fludarabine), corticosteroids (mainly dexamethasone), immunoglobulin and hemofiltration.

Altogether, 134 out of 269 (50%) patients received tocilizumab. Most patients recovered within hours after receiving tocilizumab. The dose of infused tocilizumab differed per study, ranging from 4 mg/kg[16,20] to 12 mg/kg12. Overall, 132 (99%) patients responded to this therapy. Fitzgerald et al.[12] showed a response rate of 69% after one dose of tocilizumab, and 100% after two or three doses.
40 (15%) patients were treated with corticosteroids, of which 37 (14%) combined with or after tocilizumab, and 4 (1%) as single therapy.

103 (38%) patients received chemotherapy as preventive treatment for the CRS before the infusion with CAR T-cells. Cyclophosphamide with fludarabine was the most common combination, administered in 77 (29%) patients. Cyclophosphamide with etoposide was administered in 1 (0,37%) patient, and cyclophosphamide solely in 25 (9%) patients.

Symptom management

Symptoms caused by CRS were treated by using supportive care, as reported in 6 studies, with a total of 70 (26%) patients.
This supportive care consisted of antipyretics, analgetics, anti-emetics, antibiotics, intravenous fluid, vasopressin, fresh frozen plasma and low-flow supplementary oxygen[11,12] (see SUPPLEMENTARY TABLE 3).

DISCUSSION

Reviewed literature showed a high and quick response rate to tocilizumab and also acknowledged usage of corticosteroids and chemotherapy in the management of CRS.
Tocilizumab does not interfere with the working mechanism of CAR T-cell therapy[11-13] and with a response rate of 99%, it has become a first-choice treatment for CRS.
Corticosteroids are sufficient as well, however they may inhibit the efficacy of the CAR T-cell treatment.[12]

Chemotherapy was administered before infusion with CAR T-cells. This has been mentioned to improve the response to CAR T-cell therapy[11,21,22] and it has been shown that fludarabine reduces the risk of CAR T-cell rejection.[11] In addition, chemotherapy decreases the disease burden of ALL and increases the degree of lymphocyte depletion in a

patient. Both are correlated with a lower risk of developing severe CRS.[11,15] Consequently, chemotherapy may be a useful preventive measurement when managing CRS.

Supportive care is an effective and very important management tool to relief a patient's symptom distress. However, eradicating symptoms is not equal to elimination of the syndrome itself. This is why supportive care should preferably accompany other forms of immunotherapy.
SUPPLEMENTARY TABLE 4 proposes a management protocol when treating a patient undergoing CAR T-cell therapy.

Previous research on CRS in children is limited, with some articles including only a small study population. Additionally, response rates to different therapies could not be compared due to lacking data in the articles. This makes it hard to conclude which therapy is preferred at what time. And as such, it is important to evaluate the possibility of tocilizumab as a preventive therapy.
More research should make different therapy response rates comparable and evaluate at what time a therapy should be started.

CONCLUSION

Awaiting further research, this pilot review proposes a management protocol for CRS including chemotherapy before CAR T-cell infusion and tocilizumab, corticosteroids and/or supportive care after infusion.

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Articles reviewed are references 11 to 20. Reference 10 was used for the snowball search technique.

In Amsterdam UMC, I ran into... Steven Schal

Interviewed by Hajar El Khattabi[1,2], Louise A.A. Gerbens[1]
1. Department of Dermatology, Amsterdam UMC, location AMC, University of Amsterdam
2. VUmc School of Medical Sciences, Vrije Universiteit Amsterdam

What is your background and what was your journey to your current role?
I was born the youngest of six siblings, in Paramaribo, Suriname. I studied physical sciences; chemistry, physics and math. I always worked after school, doing all sorts of jobs, among them extending the power supply to the inlands of Suriname. Even today I'm still the handyman of the family, and also the babysitter… I have a very big family here!

Steven Schal (Steve), patient transporter in Amsterdam UMC, location VUmc

In the summer of 1989 I came to the Netherlands for a holiday. Because of certain circumstances, I ended up staying here, so I'm still on holiday! It took me a few years to settle down and "integrate" as they like to say. In 1994, at the age of 27, I applied for this job through Savas, an employment agency. I've been working here ever since. I've seen a fire (May 26, 2007), a flood (September 8, 2015) and now the COVID-19 pandemic… And I'm still going, they tell me I'm part of the furniture!

Tell us more about your current role and perhaps a big recent accomplishment...
My job consists of different tasks; transport of patients, patient-related materials and the bed center. A few years ago, I got nominated during the New Year's reception for a prize that's awarded every five years to employees for their effort and I won the silver medal. This medal looks the same as the wooden artwork that's on the wall in the Amstel Foyer (see picture). I really like it!

