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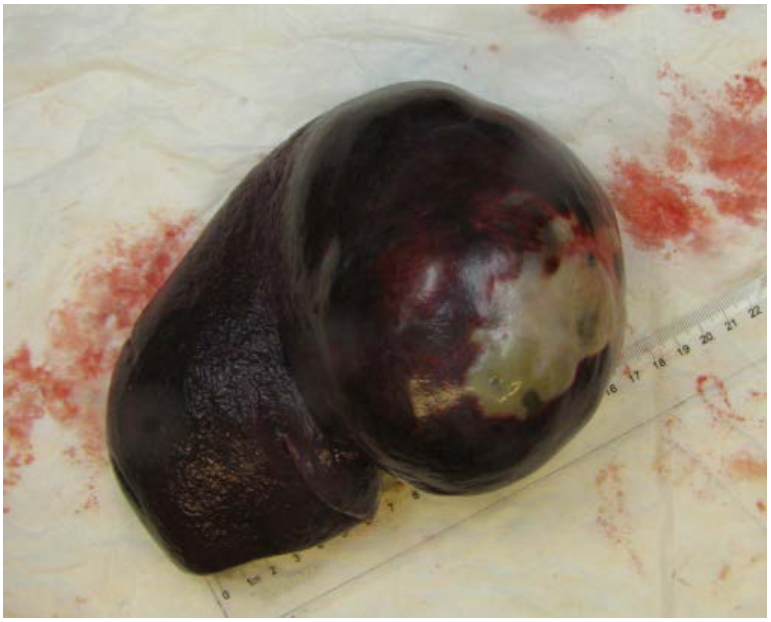

A palpable mass in the left upper abdomen: what is your diagnosis?

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To serve the needs of the physician to practice up-to-date medicine and to keep track of important issues in health care. To promote and to enhance clinical knowledge by publishing editorials, original articles, reviews, papers regarding specialty training, medical education and correspondence.

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EDITORIAL

Interbellum

P.L.A. van Daele

There is probably no medical journal that doesn't publish about covid-19 these days. *The Netherlands Journal of Medicine* is no exception. What started as a local epidemic in China has now become a pandemic in which hardly any country is spared. Some countries are in lock-down. Schools are closed, sport events have been canceled.

In the current issue Van Hilst et al describe how they fight this corona crisis in a large Belgium hospital located in the heart of the Belgium outbreak. Until April 1th 235 patients had been admitted of whom 38 died. Fighting covid-19 resembles a military campaign.

No doubt we will win this war against covid-19 like we have previously overcome viral outbreaks this century like Zika, Ebola and the Mexican flue. The question is how long this war will last. The Spanish flue pandemic lasted approximately 1,5 year. And what will be the best strategy to control this virus? A very important issue will be how we guarantee that care for other medical conditions will be sufficient? But perhaps the most important question is how long the interbellum will last once covid-19 has been constrained? When will we face the next outbreak of yet another new virus? At least then we will be better prepared.

REVIEW

Geriatric considerations in older persons with end-stage kidney disease

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ABSTRACT

Decision-making in older persons with end-stage kidney disease (ESKD) regarding dialysis initiation is highly complex. While some older persons improve with dialysis and maintain a good quality of life, others experience less benefit and multiple complications due to a high morbidity burden and (early) mortality. Geriatric impairments are highly prevalent among this population and these impairments may complicate the care of an older person with ESKD. Knowledge of these impairments can potentially help improve care and decision-making regarding dialysis initiation and advance care planning. Therefore, the aim of this review is to give healthcare providers an insight into the existing literature on geriatric impairments in older persons with ESKD. Furthermore, specific areas of concern will be discussed, in combination with some practical advice.

KEYWORDS

Dialysis, decision-making, geriatric impairments, older persons

INTRODUCTION

Currently, more than half of the prevalent and incident dialysis patients in the Netherlands are 65 years or older.[1] Taking patients who forego dialysis into consideration, the percentage of older patients among those with end-stage kidney disease (ESKD) is likely to be much higher (although exact numbers are currently lacking).[2] Furthermore, as the Dutch population is aging,[3] this number is likely to increase even further over the coming decades. The elderly population is a heterogeneous group, in terms of comorbidities, polypharmacy, and geriatric impairments,[4] such as cognitive impairment, accidental falls, functional impairment, symptoms of depression, and frailty.[4]

As a result of this heterogeneity, decision-making about the initiation of dialysis and dialysis modality is highly complex. While some older persons function very well and improve through dialysis therapy, others experience high morbidity[5-8] and increased mortality, especially early after dialysis initiation.[9-11] As geriatric impairments influence prognosis,[12] knowledge of the presence of such impairments can potentially help decision-making about dialysis treatment and advanced-care decisions in older persons with ESKD.

In this paper, we use four cases to illustrate the heterogeneity in older persons with ESKD and address different geriatric considerations that may be relevant in decision-making regarding treatment for ESKD.

TREATMENT OPTIONS FOR OLDER PERSONS WITH ESKD

Treatment options for older persons with ESKD do not differ from younger patients and include kidney transplantation, in-centre haemodialysis, (assisted) home haemodialysis, (assisted) peritoneal dialysis (both automatic peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD)), and maximal conservative management. Kidney transplantation is an option in selected older persons (e.g., the Eurotransplant Senior Program (ESP), in which a kidney of a deceased patient older than 65 years is donated to a patient older than 65 years); however, due to a shortage of transplants and health requirements, the majority of older persons will start dialysis[1] and remain on this therapy for the rest of their life.

Haemodialysis can take place at a centre or at home, in which case, the additional help of trained home care or family members can be arranged for patients who are not capable of performing dialysis independently in the home setting (assisted home haemodialysis). The same can be arranged for peritoneal dialysis, which is performed in the home setting. In general, patients treated by haemodialysis are dialyzed 3-4 times a week for approximately 4 hours; for patients treated by CAPD this is on average 4 times a day with varying lengths. In addition, APD facilitates night dialysis, usually with only one connecting and disconnecting moment from the dialysis equipment. Potential advantages of home dialysis include flexibility in the treatment schedule, less time spent in the hospital, and no need for transportation to and from the centre.[13] Home haemodialysis also facilitates more frequent and shorter treatment schedules, which may yield a shorter post-dialysis recovery time, fewer symptoms of depression, and improved sleep quality.[14] Subsequently, there is evidence that home dialysis leads to a higher quality of life.[15] However, in addition to the logistical and financial barriers,[13] patients and their caregivers sometimes find the burden of responsibility for self-care too much.[16] Furthermore, some patients, such as older persons with a limited social network, value the advantage of social contacts of in-centre dialysis and patients may feel more confident with the availability of specialized medical support. No differences are seen in survival rate[17] and quality of life[18] between older patients on (assisted) peritoneal dialysis and haemodialysis.

Patients can choose maximal conservative management (MCM). This treatment focuses on symptom management to maintain quality of life as much as possible. Over the past years, there has been increasing evidence that MCM has a survival similar to dialysis therapy in patients older than 80 years and in patients older than 75 years with a high comorbidity burden.[19-21] Furthermore, with a similar quality of life,[22,23] patients on MCM treatment are less likely to be hospitalised[22,23] and more likely to die at home or in a hospice.[8]

CASES

Patient A is a 75-year-old female with ESKD caused by diabetes. Her medical history includes peripheral artery disease, recurrent urinary tract infections (UTI), and multiple deliriums caused by infections. She is married and has no children or additional home care. Since her last UTI six months ago, Patient A appears slow, depressed, and is more dependent on her husband in her daily activities. After consulting a geriatrician, she was diagnosed with vascular type dementia, which was a surprise for Patient A, her husband, and the nephrologist who had treated her for several years. After deliberating with Patient A and her husband, the nephrologist advised against starting dialysis. The patient and her husband agree with conservative management.

Patient B is an 85-year-old male with ESKD caused by hypertension and diabetes. He has a severely reduced exercise capacity due to ischemic heart disease, for which he has been treated with multiple percutaneous interventions. He has also experienced multiple fall incidents of unknown aetiology. Patient B is married and has an adult son. In addition to home care three times a day, his wife and son support him with transport and help with daily activities. Due to his limited exercise capacity and a recent fall, he walks only inside the house with a walking cane. Although he is dependent on his surroundings, he enjoys life to the fullest and is determined to live as long as possible. Despite some hesitation from his treating nephrologist, he decided to start in-centre haemodialysis.

Patient C is a 76-year-old female with ESKD caused by amyloidosis. For the amyloidosis, she has been treated with multiple courses of chemotherapy, which resulted in haematological regression and also complaints of polyneuropathy. Consequently, Patient C experiences difficulty with undoing buttons and getting pills out of a box. In addition to the amyloidosis, she has a medical history of osteoporosis and multiple abdominal herniations (umbilical, epigastric) for which she was treated with surgery. She is a widow with two children and four grandchildren. Because of progression of the ESKD, Patient C had to choose whether she wanted to start dialysis. Patient C chose peritoneal dialysis so she could maintain her active lifestyle and remain independent.

Patient D is an 82-year-old male with ESKD caused by hypertension. He has a medical history of deep vein thrombosis and pulmonary embolism treated with anticoagulants. Patient D is fully independent and lives with his wife. In the past, a good friend of Patient D with ESKD chose maximal conservative management and experienced this as a good way to maintain quality of life; in the end he experienced a peaceful death at home. Although Patient D is fit and has an active lifestyle, he decided that dialysis will have too much of an impact on his quality of life. Therefore, he chose maximal conservative management.