If we were to shadow you, what would an average day look like?
Following me wouldn't be easy - I'm always on the move with my cart, of course. I wake up very early and I take my bike to work. One place I visit often is the quiet room. I have grown up as a Christian and having a connection with the good Lord above is very important to me. I need to feed my spirit as well.

You get to engineer a perfect workday; what would that day look like?
This is something we don't have in hand. But when I'm allowed to see the daylight again and I can get out of my own bed, in my own home, with my own two legs, I'm thankful… But otherwise, payday!

Is your current role different from what you had imagined yourself doing as a child?
Had I come to the Netherlands in my younger years I would have played football. My dad was a tailor and the concierge of a high school on a very big lot. There was a gymnasium with all the bells and whistles. That's where I grew up, the neighbors always came to our place to play. Even today, when I visit a sports complex in my sport shoes and tracksuit, I feel amazing… that's my tropical mood.

> "Together we can make things easier for each other"

Tell us about an event at work that had a big impact on you?
One day we transported a patient (I actually don't like to call them patients) to the radiology department, and we heard later on that this patient had passed away. I have seen a lot of people come and go, and sometimes they come back. What happened made me reflect a lot, people come in and don't know what state they will leave in.

What kind of people do you work with?
I work with a lot of different people but I'm not afraid of man. I'm positive and peace-loving. A lot of people think I go through life like an ostrich, that I don't see or know what's going on around me, but it's quite the opposite. If you want something from me just come to me and ask me in a respectful manner.

Is there something else you want to tell the reader?
Every hand has five fingers and they don't look the same, each one of them is different from the other. Fortunately, that is because they all have their own function. It's the same for us humans; together we can make things easier for each other. However, you also need a little bit of luck in life.

If we would run into you ten years from now, where would that be?
Paramaribo, back in my hammock!

Unable to walk

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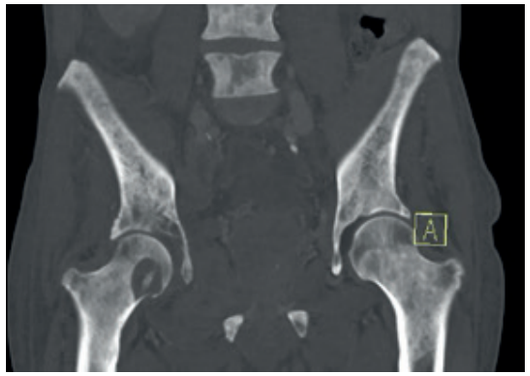
CASE
A 52 years old male presented at the emergency department with an inability to walk due to a severe pain in the hip. His medical history was unclear as the man was homeless. A CT and X-ray were taken.



QUESTION 1
What do you see? Multiple answers are possible.
A. Destruction of the right femoral head and acetabulum with lytic lesions.
B. Destruction of the right collum femoris (pathological fracture) and trochanter major with lytic lesions.
C. Destruction of the left trochanter minor with osteoarthritis and lesions.
D. Destruction of the left femoral head with sclerotic lesions

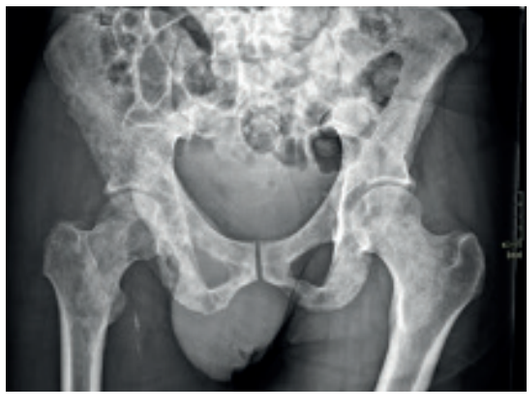
Hint: compare right and left and try to name the structures you see.

QUESTION 2
What is the cause of these lesions?
A. A primary bone tumor, possibly a chondrosarcoma
B. Multiple myeloma (m. Kahler)
C. Bone tuberculosis
D. Metastatic disease

Hint: How do lesions occur?

QUESTION 3
What do you expect to find in the lab work? Multiple answers are correct.
A. Paraproteinemia
B. Hypercalcemia
C. High PSA
D. High TSH

Hint: what test would confirm what diagnosis?



Answer on page 37

Self-quantification for prevention and treatment of diabetes type 2

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How many steps did you take yesterday? How many calories did you burn? What was your heart rate and how long did you sleep? More and more people practice 'self-quantification'[1], evidenced by for instance the steep increase in smartwatches sold worldwide.[2] People integrate new technology in their lives to gather health-related information.[3] By quantifying health aspects, people can monitor their own health. If problems are detected sooner, expensive treatments can be avoided later on.[4]

Diabetes mellitus type 2 (DM2) is one of the most frequent chronic diseases in the Netherlands. There are over 1.2 million Dutch with diabetes and a thousand patients are added to that every week. Of these people, 90% has DM2.[5] Without treatment, consisting of lifestyle adjustments and sometimes medication, diabetes causes serious complications. Self-quantification could contribute to the prevention and treatment of DM2.

Monitoring glucose levels can prevent damage to blood vessels.[6] Hyperglycemia due to the lack of insulin and insulin insensitivity can damage blood vessels and nerves, causing nephropathy, retinopathy, neuropathy and cardiovascular diseases. With continuous glucose monitoring (CGM), blood glucose levels are measured every 5 minutes with a sensor underneath the skin. Consequently, hypo- or hyperglycemias can be prevented because timely action can be taken by respectively eating something or injecting insulin.[7] HbA1c levels, the average blood glucose levels in the past 3 months and therefore an indicator for glycemic control and risk of complications, are reduced more in patients who use CGM compared to patients who do not.[8]

CGM shows a glucose trend line, giving both diabetics and healthy people the opportunity to gain insight in influences on glucose levels.[9] The way glucose levels respond to a specific food varies and may be caused by differences in microbiome and the way food is digested. By testing which specific food causes a peak, certain ingredients can be avoided. By reducing the frequency of peaks, diabetes can be prevented.[10]

Furthermore, self-quantification can be used to track how physically active you are. Lack of physical activity (PA), being overweight and a sedentary lifestyle are associated with the development of chronic diseases like DM2.[11] Monitoring behavior is one of the most powerful methods to induce behavioral change. By using a pedometer, PA levels rise with 26.9% compared to peoples' basic activity levels. The guideline of 150 minutes of moderate to intense PA a week should protect against chronic diseases like DM2.[12] Self-quantification helps people to succeed in following this guideline. For diabetics, higher levels of PA lead to better glucose control, help prevent long-term complications and improve quality of life. Yet, patients with DM2 often have a sedentary lifestyle.[13] By tracking PA with a smartwatch, PA levels rise with an average of 1.5 days a week with 30 minutes of activity.[14] Using a pedometer app establishes a reduction in HbA1c levels.[15] By providing game elements within these wearables or apps, such as rewards for completing challenges (also known as gamification), engagement can be increasingly encouraged.[16]

Self-quantification is recommended for both healthy people and diabetics to prevent the development and complications of DM2, respectively. Better information provision is key in this matter. After all, an ounce of prevention of (complications of) diabetes, is worth a pound of cure!

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Swans, Samples, Significance and Statistics: Back to the Basics

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For this edition of 'Solving Statistics', no specific question was submitted. I take this opportunity to address probably the most basic question that I have ever been asked about statistics: Why do we need statistics at all? "Patients in group A have lower pain scores than in group B, so analgesic A is evidently better", the student argued. "Why do I need a test when I can see that there is a difference, and why do I test the null-hypothesis that there is no difference when I actually want to show that there is a difference?".

Statistical methods can broadly be divided into descriptive and inferential methods. While descriptive statistics are used to summarize characteristic aspects of the data, such as their central tendency and variability, inferential statistics – most often, so-called 'frequentist' methods, on which I focus here – are used to draw broader conclusions on the population from which the data were sampled. In medical research, it is usually impossible to study an entire population of patients, e.g., all patients with a certain type of cancer. Rather, a (representative) sample is drawn and researchers then aim to make inferences about the entire population, based on the sample data. Herein, the pain score, blood pressure, survival rate – or whatever the outcome may be – in the specific study sample itself is not really of interest, but rather, whether a certain intervention, treatment or exposure generally has an effect on (or association with) the outcome in the population of interest.

Samples are inevitably affected by random sampling error. When studying the effects of a drug versus placebo on an outcome such as blood pressure, there will usually (always, if the measurement is precise enough) be some difference in the outcome between the groups just by chance, even if the drug would have absolutely no effect on the outcome. And if there is a "true" treatment effect, the observed effect in the sample could be substantially different from the "true" effect due to sampling error. When repeating the same study over and over again under the same conditions, each time with a new sample, we would get a different estimate of the treatment effect each time. So, we cannot simply base our conclusions on the observed treatment effect in a particular study sample, but rather need inferential statistics to determine (1) whether there is sufficient evidence to conclude that there actually is a treatment effect (or association) in the population from which the data were sampled, and (2) to estimate what the "true" treatment effect could plausibly be in the population.

> "Why do we need statistics at all?"

The first aim is addressed by hypothesis tests, which commonly test the null-hypothesis that there is no effect or no difference. This seems counter-intuitive, but is done because an empirical hypothesis can be proven false, but it cannot be proven true. Karl Popper, an influential philosopher of science of the 20th century, gave a classic example: "... no matter how many instances of white swans we may have observed, this does not justify the conclusion that all swans are white." The single observation of a black swan, however, disproves the hypothesis that all swans are white. The P-value obtained from a hypothesis test quantifies the evidence against the null-hypothesis: it is the probability of observing an effect (or difference, or association) as large as, or even larger than the one that was observed, if the null-hypothesis were actually true. So, a small P-value casts doubt on whether the null-hypothesis is plausible. When the P-value is below a certain threshold (often 0.05), researchers reject the null-hypothesis and conclude that there is an effect in the population. Importantly, however, a hypothesis test can only quantify the evidence against the null-hypothesis, but can never definitely disprove it. There is always a chance of reaching a wrong conclusion.