GERIATRIC IMPAIRMENTS

Cognitive impairment

Cognitive impairment is an important issue in patients with ESKD. As illustrated in Patient A, it is an impairment that is frequently overlooked by both healthcare providers and family members.[24] For example, in a study in

haemodialysis patients, 37% had a severely impaired cognition when tested, but only 3% of all patients had a documented history of cognitive impairment.[25] The prevalence of cognitive impairment in this study is in agreement with previous research, with most studies reporting more than half of older patients with ESKD having mild to severe cognitive impairment.[4,25] This is much higher compared to an age- and sex-matched general population and patients with a less severe degree of chronic kidney disease (CKD).[26]

The cognitive domains that are frequently affected are attention and executive function.[26] Both are crucial in making an informed decision because patients have to understand the information required for the decision and have to realise how the information given will impact their own life and circumstances. Patients should also be able to use the information and subsequently, logically reason which treatment option they prefer.[27] Although it makes sense that decision-making capabilities can be affected in patients with severe cognitive impairment,[28] the effect has rarely been studied in ESKD.[29,30]

Besides potential problems with decision-making, cognitive impairment is associated with a higher risk of mortality[31-34] and dialysis withdrawal.[33-35] For example, the average time until death for incident dialysis patients with dementia was 1 year compared to 2.7 years in patients without dementia.[34] Although it is not completely clear how different aspects of dialysis (e.g., clearance of uremic toxins,[36] shifts in cerebral blood flow[37]) affect cognitive impairment, the start of dialysis in the older population is more often associated with a loss of function than improvement.[38,39]

A possible solution to the diminished attention span is to dose information over multiple appointments and healthcare providers should regularly check if the information is understood (for example, by asking the patient to paraphrase the given information). In addition, since problems in executive functioning can lead to difficulties in anticipating new situations, health care providers should ascertain if patients can comprehend the potential implications of their decision for their daily life.[27]

Therefore, screening for cognitive impairment in the older population with ESKD is recommended, for example, by the use of the Montreal Cognitive Assessment (MOCA).[40] In cases where cognitive impairment that interferes with self-care and therapy adherence, referral to a memory clinic is advisable. This information can subsequently be used for prognostication and to assess decision-making capacities.

Depression

Depression is present in approximately one-quarter of patients treated by maintenance dialysis[41] and one-third of the patients display depression symptoms.[42] Similar rates of symptoms of depression are found in older patients who started dialysis therapy (31%) and in older patients with ESKD who chose maximal conservative management (35%).[4] This is an important issue to be aware of since depression symptoms are associated with a lower medical adherence, a higher morbidity,[43] withdrawal from treatment,[44] and mortality.[43-45]

To the best of our knowledge, no research has been performed on the influence of depression on decision-making in older patients with ESKD. Previous studies in the general population, however, have shown that patients with depression are less likely to accept a life-sustaining treatment,[46] while remission of depression is associated with an increase in acceptance of treatments.[46] Therefore, it is recommended to timely screen for depression and to refer patients suspected for depression for additional diagnostics and management, preferably before making a definitive decision regarding dialysis.

Of note, late onset depression is associated with dementia.[47] This is illustrated by Patient A, for whom the differential diagnosis of her lethargy, depressive symptoms, and increased care dependence was broad and may consist of uraemia, depression, adjustment disorder, medication-induced mood disorder, and cognitive impairment. Because depression is treated differently from depression symptoms caused by other disorders, making a correct diagnosis is essential. Therefore, in cases of doubt, it may be beneficial to consult an expert (e.g., psychiatrist, geriatrician).

Depression symptoms can be indicated by the 36-Item Short Form Health Survey (SF-36) or RAND-36.[48] The diagnosis of depression is made by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria, which include mood and somatic symptoms during at least two weeks, not explained by a somatic disease.[49] The latter criterion poses difficulties in ESKD, as uremic complaints such as insomnia, fatigue, and a decreased appetite frequently overlap with the somatic symptoms of depression. Sometimes the course of the symptoms can help in discriminating between depression and progression of ESKD. For example, if new complaints in combination with depression symptoms and/or anhedonia are not accompanied by changes in physical examination and/or laboratory results, the diagnosis of depression should be considered.

Although based on sparse data of medium quality, there is some evidence that different non-pharmacological (e.g., exercise training, cognitive behaviour treatment)[50] and pharmacological treatment strategies[50-51] can be beneficial in treating depression in patients with ESKD. Nevertheless, in addition to attention for a reduced renal excretion of medication, caution is advised in the older population for

the potential anti-cholinergic effects of anti-depressants (mainly tricyclic antidepressants), which can lead to a broad spectrum of symptoms including sedation, postural hypotension, confusion, and even delirium.[52] Furthermore, a higher risk of falling is reported with the use of anti-depressants.[53-55] Thus, the potential benefits and burdens should be carefully weighed each individual patient.

Accidental falls

Patient B experienced multiple falls of unknown aetiology. Falls are not uncommon in the older population with ESKD, with between approximately 30% and 55% of patients on dialysis therapy falling every year.[56-58] Interestingly, the post-dialysis initiation period is especially at high-risk for fall incidents.[57] Injurious falls in the dialysis population are also common[58] and are associated with loss of independence[54] and increased mortality.[59] In addition to injury, falls can also lead to fear of falling, which can subsequently lead to loss of mobility and social isolation.[60]

Most risk factors for accidental falls in older persons with ESKD are similar to the general population and include age, a previous fall, diabetes, frailty, mobility impairment, use of anti-depressants, and decrease of systolic blood pressure.[60] Thus, additional analysis of a patient such as Patient B in a falls clinic before the start of dialysis is recommended to identify potentially modifiable risk factors. In the general population there is extensive evidence that a multifactorial fall risk assessment and management program can lower the number of falls[61] and subsequently fall-related injury.[62] In addition, considering most patients do not tell their healthcare providers they have experienced a fall,[63] it is recommended to periodically ask patients with ESKD about falls.

Functional impairment

Approximately 80% of older persons with ESKD are dependent on others in one or more often instrumental daily activities.[4] These include activities that are necessary for self-care (such as bathing, dressing, and continence) and more complex tasks that are essential for independent living (such as shopping, housecleaning, and telephone use). To perform these tasks, cognition, physical ability, and perceptual capacities are necessary. For example, Patient C has severe polyneuropathy in both hands, limiting her ability to perform activities that require fine motor skills. This could potentially affect her ability to connect to the PD machine. This is important to consider, especially since the main reason Patient C had chosen peritoneal dialysis was to remain independent.

Irrespective of treatment modality, the start of dialysis in older persons is frequently accompanied by a loss of independence, both in the short[7] and long term.[64] For example, we showed that in older patients starting dialysis, 40% experienced a decline in functional status within six months.[7] This rate was even higher in frail older adults.[7] Similar results were seen in very frail nursing home patients, of whom only 13% maintained their functional status one year after the start of dialysis.[5] In contrast, the limited data on functional course of maximal conservative management shows that loss of independence does not occur until the month before death.[65] In addition, functional dependence is strongly associated with mortality,[66,67] therapy withdrawal,[66] time to first hospitalisation,[67] and can negatively influence quality of life.[68,69] Regarding Patient C, this information could have assisted her, her caregivers, and treating physicians in making a well-informed decision.

To the best of our knowledge, there is no consensus on the most appropriate tool for assessing functional performance in older patients with CKD.[70] A combination of a self-reporting questionnaire and field tests (e.g., sit to stand, gait speed, and the 6-min walk) is recommended for assessing physical performance.[70] Self-reporting questionnaires that are frequently used to assess daily function[48,70] are the Katz ADL[71] (assessing activities of daily living), Lawton Brody Instrumental ADL[72] (assessing instrumental activities of daily living), and questionnaires assessing quality of life (36 Short Form Health Survey (SF-36) and RAND-36).

A potential treatment strategy to maintain functional status is to improve physical functioning. Different studies showed that regular exercise is able to improve physical function[73] by enhancing aerobic capacity, muscular function, cardiovascular function, and walking capacity.[74,75] Interestingly, patients who performed physical exercise during dialysis sessions demonstrated more improvement of physical function compared to patients who exercised outside the dialysis unit.[73] This is probably the result of a better compliance with exercise during dialysis.[74] Hence, it may be beneficial to encourage physical activity in older persons with ESKD, for example, by offering intradialytic exercise.

Caregiver burden

Caregivers of patients with ESKD are at risk for high burden, because of a high prevalence of symptoms (e.g., fatigue, anorexia, sleep disturbance, pruritus)[76] and the frequent coexistence of other impairments, such as cognitive impairment, depression symptoms, and functional impairment.[4] High caregiver burden is associated with a decreased quality of life and more depression symptoms for the caregiver.[77] Also, for the patient it is important to maintain good social support, as poorer social support is associated with a higher mortality risk,[78,79] lower adherence to medical care,[79] and poorer physical quality of life.[79] On the other hand, being

a caregiver also comprises positive experiences, such as feelings of personal growth and gratification.[80] The help of a caregiver can potentially give both the patient and the caregiver more freedom. For example, in the setting of home dialysis, a caregiver who facilitates the dialysis procedure can create more flexibility in the treatment schedule. Thus, when aiming to optimise care for older patients, supporting the caregiver, and regularly inquiring about the burden of care they experience, is as important as the support given to patients themselves.