The second aim is addressed by effect sizes and their confidence interval, which allows gauging of the clinical relevance of the findings. An effect size, such as a mean difference between the groups, a relative risk, or a correlation coefficient, quantifies the magnitude of an effect or relationship. As stated above, an effect observed in the sample (the point estimate) is not sufficient to make inferences on the population, so it should generally be accompanied by a confidence interval. This interval is a measure of the uncertainty of the estimate, and provides a range of values of what the "true" effect could plausibly be in the population of interest. Whenever the confidence interval contains clinically important effects, an important effect cannot be ruled out, irrespective of its statistical significance.

Notably, statistical methods have specific assumptions that must be met, and various sources of bias can invalidate conclusions. Thus, while statistical methods are required to make inferences on a population, using such methods does not guarantee that the inferences are correct.

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

The relationship between obesity, calorie delivery and outcome in the critically ill – My time in Australia

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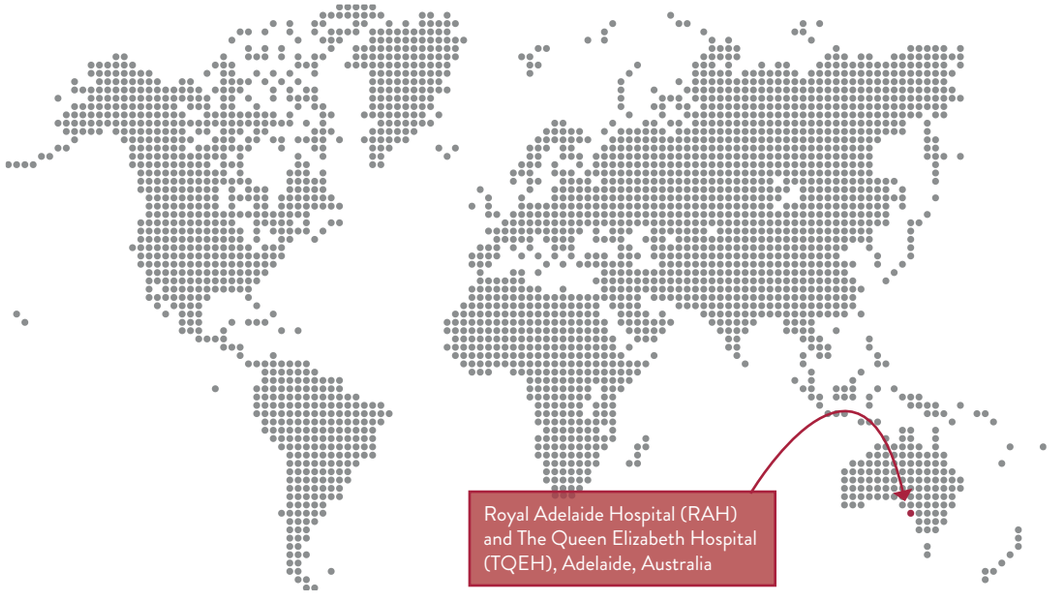


BACKGROUND

Since my Bachelor's I have been interested in critically ill patients and their management. I had been involved in a few research projects in the intensive care unit (ICU) and one of my supervisors asked me if I would like to go to abroad for my scientific internship. As I am writing this article for 'Research Abroad', my answer to his question is quite obvious. After he told me he had a contact in Australia who was willing to supervise me, the planning could start. This was easier said than done. Flights, visa, police clearance, housing, contracts, a (pretty expensive) medical check; all had to be arranged before I could even leave The Netherlands and start my trip to Adelaide, the capital of South Australia.

INTERNSHIP AND CLINICAL OBSERVERSHIP

After a long flight I arrived in Adelaide, and after a few days of adjusting to the new time zone, my internship could start.

I was based at the Royal Adelaide Hospital (RAH) and The Queen Elizabeth Hospital (TQEH). During my four-month stay I investigated the relationship between obesity, calorie delivery and outcome in the critically ill. Optimal energy delivery in the ICU is still a major point of discussion, especially for the obese. International nutrition guidelines recommend that obese patients

receive hypocaloric feeds. However, there is little evidence to support these guidelines. By studying literature and performing a sub-group analysis of a previously published trial, we found no discernible effect of (increased or decreased) caloric intake on outcome in patients with obesity.

The results of my thesis were interesting, I learned a lot about the subject and I had a great time with the research team. However, the improvement in my English, close supervision and my introduction to R and education from an experienced statistician were of even greater benefit to my academic development.