Frailty

Frailty is frequently defined as a "biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, resulting in increased vulnerability to adverse outcomes".[81] Multiple operationalisations of frailty exist, and the diagnostic method strongly affects the prevalence of frailty. Irrespective of this, at least half of ESKD patients appear to be frail.[82] Previous research in ESKD shows that frailty is associated with functional deterioration,[7] hospitalisations,[83,84] and mortality.[85] Therefore, for frail older persons in particular, conservative management seems to be a good alternative to dialysis therapy as these patients are less likely to benefit from dialysis.[70]

One manner in which frailty is operationalised is through the number of geriatric domains identified as impaired in a geriatric assessment. This multidimensional assessment includes physical, functional, and psychosocial domains and includes all the impairments previously discussed. For older ESKD patients, a regularly performed geriatric assessment (e.g., yearly or when major events occur) may be beneficial to ensure a timely diagnosis of issues that are potentially modifiable or can influence treatment decisions and care provision. However, it is still unclear how a geriatric assessment will affect decision-making regarding the start of dialysis and dialysis modality. This is the focus of two studies currently ongoing in the Netherlands: the 'Pathway for Older Patients Reaching End Stage Renal Disease (POLDER)'[86] and 'DIALysis or not Outcomes in older kidney patients with GerIatric Assessment (DIALOGICA).[87] Frailty can also be assessed by frailty screening tools. In nephrology, the most frequently used frailty screening instrument is the Fried Frailty Index. This is an instrument that uses five criteria mainly focused on physical frailty (unintentional weight loss, exhaustion, physical activity, walking speed, and handgrip strength).[81] Although physical frailty is related to poor outcome,[7,84,85,88] it is important to note that non-physical geriatric impairments (e.g., cognitive impairment, depressive symptoms, social impairment) that are previously discussed and may be important for decision-making would not be observed using the Fried Frailty Index. Frailty screening instruments should therefore be use cautiously, as many vulnerable patients will be potentially missed.[82]

The list of geriatric impairments is more extensive than described above. For the purpose of this review, we chose to limit the discussion to geriatric impairments with considerable influence on quality of life or potential influence on survival, and consequently of importance in the decision-making process regarding dialysis initiation.

HEALTH OUTCOME PRIORITIES IN OLDER PERSONS WITH ESKD

In our case descriptions, fear of the potential loss of quality of life was the reason Patient C chose MCM, despite his good clinical condition. Although he had the physical reserves and the resilience to undergo dialysis, his good condition could potentially decrease substantially by starting dialysis (e.g., much time spend on dialysis, potential dialysis-related complications, and hospitalisations).[23] Therefore, MCM should always be actively discussed as an option for the (older) patient with ESKD, irrespective of their health status.

It is important to realise that most older persons may identify more with problems or outcomes that are not disease-specific.[89] For example, a recent study in the United States showed that most older persons with advanced CKD value maintaining independence as their top health priority.[90] In addition, a study in older non-CKD patients with a limited life expectancy, demonstrated that if the outcome is increased survival, but with severe functional impairment or cognitive impairment, most patients would not choose to undergo treatment.[91] However, as illustrated with Patients B and D, how quality of life is experienced is very personal and strongly affects their treatment decisions. Identifying and prioritising patients' healthcare goals (e.g., living independently at home, take care of a loved one as long as possible) should be an important part of ESKD management in all patients. Knowing healthcare goals can also help in discussing end-of-life choices. A recent study showed that in only 35% of the patients with advanced CKD, the healthcare provider was aware of their patients top health priority.[90] This suggests that these questions are currently insufficiently discussed in clinical practice. Another study showed that older ESKD patients had lower rates of advance care planning near the end of life compared to similar patients dying of cancer, resulting in higher treatment intensity at the end of life and more patients dying in the hospital.[92] This is also illustrated by Patient D, who valued dying at home highly - something that is relatively easy to accomplish if this is established early.

CONCLUSIONS

As the ESKD population is aging, geriatric impairments in this population become more prevalent and decision-making regarding dialysis becomes more complex. Knowledge about geriatric impairments can help advance decision-making regarding dialysis therapy and modality by improving information on prognosis and decision-making capacities. Treatment strategies can also be implemented to optimise health and quality of life. A geriatric assessment covers all important geriatric impairments and can therefore be used to identify these problems. The information retrieved from a geriatric assessment can be used to support the decision-making process regarding dialysis and may help in making an individualised treatment plan according to patients' personal health goals, preferably together with family and/or potential caregivers.

DISCLOSURES

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The authors have no conflicts of interest to declare.

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REVIEW

Anaemia: A disease or symptom?

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ABSTRACT

Anaemia is a common diagnosis for clinicians. This mini-review summarises criteria for diagnosing the cause of anaemia. Within the microcytic anaemias, iron-deficient anaemia is most common. In addition, we would like to raise awareness of thalassaemia as a differential diagnosis. A normocytic anaemia, such as anaemia of chronic disease, is a diagnosis of exclusion. A macrocytic anaemia scheme is provided and differentiates based on reticulocyte count. We aim to provide the readers a clear overview of anaemia and when to refer to haematologists.

KEYWORDS

Anaemia, iron deficiency anaemia, thalassaemia, vitamin B12 deficiency

INTRODUCTION

Anaemia is a haematological abnormality commonly encountered by general practitioners and hospital physicians. Worldwide, anaemia is estimated to affect 1.6 billion people.[1] Anaemia is diagnosed using a patient's haemoglobin concentration; however, this information does not determine the causative underlying pathology of the anaemic state. Anaemia pathology can be divided into three broad categories: a decreased production of red cells, an increased destruction of red cells, or a loss of red cells through bleeding. However, anaemia pathology is often multifactorial and can present as the manifestation of an underlying disorder.

DEFINITION OF ANAEMIA

The World Health Organization defines anaemia as a condition in which the number of red cells or their oxygen-carrying capacity is insufficient to meet physiological requirements. The United Kingdom (UK) laboratory definition of anaemia is a haemoglobin level two standard deviations below the normal for age and sex. This correlates as the following:

- Men, over 15 years of age: Hb below 130 g/l
- Non-pregnant women, over 15 years of age: Hb below 120 g/l
- Children, aged 12-14 years: Hb below 120 g/l

During pregnancy, homeostatic changes occur that necessitate an alteration of anaemia definitions. The definition of anaemia during pregnancy is as follows:

- First trimester: Hb below 110 g/l
- Second and third trimesters: Hb below 105 g/l
- Postpartum: Hb below 100 g/l

The mean cell volume (MCV) can be used to categorise anaemia and therefore guide subsequent investigations. Using MCV, anaemia can be categorised accordingly:

- Microcytic anaemia: MCV < 80 fL
- Normocytic anaemia: MCV 80-95 fL
- Macrocytic anaemia: MCV > 95 fL

MICROCYTIC ANAEMIA

Microcytic anaemia is defined as anaemia with an MCV of < 80 fL. The most common cause of microcytic anaemia, and indeed the most common cause of anaemia worldwide, is iron deficiency. Iron deficiency anaemia remains a significant problem in developed countries, with an estimated prevalence of 2-5% among men and post-menopausal women.[2] Rates of iron deficiency anaemia in women of childbearing age exceed this due to menstruation and pregnancy-related blood loss.[3]

Other causes of microcytic anaemia include anaemia of chronic disease, haemoglobinopathies, and sideroblastic anaemias. Table 1 demonstrates the use of full blood count parameters and iron studies to help differentiate between the causes of microcytic anaemia.

Table 1. *The differential diagnosis of microcytic anaemia*

Investigation	Iron deficiency	Anaemia of chronic disease	Thalassaemia (α or β)
MCV	Low	Low/normal	Very low for degree of anaemia
Serum ferritin	Low	Normal/ raised	Normal
Serum TIBC	Raised	Low	Normal
Transferrin saturation	Low	Low	Normal
Serum Iron	Low	Low	Normal
Reticulocyte count	Low	Low/ normal	Normal/ raised

Note: When iron deficiency occurs in combination with an inflammatory state, the ferritin may be spuriously high. In these instances, it is advised to perform a zinc protoporphyrin level.
MCV = mean cell volume; TIBC = total iron binding capacity

IRON DEFICIENCY ANAEMIA

In developed countries, iron deficiency anaemia is most commonly caused by chronic blood loss, usually from the gastrointestinal tract or uterus. Poor diet is rarely the sole cause in patients with iron deficiency anaemia in Western Europe. Nonetheless, diet-related iron deficiency remains an important cause of iron deficiency anaemia in the developing world. Malabsorption, particularly related to gluten-induced enteropathy or atrophic gastritis, is an important cause to exclude when considering an alternative aetiology to chronic blood loss. Furthermore, in women displaying iron deficiency anaemia, it is crucial to ask questions pertaining to their menstruation pattern. Extensive vaginal blood loss can be regulated with anti-conceptive drugs. In the event that vaginal blood loss continues, in the presence of an anti-conceptive drug, un-diagnosed von Willebrand disease should be considered. These patients can benefit from the use of tranxenamic acid administration.

Accordingly, the investigation of iron deficiency anaemia should be guided by a thorough history and examination, particularly focusing on causes of blood loss. Table 2 summarises possible investigations for patients presenting with iron deficiency anaemia.

The management of iron deficiency anaemia consists of:

- Identification and treatment of the underlying cause of iron deficiency (e.g., treatment of peptic ulcer disease, treatment of extensive vaginal blood loss during menstruation)
- Correction of the iron deficiency by replacement with iron (oral or intravenous)

In the majority of patients, iron stores can be replenished through the use of oral iron supplements. Typical treatment regimens for iron deficiency anaemia advise 100-200 mg elemental iron per day in one dose (200 mg PO (orally) ferrous sulphate = 65 mg elemental iron).[4] For children and infants, a dose of 3-6 mg/kg (max. 200 mg) daily is advised.[5] However, current evidence would suggest

Table 2. *Investigation of iron deficiency anaemia*

1st line investigations	2nd line investigations	Additional investigations to consider
FBC	Coeliac serology	Zinc protoporphyrin (if normal/raised ferritin, but high suspicion of IDA)
MCV	Faecal occult blood	Blood film
Ferritin	Gastroscopy (upper GI symptoms)	Reticulocyte count
Serum TIBC	Colonoscopy or CT colography (lower GI symptoms)	
Serum iron		

Second-line investigations should be guided by the history and examination.
CT = computed tomography; FBC = full blood count; IDA = iron deficiency anaemia; GI =gastro-intestinal; MCV = mean cell volume; TIBC = total iron binding capacity

that lower doses of iron may be as effective and better tolerated.[6] Haemoglobin should be re-checked after 2-4 weeks of iron supplementation. A haemoglobin rise of 20g/l over 3-4 weeks is indicative of a response. Once the haemoglobin and red cell indices have normalised, iron supplementation should be continued for three months. If faster repletion is required or if gastrointestinal absorption is impaired, intravenous (IV) iron can be an effective treatment modality. Nonetheless, it should be noted that IV iron supplementation requires administration by a healthcare professional and consequently, can increase the burden on healthcare resources. Furthermore, IV Iron therapy is associated with an increased risk of hypersensitivity reaction.[7]

THALASSAEMIAS

In patients with a microcytic anaemia and normal iron studies, a diagnosis of thalassaemia should be considered. Thalassaemia is often associated with a strong family history, and occurs predominately in patients of Mediterranean, Indian, South East Asian, or Chinese descent. Thalassaemias have a highly variable phenotype, ranging from asymptomatic patients to those who are transfusion dependant. Mehtzer's index (MCV/red blood count) can be used as a tool to differentiate between IDA and thalassaemia: - < 13 is suggestive of thalassaemia and > 14 is suggestive of IDA.[8] A recent meta-analysis has demonstrated that although this index is easy to calculate, it is associated with false positives and false negatives. Consequently, this index is best suited as a screening test in combination with other factors (e.g., ethnicity, age).[9] To accurately diagnose thalassaemia, a peripheral blood film and haemoglobin electrophoresis is required. In patients with a high index of suspicion of alpha thalassaemia trait (Chinese, South East Asian, and Indian descent) combined with low MCV and normal Hb electrophoresis, it is recommended that a DNA analysis is performed to detect the alpha thalassaemia gene. An alternative technique for detecting deletions in the haemoglobin alpha gene is multiplex ligation-dependent probe amplification (MLPA).[10] However, MPLA can only detect the seven most common alpha gene deletions. Therefore, if the suspicion of alpha thalassaemia persists and the MLPA testing is negative, further DNA analysis is warranted.

NORMOCYTIC ANAEMIA

A normochromic normocytic anaemia is frequently present in hospitalised patients. Sudden normochromic normocytic anaemia is often as a result of acute blood loss. Chronic normocytic anaemia is predominantly a manifestation of an underlying systemic disorder. This is either as the termed 'anaemia of chronic disease' (ACD) or secondary to another disorder such as renal failure, hypothyroidism, multiple myeloma. Assessment of patients with normocytic anaemia should include a focused analysis of these systemic disorders through a systematic approach including history, examination, and initial investigations (e.g., renal function, immunoglobulins and protein electrophoresis, and thyroid function tests, etc).

ANAEMIA OF CHRONIC DISEASE

ACD is a diagnosis of exclusion that is characterised by functional iron deficiency. Worldwide, it is the second most common cause of anaemia, after iron deficiency anaemia, and is associated with a wide variety of inflammatory, infective and malignant diseases (see figure 1). These chronic inflammatory states cause anaemia to develop due to three pathophysiological mechanisms:

- Altered iron homeostasis due to excess hepcidin production[11,12]
- Reduced production of erythropoietin[13]
- Reduced red cell survival[14]

Anaemia of chronic disease should be considered in patients with a normal/raised ferritin, chronic inflammatory state, low haemoglobin and normal mean cell haemoglobin. It is important to rule out other causes of anaemia (e.g., iron deficiency, haematinic deficiency) before making a diagnosis of ACD.

Figure 1. *Conditions associated with anaemia of chronic disease*

Chronic infection
E.g., osteomyelitis, bacterial endocarditis, tuberculosis, abscesses, bronchiectasis, chronic urinary tract infections
Non-infective chronic inflammatory disorders
Rheumatoid arthritis
Polymyalgia rheumatica
Systemic lupus erythematosus
Inflammatory bowel disease
Malignant diseases
Most commonly metastatic disease
Other associations
Congestive cardiac failure
Ischaemic heart disease
Age > 85 years

It is important to note that in elderly patients, anaemia is more frequent. The prevalence of anaemia in those > 85 years exceeds 20%. Furthermore, a lower haemoglobin (< 110 g/l) was independently associated with a greater mortality.[15] In addition to age, the severity of the anaemia can often correlate with the severity underlying disorder. Therefore, the successful treatment of the underlying disorder has been shown to improve the anaemia.[16,17] However, in some conditions (e.g., heart failure, incurable cancer) it may not be possible to reverse the underlying pathology. There is some evidence demonstrating that IV iron may be able to overcome hepcidin-associated reticuloendothelial blockade of iron. IV iron is not recommended for use in ACD associated with chronic infections, but may be a possible therapeutic option for ACD associated with malignancy or a chronic inflammatory disorder.

ANAEMIA ASSOCIATED WITH CHRONIC KIDNEY DISEASE

Normocytic anaemia is a common finding in patients with chronic kidney disease. This can be managed with erythropoietin stimulating agents (ESA), following consultation with a renal physician. Nonetheless, ESAs should be avoided if the benefits of improving the anaemia are negated by intractable co-morbidities or where the individual patient prognosis does not warrant such an approach.[18,19]

MACROCYTIC ANAEMIA

The causes of macrocytic anaemia are broadly divided into megaloblastic and non-megaloblastic anaemia. Megaloblastic anaemia is characterised by hypersegmented neutrophils and macro-ovalocytes on peripheral blood film, caused by defective RNA and DNA synthesis. These morphological abnormalities are not seen in non-megaloblastic anaemia.

Clinical history and examination are critical to help narrow down the differential diagnosis of macrocytic anaemia. Figure 2 lists the most common causes of macrocytic anaemia. Alcohol, liver disease, and anti-folate drugs (methotrexate) are common causes of macrocytic anaemia that can be identified through focused history taking. Figure 3 shows an algorithm for the further investigation for macrocytic anaemia. B12 and folate deficiency remain the most common reversable causes of macrocytic anaemia and should therefore be routinely screen for in any patient with a macrocytosis.

Figure 2. *Causes of macrocytic anaemia*

Megaloblastic
Vitamin B12 deficiency
Folate deficiency
Anti-folate drugs (e.g., methotrexate, anti-convulsants)
Drugs interfering with DNA synthesis (e.g., cytarabine, hydroxyurea, 6-mercaptopurine, azidothymidine (AZT))
Non-megaloblastic
Alcohol
Liver disease
Myelodysplastic syndrome (MDS)
Haemolysis
Hypothyroidism
Congenital bone marrow failure syndromes

As an initial evaluation of macrocytic anaemia, we recommend performing the following investigations:

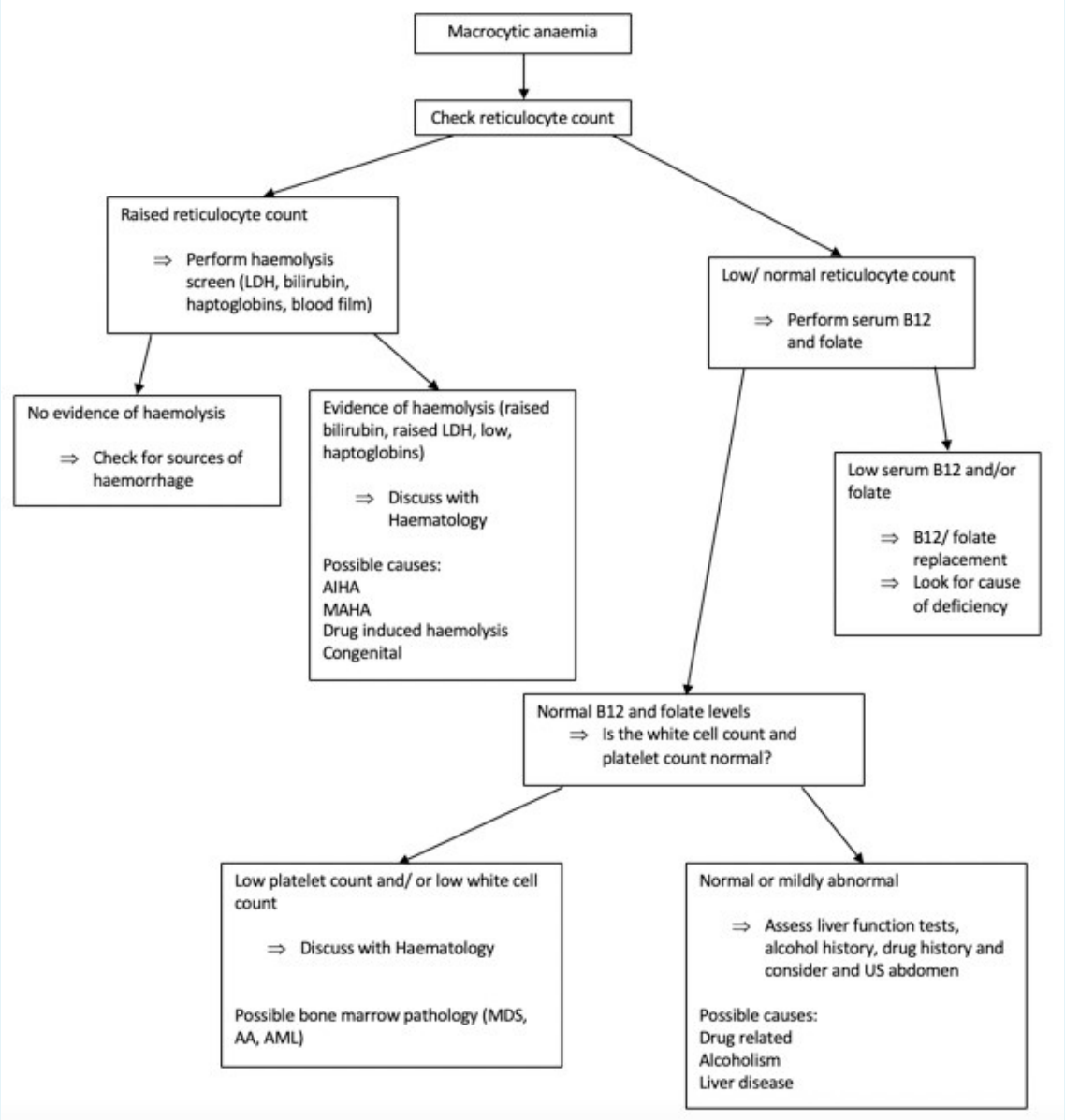
- Serum vitamin B12 and folate
- Peripheral blood smear
  Red blood cell and white blood cell morphology can help establish the underlying cause (e.g., haematinic deficiency, MDS, haemolysis)
- Reticulocyte count
  Raised reticulocyte count indicates increased destruction of red cells (e.g., haemolysis) with an appropriate bone marrow response