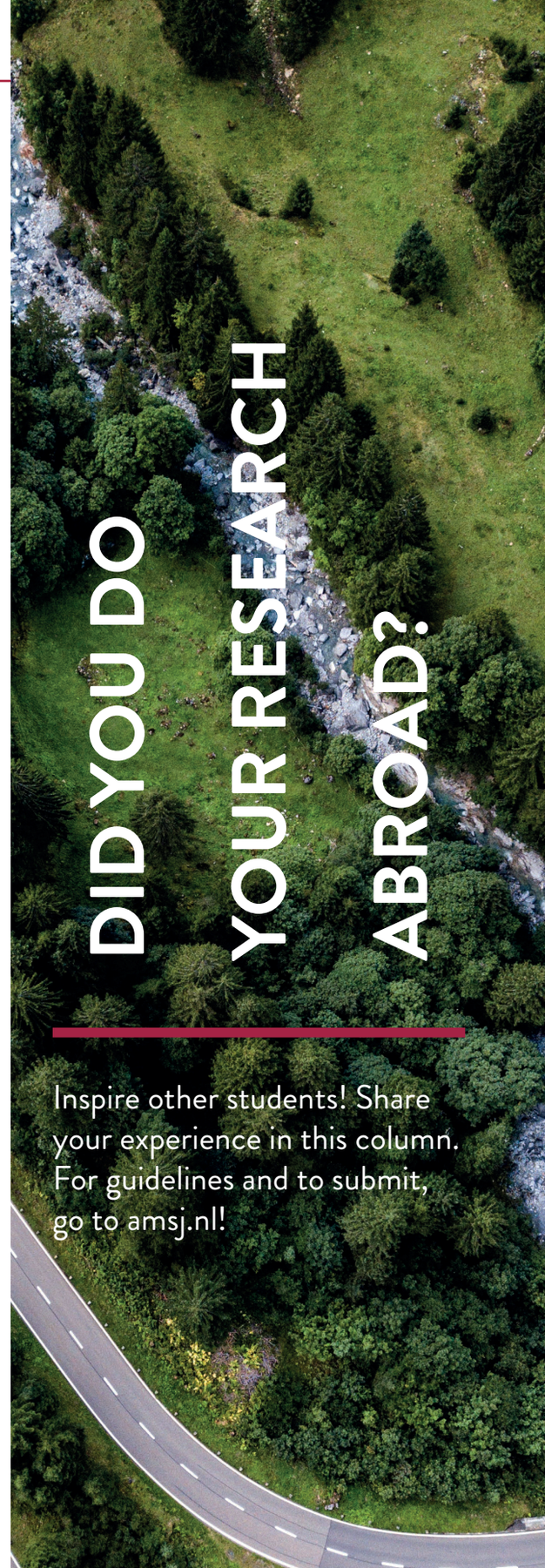
Besides working on my thesis and performing some other research-related activities, I also went along on rounds in the ICUs. The level of healthcare in Australia is similar to The Netherlands. However, there are some minor differences which are interesting to see.

PERSONAL LIFE

In my experience, Australians are relaxed and outgoing, making it relatively easy to make new friends. My supervisors were busy professors, but still very accessible and willing to show you around and help you settle. My direct colleagues were nice, however, a "vrijmibo" culture wasn't really in place. I would recommend joining a sports club or finding other (social) activities to do in your spare time. Student organizations were also very active. Make sure you make the most of your time and travel around while you are in the country, which was also encouraged by my supervisors. Australia is beautiful!

TIPS

When you're thinking about doing an internship in Australia, make sure you have enough money saved and start preparation at least 6 months in advance to save yourself some stress. I had to arrange my own accommodation, so as a start I booked an apartment via Airbnb for the first few weeks. Ask around and you will probably find a nice place to stay afterwards. To help in some of the costs I requested a travel grant from Amsterdams Universiteitsfonds. If you would like more information about my internship abroad, feel free to contact me.



Women are not men, especially not in medicine

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Feminism states that women and men should be treated equally. However, in healthcare things can be different. As stated by Perez in *Invisible Women*[1]: "Women are not small men".