VITAMIN B12 AND FOLATE DEFICIENCY

Vitamin B12 and folate deficiency remain the most common causes of megaloblastic anaemia worldwide. Vitamin B12 deficiency remains a common problem in developed countries, despite the fortification of some food groups. Those over the age of 60 years old are at particular risk, with deficiency or mild depletion found in > 20% of those > 60 years old in a United States (US) population-based study.[20]

Folate deficiency has become increasingly rare in countries where certain food groups have been supplemented with folate. Folate fortification of food in the US has reduced the prevalence of folate deficiency to < 1% of the population.[21] However, in countries where the supplementation of foods does not occur, folate deficiency is subsequently more frequent.[22] A 2015 report on a UK-based epidemiological study published serum folate levels below the WHO threshold for folate deficiency in 15.5% of men and 13.9% of women aged 19-64 years.[23]

Figure 3. *Algorithm for the investigation of macrocytic anaemia*



AA = aplastic anaemia; AIHI = autoimmune haemolytic anaemia; AML = acute myeloid leukaemia; LDH = Lactate dehydrogenase; MAHA = microangiopathic haemolytic anaemia; MDS = myelodysplastic syndrome

The underlying aetiology of B12 and folate deficiency is outlined in table 3. Although serum folate and serum B12 (cobalamin levels) are readily available and easy to perform tests, they are both associated with significant false-negative rates. Therefore, in instances where the clinical suspicion of B12 deficiency and serum B12 levels are borderline, it is recommended to perform methylmalonic acid levels or Holotranscobalain levels.[24] Similarly, in the presence of strong clinical suspicion of folate deficiency, but a persistently normal serum folate level (and B12 level), a red cell folate assay may be undertaken. Importantly, this assay is not available in all laboratories and is less cost effective.[25]

HAEMOLYTIC ANAEMIA

The term haemolytic anaemia encompasses anaemias caused by increased red cell turnover, due to abnormal breakdown of red blood cells. This broad category of anaemias includes microangiopathic haemolytic anaemias, autoimmune haemolytic anaemia, haemolysis-associated

Table 3. *Summary of the aetiology of vitamin B12 and folate deficiency*

Patient population	Vitamin B12 deficiency	Folate deficiency
All age groups	**Inadequate dietary intake** Strict vegan diet at increased risk **Malabsorption** Pernicious anaemia **Medical conditions** Gastric resection Bariatric surgery Coeliac disease Upper GI tract inflammation (e.g., Crohn's disease) **Infective cause** *Helicobacter pylori*, giardia	**Inadequate dietary intake** **Malabsorption** Coeliac disease Upper GI tract inflammation (e.g., Crohn's disease)
Infants and children	**Congenital disorder** Transcobalamin deficiency Cobalamin mutations **Inadequate dietary intake**	**Congenital disorder** Mutations in the SLC46A1 gene (proton-coupled folate transporter deficiency)
Older persons	**Malabsorption** Proton pump inhibitors (achlorhydia) Gastritis	**Malabsorption** Poor bioavailability

Table 3 summarises the most common causes of B12 and folate deficiencies in the relevant population groups.[24] GI = gastrointestinal

inherited red cell disorders, transfusion-related haemolysis, and haemolysis as a result of drugs, infections, or burns. An elevated reticulocyte count indicates increased red cell turnover and should raise the possibility of haemolysis. Other laboratory markers of haemolysis are:

- Raised lactate dehydrogenase
- Raised bilirubin
- Low haptoglobins
- Peripheral blood smear: spherocytes, bite cells, schistocytes (dependent upon the cause of the haemolytic anaemia)

Patients presenting with features of haemolytic anaemia should be discussed with a haematologist for further advice on investigation, management, and potential referral.

OTHER CAUSES OF MACROCYTIC ANAEMIA

Alcohol and liver disease remain important causes of macrocytosis and macrocytic anaemias. A full medical, drug, and social history should be included in the initial work-up of macrocytic anaemia. Alcoholism is a common cause of macrocytosis in the UK, and alcohol-induced anaemia may persist even after months of abstinence. A history of liver disease or stigmata of chronic liver disease on examination should prompt consideration of liver disease-related anaemia.

Myelodysplastic syndrome and other bone marrow failure syndromes are also important causes of anaemia. In bone marrow pathologies, normocytic or macrocytic anaemia often occurs in combination with thrombocytopenia and/or leucopenia. Peripheral blood film should be performed to look for distinctive morphological abnormalities (e.g., Pseudo Pelget Huet cells, immature granulocytes), which can help guide whether a patient requires further investigation with a bone marrow biopsy.

DISCLOSURES

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ORIGINAL ARTICLE

Care for adult non-ICU Covid-19 patients: early experiences from a Belgian tertiary care centre

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ABSTRACT

The current Covid-19 outbreak poses many challenges on hospital organisation and patient care. Our hospital lies at the epicentre of the Belgian epidemic. On April 1st, a total of 235 Covid-19 patients had been admitted to our hospital. This demanded an unprecedented adaptation of our hospital organisation, and we have met many clinical issues in the care for Covid-19 patients. In this article, we share our experience in the handling of some of the practical and organisational issues in the care for Covid-19 patients.

KEY WORDS

Clinical care, corona, Covid-19

INTRODUCTION

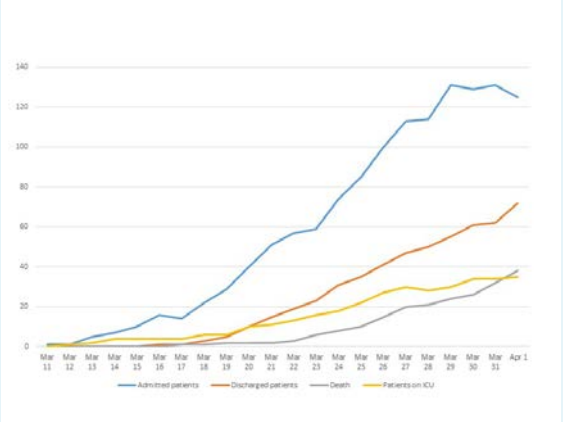
On February 3rd, 2020, the first case of SARS-CoV-2 (Severe acute respiratory syndrome – Coronavirus-2) infection was diagnosed in Belgium in an asymptomatic patient who was quarantined after evacuation from Wuhan, China. On February 29th, the second Belgian patient was admitted to the Antwerp University Hospital after travel from France.[1] Since then, there was a rapid rise in cases, with 13964 confirmed cases, 6132 admissions, and 828 deaths as of April 1st.[2] Limburg Province has become the epicentre of the Belgian outbreak with the highest incidence across the country. Jessa Hospital is a 981-bed non-academic tertiary care centre, located in the centre of the Limburg Province in Belgium. In our hospital, the first diagnosis of the coronavirus disease-2019 (Covid-19) was made on March 3rd in an ambulatory patient and the first patient was admitted on March 11th. As of April 1st, a total of 235 patients had been admitted to our hospital of whom 72 were discharged, 38 died, and 125 are still in the hospital (figure 1).

In this article, we would like to share our experience in the handling of some of the practical and organisational issues in the care for Covid-19 patients.

ORGANISATIONAL MEASURES

We started preparing for the upcoming outbreak six weeks before the first patient was admitted, when an outbreak management team was installed. Since then, we

Figure 1. *Local epidemiology of Covid-19 patients*



encountered many challenges in the organisation and care for Covid-19 patients. In a timeframe of only a few weeks, a large hospital had to be transformed into a 'Covid' hospital that would be able to treat a large number of Covid-19 pneumonia patients, while at the same time, be able to ensure safe urgent care for non-Covid-19 patients. Close follow-up of data and information from China, Singapore, Italy, and other affected countries was paramount in this organisational transformation. Supported by governmental measures, we cancelled all consultations, ambulatory surgery, and elective admissions.

We implemented general principles for hospital disaster preparedness from the beginning. As stated in the official Belgian emergency plan, the Chief Medical Officer (CMO) of the hospital was granted expanded authority to implement the measures needed to cope with the epidemic. In the deployment of admission capacity, a ratio of 1:4 (ICU : non-ICU patients) was used to estimate the intensive care capacity needed. We increased the number of intensive care unit (ICU) beds from 48 to 60 (and in extreme conditions expandable to 70) by transforming a large part of our operating rooms into an ICU. Since the Jessa Hospital is a reference centre for cardiology and oncology, we were able to convince the authorities that 40% of our full intensive care capacity needed to be reserved for non-Covid-19 patients such as, for example, urgent cardiac surgery and surgical oncology.

Our experience so far shows that pro-active communication of planned organisational measures is of crucial importance. In a daily newsletter, full transparency was created to all physicians about the hospital metrics of COVID-19 and the national and international evolution of the epidemic, as well as all organisational adaptations needed to cope with the expected surge of Covid-19 patients. In addition, the press officer of the hospital informed both the local and national media from the beginning of the numbers of admissions, deaths, and discharged COVID-19 patients.

In the implementation of the transformations of the emergency department (ED), ICU, and multiple standard wards towards COVID-wards, our general principle was to stay at least one week ahead of the epidemic impact. In reality, this provided a timeframe of several days in which both physicians and nurses could adapt to their new ward and receive education on, for example, the use of protective measures and other protocols before the first patients were admitted.

As much as possible, existing teams of physicians and of nurses were kept together on the new wards. At the start of deployment, pulmonologists, geriatric physicians, and infectious disease specialists were responsible for to the first wards. Quite rapidly, all specialists in internal medicine of the hospital were appointed to a specific Covid-19 ward. Since all elective surgery was cancelled, we were able to integrate the majority of anaesthesiologists within the team of intensive care specialists to supervise all Covid-19 ICUs. We also reserved part of a paediatric ward for Covid-19 and created a small unit for Covid-19 postnatal care.

In the final stage of deployment, these teams of internal medicine specialists – taking into account that we expected up to 20% of physicians to be affected by Covid-19 and would be on sick leave for 1-2 weeks - were supported by a backup of specialists from surgical disciplines.

Empirically, the ratio of geriatric versus non-geriatric wards was about 1:1. Nightly permanence on-site had to be doubled for nurses on the wards, and tripled for intensive care specialists for the Covid-19 ICUs and for supervision of the multiple regular Covid-19 wards.

Notably, we were able to control the number of inappropriate referrals to the ED by establishing an integrated care Covid-19 protocol with local general practitioner (GP) circles. The local GPs created and manned a specific Covid-19 referral centre for GPs, located next to the hospital. Based on elaborate ethical triage measures, admission policy from local residential care homes for Covid-19 intensive care was also highly restricted.

ORGANISATION OF THE CLINICAL PATIENT FLOW

From the start of the epidemic, the ED was separated into a corona unit and a corona-free unit. Patients with possible Covid-19 were seen by emergency physicians in a separate location within the ED department where three linked rooms provided a waiting space, a patient assessment room with a negative-pressure system in place, and a dressing room for personnel. From there, the patient was admitted to an isolation negative-pressure room in the Pulmonology Department while awaiting test results. Soon it became clear that the influx of patients would outnumber the capacity of the ED and the pulmonology ward. Therefore, on March 13th two transit wards were opened with 20 beds each. All patients who were triaged in the ED with possible Covid-19 based on clinical assessment, arterial blood gas test, and indication for hospital admission were tested for SARS-CoV-2 by nasopharyngeal swab and subsequently admitted to one of the transit departments for further clinical assessment while awaiting test results. Patients with a geriatric profile, defined as over 75 years of age and/or with multiple comorbidities were admitted to a ward supervised by a geriatric specialist. All other patients with possible Covid-19 virus were admitted to a ward supervised by an infectious disease specialist. As soon as the test results became available, the patient was transferred to a non-Covid-19 ward in cases of a negative results or to

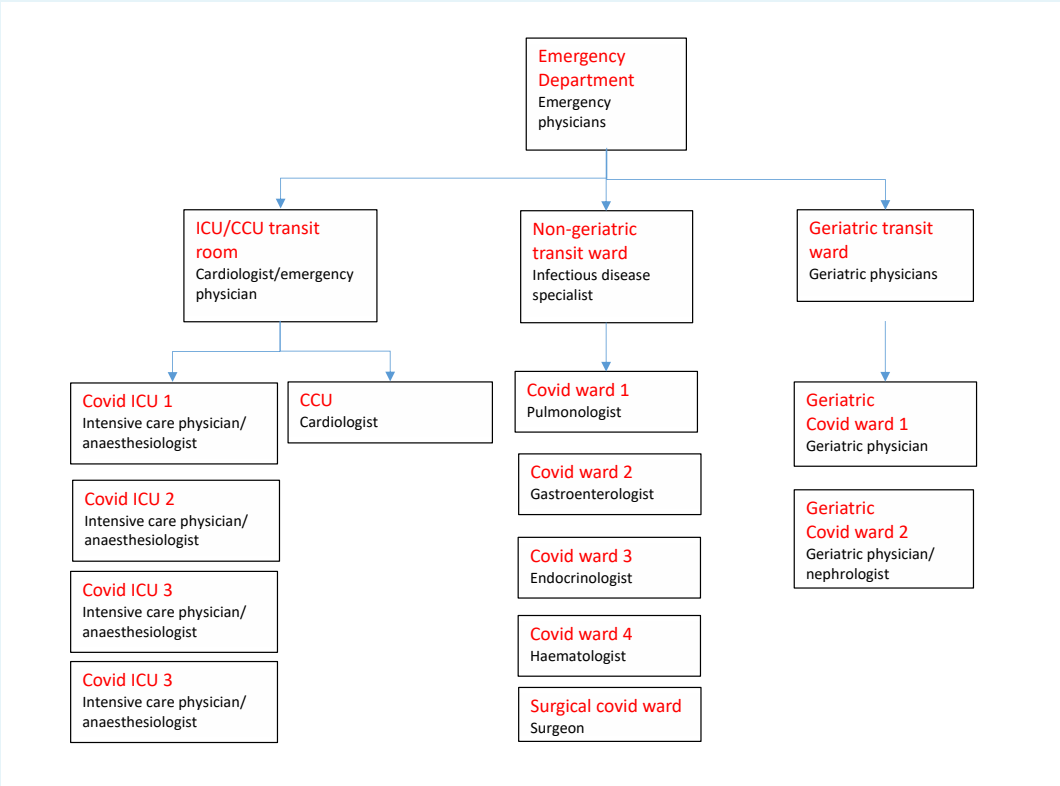
a dedicated Covid-19 ward in cases of a positive result. In addition, in the geriatric corona ward a section of eight beds was reserved for palliative care.

Initially, patients with suspected Covid-19 who presented at the ED and who needed immediate intensive care or cardiac monitoring were directly transferred to a dedicated corona ICU unit (with 14 beds) without awaiting the SARS CoV-2 PCR results. However, to prevent nosocomial transmission of Covid-19 to patients with a Covid-19-negative test, one intensive care room ('crash box') was created at the non-geriatric transit ward where intubation, ventilation, vasopressive support, and cardiac monitoring could be performed while awaiting test results. In addition, for patients who needed emergency surgery for any reason and were Covid-19 positive, a dedicated surgical ward was opened for optimal post-surgical care. This ward also functioned as a post-intensive care rehabilitation unit. With the increase in Covid-19-patients, subsequential Covid wards were opened. On April 1st, a total of 10 Covid wards and 5 ICU wards were operational (figure 2). This resulted in a total capacity of 200 Covid beds including 41 ICU beds.

DIAGNOSIS

We noted a remarkable similar preadmission disease course in most patients, which reflects the first reports from China.[3,4] The disease starts with mild respiratory symptoms, fever, and malaise. During the course of 5-8 days there is a gradual progressive dyspnoea. Although during the course of the epidemic, it became clear that a significant portion of patients present with atypical symptoms such as anosmia, abdominal pain, vomiting, and diarrhoea.[5,6] Triage criteria in the ED were adjusted accordingly. Findings in laboratory evaluations that we see also reflect the first clinical reports.[6,7] The combination of elevated lactate dehydrogenase (LDH), elevated ferritin, a decreased partial pressure of oxygen (pO2) and partial pressure of carbon dioxide (pCO2) in arterial blood gas, and lymphocytopenia is almost universal. The C-reactive protein (CRP) levels may vary considerably. Nasopharyngeal swabs were analysed with an in-house developed reverse-transcriptase PCR for the *E-gene* on the ARIES analyser (Luminex Corporation). Test results were available within three to four hours. Additionally, a chest X-ray was performed for all suspected cases.

Figure 2. *Organisation of patient flow*



CCU = critical care unit; Covid = our abbreviation for units/wards transformed for care of patients with Covid-19; ICU = intensive care unit

A dilemma arises in patients with a high clinical suspicion and a negative PCR test result. The exact sensitivity of the test depends on the location where the swab was taken and the duration of symptoms, and is obviously influenced by the sampling technique of the person collecting the swabs.[8] Training of personnel in correct sampling technique was therefore provided with online instructional videos.

In patients with a clinical suspicion based on history, laboratory and/or chest X-ray results, and a negative initial PCR test, the following strategy was adopted: a second nasopharyngeal swab was taken after 24-48 hours. If it is possible to collect a deeper sample such as sputum, the PCR is repeated on this sample. If a patient is intubated, a lower respiratory tract aspirate is collected, as this has been shown to be more sensitive than a nasopharyngeal swab.[8,9] In the second sample, additional screening for other viral pathogens and atypical bacterial pathogens by PCR is performed. While awaiting the second test, a urinary antigen test for *Streptococcus pneumoniae* and *Legionella* species is done, and additional serological testing for HIV is performed. When the additional investigations are all negative, a chest computed tomography (CT) scan is performed to evaluate for typical signs of viral pneumonitis (peripheral ground-glass opacities and/or mixed consolidations).[10] If the CT scan is suggestive of COVID-19 and no other diagnosis is established, the patient is considered as having COVID-19. During all these investigations, the patient remains in isolation in the transit wards.

To date, we have identified 10 patients where a second nasopharyngeal swab tested positive after a first negative test. In addition, we saw one patient with two negative nasopharyngeal swabs, who tested positive on a lower respiratory tract aspirate taken after intubation. Studies are needed in order to develop the best strategy in these situations.

THERAPY

As there is currently no specific evidence-based antiviral therapy for Covid-19, patients were treated with optimal supportive care, including oxygen therapy.

Covid-19 stewardship team

To support the physicians on the Covid-19 wards and to guarantee a uniform approach throughout the hospital, we installed a Covid-19 stewardship team. This team includes an infectious disease specialist, a pulmonologist, a clinical microbiologist, and a clinical pharmacist. The team visits the different Covid-19 wards and ICU twice a week to discuss any issues on therapy and other patient care with the treating physician. In addition, a hospital clinical guideline containing all Covid-19 related procedures was available through the hospital intranet and distributed actively to all physicians supervising Covid units. This document continues to be updated twice a week.