On average women are shorter, weigh less and have a higher fat percentage with a different distribution compared to men. Women's estimated glomerular filtration rate (eGFR) declines quicker when aging than those of men[2], which influences pharmacokinetics such as absorption, distribution, and elimination of drugs. These differences might explain why women often experience more adverse effects from medication.[3] Also, women can present different symptoms of certain diseases than men. For example, 30-37% of women do not experience chest discomfort during a heart attack.[4] Besides this, the efficacy of some drugs may be lower in women. For example, the widely used drug acetylsalicylic acid has been shown to be ineffective or even harmful to women when used to prevent cardiovascular accidents.[5,6]

These findings could have easily been missed in "normal" non-gender segregated studies. Especially in studies that investigate pharmacokinetics of new drugs, or studies with healthy volunteers, women are often underrepresented. Besides, in clinical trials there is often no sex differentiation in the analysis of results. This could cause studies to find a positive overall result while this could be different for men and women.[7]

Nowadays, a slowly increasing number of studies pay attention to gender differences. The Dutch Heart Foundation has started funding research that looks at the differences between women and men for symptom presentation, medication and diagnostics of heart diseases.[7] The Dutch government and Vrije Universiteit Amsterdam also provide funding for research looking into the difference in aging between men and women.[8] The Federal Drug Agency (FDA) in the United States has started several projects to identify sex differences. The American National Institute of Health funds projects on sex differences and tries to increase data on women's health.[5] Some of the results of these funds have been mentioned above.

In conclusion, if we want to treat women and men the same, we sometimes need to treat them different. More and more organizations start to realize this, which will hopefully lead to better healthcare for women in the future.

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Letter to the editor - The role of (future) health care professionals in the face of three existential threats: COVID-19, global warming and nuclear war

Dear Editors,

Once again our triumph over nature has shown how vulnerable we are to nature's forces. Had it not been for globalization, growing cities and extensive air travel, we might not be living through a pandemic. We can draw hope from the first response to COVID-19 we saw in Europe: leadership that recognized the threat, listened to science, and took action. Crucial was the fact that the field of science and medicine let itself be heard.

Unfortunately, the novel coronavirus is not the only existential threat we are facing. Man-made climate change is threatening the livelihood of future generations and has already led to people fleeing their homes.[1] Again our technological triumphs have brought us into difficulties, like a pill with side-effects. This regimen is too damaging to continue. This threat also asks for leadership that listens to the science and is ready to act.

But how should we trust governments to tackle this crisis, if for decennia they have been relentlessly threatening each other with destruction? There are at this moment 13.400 nuclear weapons in this world[2]; enough to end all life on earth numerous times. Most of those weapons, including the 22 American bombs in the Netherlands[3], are many times more powerful than the bombs that caused death and suffering for almost a quarter million people 75 years ago in Hiroshima and Nagasaki. Many people seem to think that a new nuclear catastrophe is unthinkable, either in war or by accident. However, the truth remains that as long as these weapons exist, they can be used – intentionally or not.

In fact, the combined threat of global warming and nuclear weapons led the Bulletin of Atomic Scientist (just before the pandemic) to advance the Doomsday Clock to 100 seconds before midnight.[4] We have never lived so close to extinction.

One might feel paralyzed facing these enormous threats. However, when we take our Hippocratic Oath, we take upon us the responsibility to protect life. I propose the same approach that was so successful in averting the immediate threat of COVID-19 that we lived through in March and April: we need to raise our voices. Governments should acknowledge the threats and should listen to the science. We need to demand them to act. If not to the most vulnerable around the world, we owe it to ourselves that humankind shall survive another century.

Dirk G. Hoogenkamp
Medical student at Amsterdam UMC and board member of NVMP-Artsen voor Vrede, the Dutch affiliate of International Physicians for the Prevention of Nuclear War.

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Guideline update: Recent updates in the inhalation therapy protocol for children with COVID-19

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It has been nearly eight months since our country, like so many others, was struck by COVID-19 and put on intelligent lockdown. Especially at the beginning of the pandemic health care professionals were in doubt about how to adjust to this entirely new situation and how to treat patients infected with this novel coronavirus. Although especially the elderly population seems to be at risk of developing serious health issues and complications as a result of COVID-19, it must not be forgotten that also children, although much less frequently, can develop serious symptoms. Taking into account that using a nebulizer may put a medical caregiver at risk for transmission of disease and personal protective equipment (FFP2 masks) was scarce, the Nederlandse Vereniging voor Kindergeneeskunde (NVK) introduced an alternative inhalation therapy protocol for children with respiratory signs due to (suspected) COVID-19.

There has been some controversy surrounding the probability of an increased risk of viral transmission when using a nebulizer. Although no studies were published to quantify this risk for COVID-19,