Hydroxychloroquine

Patients were offered hydroxychloroquine if they met the criteria defined by the Belgian national guideline for treatment of Covid-19.[11] Preferably, an echocardiogram (ECG) was performed before the start of hydroxychloroquine treatment to rule out QTc prolongation. However, we decided that in patients without risk factors for QTc time prolongation (history of cardiovascular disease, bradycardia < 50/min, hypokalaemia, hypomagnesaemia, renal insufficiency, hepatic insufficiency, other QTc prolonging drugs) hydroxychloroquine could be started and the ECG was to be performed the next day. In patients with a QTc > 500 ms, hydroxychloroquine is not started or is stopped. In patients with a QTc between 450 and 500 ms, a daily ECG was conducted. If QTc time is < 450 ms, there is no follow-up ECG.

Empiric antibiotic therapy

Because little was known about possible bacterial superinfection, we initially decided to start empiric antibiotic therapy with amoxicillin-clavulanic acid for five days in all patients with pulmonary infiltrates on chest X-ray. However, we changed this policy because, based on our clinical judgement, antibiotics were unnecessary in many patients. In addition, we noticed that in patients admitted to the ICU, there was a tendency of early empirical switch to broader spectrum antibiotics such as piperacillin-tazobactam in cases of clinical deterioration. After a consultation round with our infectious disease specialists, pulmonologists, clinical microbiologists, and intensive care physicians we reached a consensus to limit empirical antibiotics to patients with signs of bacterial pneumonia. This was arbitrarily defined as patients with at least one of the following: leucocyte count > 15,000 $*10^6$/l, cough productive with sputum, or a lobar infiltrate on radiology.

Prevention of thromboembolism

Covid-19 is a pro-thrombogenic condition. A recently published study showed that therapeutic doses of anticoagulation with low molecular weight heparin (LMWH) decreases mortality in patients who need ICU care and in patients with a D-dimer of > six times the upper limit of normal.[12] We give all our patients with Covid-19 LMWH in prophylactic dosage unless there is a clear contraindication or if the patient already uses therapeutic anticoagulants.

Fluid resuscitation

Acute respiratory distress syndrome (ARDS) is a frequent complication of Covid-19 with high mortality.[3,4,6] Previous studies have shown that in general, restrictive fluid

policies prevent ARDS in intensive care patients.[13] On the other hand, many ICU patients develop acute tubular necrosis.[14] Therefore, it is a delicate balance to restrict fluid administration but also prevent hypovolaemia.

Bronchodilators

Bronchospasm is infrequent in our patients without history of bronchial asthma or COPD. In patients who do need bronchodilators, we try to give inhalation medication only through a dose inhalator with spacer to prevent excessive exposure of health care workers to contaminated aerosols.

Psychosocial support team

A Corona support team was formed to support patients and families in addition to the regular support provided by medical staff. The Corona support team consists of a psychiatrist and psychologist who visit the Covid-19 wards at fixed hours on a daily basis. In addition to psychosocial support to patients and families, the Corona support team is also available for psychological support of health care professionals.

DISCHARGE AND FOLLOW-UP

Initially, we noticed a reluctance to discharge patients who were hospitalised in a ward supervised by physicians who have less experience with patients with pneumonia because of fear of late clinical deterioration. In our experience, however, sudden clinical deterioration is unusual in patients who show a consistent clinical improvement. We have adopted the following rule of thumb to discharge a patient: All patients who do not need oxygen for 24 hours AND have a $sO_2 \geq 94\%$ AND no apparent respiratory distress AND temperature < 38°C in last 48 hours are discharged. In addition, patients with a clear clinical improvement who need ≤ 2 l O_2/min are also discharged with home oxygen supply. All patients are instructed to contact the hospital in case of clinical deterioration. As of April 1st only 3 of 72 discharged patients have been readmitted because of late clinical deterioration.

CONCLUSION

We have faced many challenges with the onset of the Covid-19 outbreak in our region. The situation is constantly evolving with continuing great impact on our health care system. The extraordinary transformation of the hospital organisation and multiple care processes was undertaken using principles of hospital disaster preparedness with, as much as possible, pro-active deployment of hospital capacity, in an attempt to stay ahead of a possible collapse of the local health care system. In our experience, it has been useful to install transit wards where patients wait for their SARS-CoV-2 PCR test results. This prevents an overflow of the ED and unnecessary contact between Covid-19-negative and Covid-19-positive patients. In addition, because of the scale of the outbreak, physicians with different specialities are currently involved in the care of Covid-19 patients. This complicates a uniform policy for admitted patients. We have adopted a hospital-wide guide on the care of Covid-19 patients and have installed a multi-disciplinary Covid-19 stewardship team. A clear internal and external communication policy proved to be paramount to ensure an unforeseen organisational transformation of this large tertiary hospital.

In this paper, we have shared our experiences and we hope that this may be useful for other hospitals during the current crisis.

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ORIGINAL ARTICLE

The implementation of POCUS and POCUS training for residents: the Rijnstate approach

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ABSTRACT

Point-of-care ultrasound (POCUS) is gaining interest in intensive care medicine and good reviews and guidelines on POCUS are available. Unfortunately, how to implement POCUS and practical examples how to train staff and junior doctors is not well described in literature. We discuss the process of POCUS implementation, and a POCUS training program for residents prior to their intensive care rotation in a Dutch teaching hospital intensive care unit. The described four-day basic POCUS course consists of short tutorials and ample time for hands-on practice. Theoretical tests are taken shortly before, on the last day of the course, and after three months to assess learning retention. Practical tests are taken on the last day of the course and after three months. We stress the importance of POCUS for intensive care and hope that our experiences will help colleagues who also want to go forward with POCUS.

KEY WORDS

Implementation, intensive care, point-of-care ultrasound, training program

HIGHLIGHTS

- A stepwise implementation strategy for POCUS is presented
- Implementation of POCUS requires: training of staff, defining components of basic and advanced POCUS, and training of junior staff
- Support by radiology and cardiology departments can be of significant value in the acquisition of POCUS knowledge
- A course curriculum for residents in internal medicine is presented
- POCUS beginners should know their own limitations and ask for help without hesitation

INTRODUCTION

Today, point-of-care ultrasound (POCUS) is considered an important tool for intensivists.[1] Reviews and guidelines on POCUS are published but there is still debate surrounding it, including definitions, content, and training requirements,[2-8] but POCUS is still considered an indispensable tool for every intensivist.[8,9] Although recognised as an important skill by national societies, POCUS is trained differently in various countries.[10] In the Netherlands, the Dutch Society for Intensive Care (NVIC) provides a basic course (two days on heart and lungs) and a consolidation course in which 40 supervised heart/lung ultrasound exams are included.

In addition to intensivists, the Dutch Society of Internal Medicine recently decided that residents in internal medicine should also be trained in POCUS; a national training program is under construction with some aspects already published.[11]

While literature provides professionals with theoretical guidelines on how to use POCUS, there is far less literature discussing the practical issues of implementing and training in POCUS. The Rijnstate Hospital Department of Intensive Care has used POCUS since 2009 and in 2017, implemented a training program for residents in internal medicine prior to their intensive care rotation. In this narrative review, we share our experiences with the process of implementing POCUS and how we designed our resident POCUS training program on the basis of current literature. We have received questions from colleagues from other hospitals on these issues and hope that by publishing our experiences, both successes and weakness,

we can inform and help other educators who want to develop their own local educational POCUS program.

1. IMPLEMENTING POCUS

This section is divided into three elements: the start, equipment, and collaboration.

1.a. The start

With the increase in publications on the use of POCUS in intensive care, the intensivists of the Rijnstate Hospital Intensive Care Department decided in 2009 that they also wanted to use this technique. Within a week of this decision, the process of POCUS training and implementation was initiated, and training in the basics of cardiac and lung POCUS were provided by an Australian team of POCUS experts (Marek Nalos et al, Nepean Hospital, Australia), a week prior to an international ICU congress. This training-on-the-job approach led to a leap in knowledge and ability to perform basic cardiac and lung ultrasounds by all members of the intensive care staff. Three out of 10 intensive care staff members added skills for abdominal ultrasound by attending a basic abdominal ultrasound in Dusseldorf Germany (Matthias Hofer; http://medidak.de/semester/sono) and during daily practice, all staff members and residents were trained in using ultrasound during insertion of central venous catheters. As of the writing of this manuscript, the entire intensive care staff is trained in at least basic cardiac and lung POCUS. Two of the staff members are more experienced and participate in national training programs for POCUS for the Dutch Intensive Care and Internal Medicine Societies In our experience, the simultaneous training of the entire staff helped boost POCUS use in our department and we would recommend this approach.

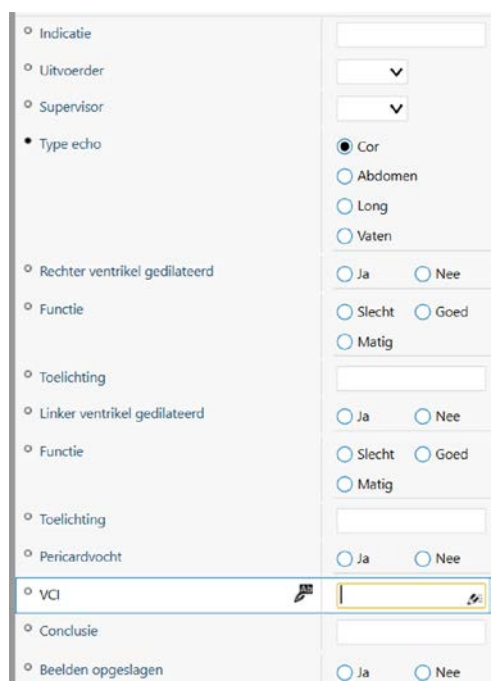
Success: Every intensivist in our intensive care department is trained in basic lung and cardiac POCUS. All procedures, such as the insertion of central lines are guided by the real-time use of ultrasound.

We published our view on POCUS content,[12,13] and have integrated POCUS into our daily practice. Today, ultrasound is part of daily care at the Rijnstate Intensive Care Department. In almost all patients, thoracic ultrasound is performed during or shortly after admission and if indicated, also abdominal ultrasound (for example, of the kidneys in cases of urosepsis). Ultrasound is also performed in cases of clinical deterioration. POCUS exam results can be described in our electronic health record (figures 1, 2, 3, and 4, in Dutch).