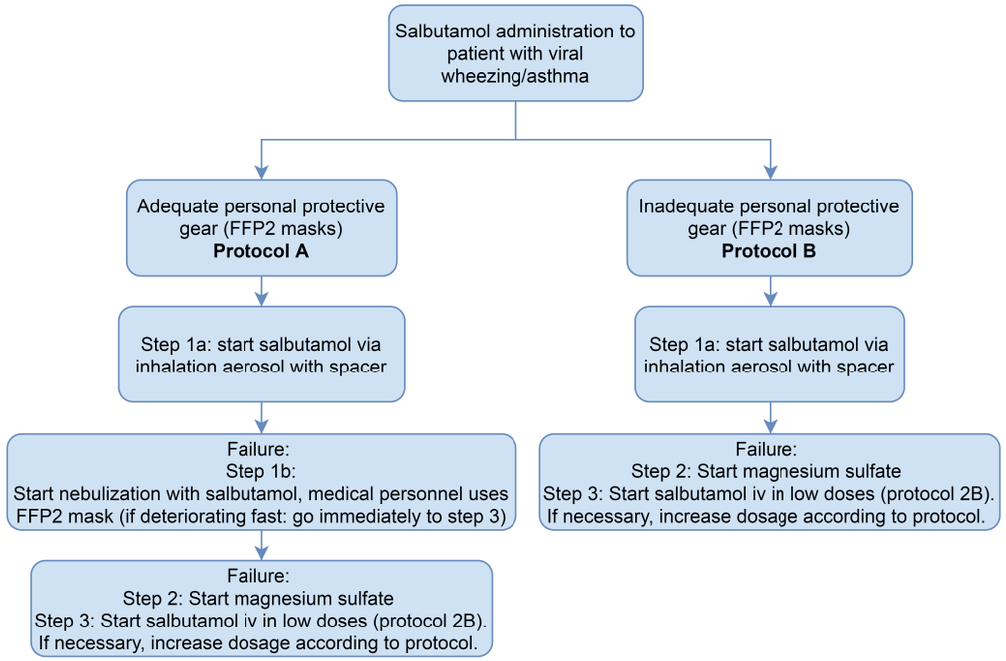

FIGURE 1 Flowchart of the inhalation therapy protocol for children with respiratory signs due to (suspected) COVID-19 (amended from Reference 1)

there are clues that nebulizing patients led to nosocomial infections during the SARS epidemic. Nebulizers generate aerosol particles with a diameter of 1-5µm. A large volume of aerosols can be generated during nebulizing therapy, which can spread through the room and remain in the air for as long as three hours after treatment. For this reason, the use of nebulizers is considered to increase the risk of COVID-19 transmission and should therefore only be done if enough personal protective equipment is available.

In the NVK protocol the preferred treatment for children with acute respiratory distress as a result of (suspected) COVID-19 consists of salbutamol (and ipratropiumbromide) via dose aerosol with an aerochamber, with concomitant oral steroids. If the effect is insufficient, salbutamol (and ipratropiumbromide) is administered through a nebulizer. When doing so, medical staff are required to use an FFP2 mask. If the dyspnea is persistent, magnesium sulphate IV must be administered, followed by a low dose of salbutamol IV. As a result of the worldwide shortage of personal protective equipment at the beginning of the pandemic, a second arm was provided (protocol B), leaving out the nebulizer and skipping to magnesium sulphate and salbutamol IV immediately after salbutamol and ipratropiumbromide via dose aerosol. Thankfully, now that the shortage is no longer a problem, nebulizing has been re-introduced as part of the inhalation therapy protocol for children with (suspected) COVID-19 since July 16th (Protocol A).

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Five years later

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Wow, it has already been five years since I published the case report on Clearsight hemodynamic monitoring during anaphylactic shock.[1] At that time I had just finished my ICU fellowship and had started as a staff anesthesiologist at AMC. I was at that time implementing cardiac output monitoring in the operating room and especially in the esophagectomy patient population. Although I had finished a PhD in 2010 I was not especially focusing on a research career at the time. However, after this project came another and another and now I have (the beginning of) a research line established in the field of hemodynamic monitoring and perioperative outcome optimization. We especially focus on innovative research, including machine learning application, and our research group has expanded ever since.

> "When specializing find something within your specialization that makes you tick, your own niche"

The choice to become an anesthesiologist was only made after finishing my internships. In the curriculum of the university anesthesiology was never much in the picture so I did not know much about it. Only after I did an internship I knew this specialization was very interesting and exciting. It contains so much more than just giving anesthesia in the operating room. We also cover all the acute care in the hospital such as resuscitation and trauma, but also acute and chronic pain services. I especially like the combination of research and clinic as this enables me to innovate and be creative.

I would advise students to take time to find your specialty and use your internships to be as broadly orientated as possible. Afterwards, do not hurry, and broaden your knowledge by doing a PhD or just work in the field as ANIOS and possibly, abroad. The experience you will get there will make you more interesting and also you can take your experiences with you in any future specialization. When specializing find something within your specialization that makes you tick, your own niche. Working in the field of medicine is generally hard work so it helps if you do what makes you happy.

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> "Working in the field of medicine is generally hard work so it helps if you do what makes you happy"

Answers 'An ill female with yellow skin color'

T. van Ramshorst and K. de Wit

Correct answers: 1B, 2D, 3A

EXPLANATION

QUESTION 1

What is the diagnosis based on the imagery?

B. The imagery shows a severe diaphragmatic hernia. This is a medical condition where a defect or hole in the diaphragm causes a protrusion of abdominal organs into the chest cavity. In the CT-scan of this case you can clearly see the small intestine in the chest cavity.
Gastric perforation and paralytic ileus do give different clinical presentations and CT-scans of these conditions show other findings. For a gastric perforation pain in the epigastric area is typical with free fluid or gas and extravasation of oral contrast on the CT-scan. Mechanical ileus causes vomiting and absence of stool because of obstruction (adhesions, tumor, torsion) of the intestines which mostly can be seen on imagery, with dilated small bowel loops. Diagnosis of a tapeworm infection is made by examining stool samples for worm segments or eggs.

QUESTION 2

What is the most probable cause of the diagnosis in this case?

D. A diaphragmatic hernia can be divided into congenital or acquired types. Congenital types are caused by congenital weakness of the diaphragm. Acquired types can occur later and are associated with smoking, increased abdominal pressure (after pregnancy or deliveries, severe coughing, obstipation), after abdominal injuries, obesity, age above 60 and after major abdominal surgery. In this case the medical history is very important. During a McKeown operation a part of the esophagus and stomach is removed. The remaining part of the stomach is formed into a gastric tube which is pulled up through the diaphragm to then make an anastomosis with the remaining part of the esophagus. This often causes a slightly dilated hole in the diaphragm where the esophagus was originally located, which eventually can cause a diaphragmatic hernia in the long term.

QUESTION 3

What is usually the treatment for a condition of this severity?

A. Most of the time, a minimal diaphragmatic hernia exists without complaints and therefore remains untreated. In cases of bigger defects, where the top of stomach has slid above the diaphragmatic, it can give complaints such as reflux for which proton pump inhibitors are given. However, diaphragmatic hernias of such severity as this case do require surgical repair. During surgery, the shifted structures will be replaced into the abdominal cavity and the defect will be repaired by placing a soft plastic mesh which gets sutured to the surrounding diaphragm edge.

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Answers ‘Unable to walk’

Sanne van Beem and Mario Maas

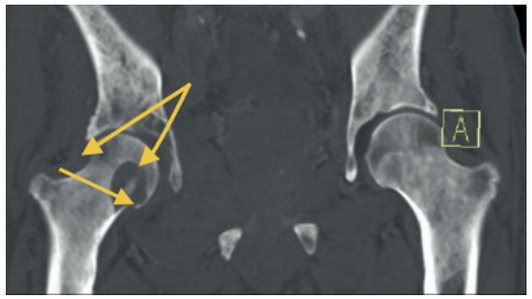
Correct answers: 1AB, 2D, 3BC

EXPLANATION

The X-ray and CT show destruction of the right femoral head and acetabulum with lytic lesions, which are indicative for a malignant process. This can either present with lytic lesions, sclerotic lesions or mixed lesions, which amongst others depends on the primary cause of the malignant process. Lytic lesions are the most commonly occurring and are characterized by areas of destroyed bone or holes where once was bone as a result of increased osteoblastic activity. Sclerotic lesions are unusual white spots in the bone shown on an X-ray as increased bone density. Sclerotic lesions are often benign, and if malignant the source is often a prostate carcinoma.

A bone malignancy is most commonly a metastasis of another tumor. Primary tumors that have a tendency to metastasize to the bone include breast cancer, lung cancer, thyroid cancer and, as in this case, prostate cancer. The most common primary bone tumor in adults is a chondrosarcoma. It may present with pain or a spontaneous fracture. Bone tuberculosis is very rare, but should still be considered as our patient is homeless. However, bone TB often presents in the thoracic or lumbar segment of the vertebrae (spondylodiscitis, or “Pott’s disease”) and patients often have a concomitant HIV-infection.

The source of the lesions can be found by ordering lab and imaging modalities such as (PET-)CT. In our case, diffuse skeletal disease was discovered on an abdominal and chest CT. If you look closely at the X-ray and CT presented with the case, you can also spot diffuse sclerotic lesions in other parts of the skeleton. This represents mixed sclerotic and lytic bone disease. However, this is often overlooked as the cause of the pain is found by looking at the X-ray. This is called a satisfaction of search error and often happens in radiology and other visual based techniques such as arthroscopy or laparoscopy. Physicians sometimes fail to look



for other abnormalities after the initial abnormality is found. This is often the result of a lack of time due to the demand of hyperefficient radiology departments, fatigue of the radiologist and limited information on the medical history of the patient. A laboratory test was also performed, which revealed a PSA of 27000, indicative of a prostate carcinoma. Other findings may include hypercalcemia as the breakdown of bone releases high amounts of calcium into the blood.

Prostate carcinomas carry a good prognosis until they metastasize. Metastasized prostate carcinoma, as found in our patient, carries a very poor prognosis: no curative treatment options are currently available, so patients are started on palliative care which includes androgen deprivation therapy to minimize symptoms.

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Colophon

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ISSN 2589-1243 (print); 2589-1251 (online)

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