We are involved in scientific ultrasound research projects, both self-instigated[14,15] and in collaboration with other institutes,[16] and are currently investigating the use of POCUS for our emergency team; other projects are in preparation.

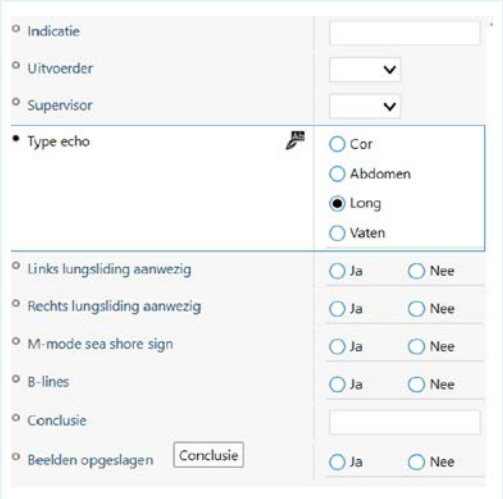
Weakness: The acquisition and retention of POCUS skills took almost a decade and still, not every intensivist in our

Figure 1. *Cardiac POCUS*



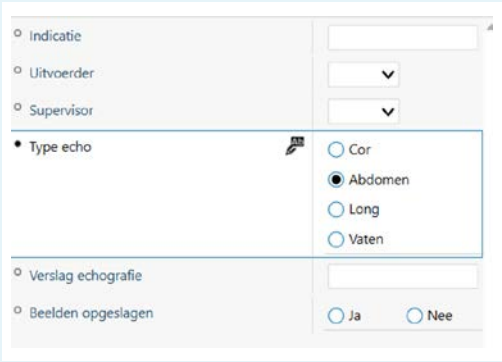
POCUS = point-of-care ultrasound; VCI = vena cava inferior

Figure 2. *Lung POCUS*



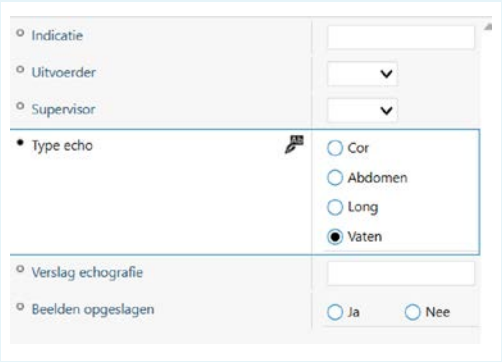
POCUS = point-of-care ultrasound

Figure 3. *Abdominal POCUS*



POCUS = point-of-care ultrasound

Figure 4. *Vascular POCUS*



POCUS = point-of-care ultrasound

department has the same POCUS skills. Reasons for the time needed: some have more interest in POCUS than others and POCUS skills must be learned without a pause in daily routine and night shifts. The development of these skills on our ward is not very different from what the literature reports. Although POCUS is seen as an important tool, it is not used on every patient,[17] and there are intensive care colleagues who state that an intensivist can still be a good intensivist in the absence of POCUS skills.[18]

How can we speed up this process? First, by training internal medicine residents, the use of POCUS in the intensive care department will be stimulated. Forty-four percent of Dutch intensivists have internal medicine as their primary specialism (data from NVIC, personal correspondence), meaning that in the near future, these intensivists will already be trained in basic POCUS. A basic ultrasound course is also advised to residents in anaesthesiology but is not obligatory (https://www.anesthesiologie.nl/uploads/files/Opleiding_LOP2019NVA.pdf); 40% of Dutch intensivists have anaesthesiology as their primary specialism (data from NVIC, personal correspondence). At this moment, there is no national obligatory ultrasound training program for intensive care fellows (https://nvic.nl/sites/nvic.nl), although most fellows will come across POCUS during their fellowship and will be trained on the job. We speculate that in the near future, the Dutch board for intensive care training (GIC) will present formal ultrasound training requirements for fellows which will speed up POCUS implementation in the Netherlands.

In the meantime, current intensive care staff should be motivated to enrol in at least a basic POCUS course. The NVIC basic course is always fully booked, but there are other (inter)national courses (www.deus.nl, https://www.esicm.org/education/courses-2/lives-mc-basic-course-echocardiography/). Publications like our paper can help generate awareness of POCUS and can stimulate colleagues to start a POCUS implementation process on their own intensive care departments.

It is a challenge to train all intensivists, fellows, and residents in POCUS, and unfortunately, there are too few available educators to train the large number of physicians. Although guidelines exist on the requirements for the POCUS learner on how to achieve competence, there are less-clear guidelines for the requirements of POCUS-educating staff. POCUS trainers can be physicians from different disciplines, preferably certified in echocardiography, but should at least have significant experience in critical care ultrasound.[6] In our situation, we combine the knowledge of experienced intensivists (without formal advanced certification) with the knowledge of cardiology and radiology colleagues, who are co-authors of this paper.

Some larger intensive care departments may have one or more cardiologists on staff. According to most guidelines, a fully trained cardiologist can be seen as an advanced ultrasound user, thereby capable of educating others in basic cardiac ultrasound. For intensive care departments without a cardiologist, close cooperation with the local cardiology department is advised.[19] An alternative way of ensuring advanced skills is to have one or more intensive care staff members follow an advanced cardiac ultrasound course, for example, the European Diploma in advanced critical Echocardiology (EDEC, https://www.esicm.org/education/edec-2/), but this requires a significant time investment. To our knowledge, there is no advanced abdominal ultrasound course for intensivists, meaning that for expert help, local radiology departments should be available.

1.b. Equipment

In our opinion, every intensive care department should have their own ultrasound equipment. Today, even the handheld machines are capable of producing adequate images and the development of portable ultrasound

systems has contributed to the increased use of POCUS,[20] but one should be aware of their shortcomings.[21] In this article, we will not discuss the various options; we chose to obtain two high-end ultrasound machines (Philips Affinity) for optimal image quality. In particular, in the beginning when trying to acquire reasonable ultrasound images, it is wise to use an ultrasound machine with optimal image resolution. A hand-held ultrasound device (Philips Lumify) is attached to our emergency trolley and can be used during medical emergency calls in the hospital.

In addition to data storage on the ultrasound machine itself, we encourage the use of digital image storage facilities to be able to re-assess ultrasound examination for quality or educational purposes.

Success: Both our two intensive care wards have their own high-end ultrasound machines and are connected by WIFI to a digital storage facility.

Weakness: We became highly dependent on our ultrasound machines and, in the beginning, had some technical challenges that were resolved together with the Department of Technical Engineering. We advise having a spare machine available in case of break-down or maintenance.

1.c. Collaboration

From the start, we involved the radiology and cardiology departments in our plans. We have previously reported on POCUS as an important tool for intensive care and that this development was embraced by not only international intensive care societies but also by cardiology societies as well.[3-5,22,23] We asked the departments of radiology and cardiology to assist us in our ambitions by helping us train our staff, and later our residents, and to share their ultrasound experience and skills. Their involvement enables them to actively contribute to our training program, and by training together, we emphasise the difficulty of ultrasound and the need to be critical towards the acquired ultrasound skills.[24] In many cases, the radiology or cardiology departments currently receive much more precise clinical questions from the Intensive Care Department because the POCUS examination is performed upfront. In addition, POCUS is likely to become more widespread and thus, we have an opportunity to shape an effective training program; this view is shared[3,4] by scientific cardiology ultrasound societies. The storage of POCUS examinations is encouraged in order to be able to evaluate POCUS examinations afterwards.

During the start of POCUS training, we also collaborated with the pulmonology department, even though they too, were beginners at ultrasound. We still do ultrasound projects together, and recently the Departments of Pulmonology, Radiology, and Intensive Care published a handbook for pulmonary ultrasound (*Springer Healthcare Benelux ISBN/ISSN 9789492467225, July 22, 2019, Echografie van de thorax, Corien Veenstra, Michiel Blans et al*).

Success: We were fortunate that our cardiology and radiology colleagues were willing to help. Since we were able to discuss our plans in advance, we could take advantage of their advice and consider justified concerns. We were aware of the absolute prerequisite that we had to implement ultrasound in a safe and responsible way. After many years of (inter)national experience with POCUS in the Intensive Care Department, we hope that, in the Netherlands, the controversy on this topic will disappear and we encourage intensive colleagues to discuss POCUS with their cardiology and radiology colleagues. We acknowledge the differences between a POCUS study performed by one of our intensivists, compared with a fully comprehensive 'normal' ultrasound study completed by our cardiology or radiology departments, and we have discussed this with both departments prior to developing our program. POCUS is aimed at detecting a limited number of acute clinical problems and its results are immediately useful. This method of using ultrasound is different from the comprehensive ultrasound studies done by cardiologists, radiologists, or their ultrasound technicians. Usually, the latter ultrasound studies are not aimed at a specific clinical situation, but are more often done by examining the heart or all abdominal organs using a fixed framework, with the results given afterwards. Major intensive care and ultrasound scientific organisations state that POCUS can be performed by intensivists, but that it is important that the intensivist using POCUS knows his or her own limitations in ultrasound skills and asks for help if needed.[3,6,20,25] POCUS and 'normal' ultrasound can therefore be seen as complementary; POCUS is not a replacement of a 'normal' ultrasound or other radiology modalities.

Weakness: On an individual level, there are still some colleagues in our hospital who are less enthusiastic about the intensive care department performing their own ultrasound exams; so far, this not resulted in serious conflicts. To date, no ultrasound-related incidents in direct patient care in our VIM database (hospital system for medical errors) have been registered.

2. TRAINING RESIDENTS

The Dutch Society for Internal Medicine has recently stated that POCUS is an obligatory element in the curriculum for internists (Landelijk opleidingsplan 2019). By designing a POCUS training program for intensive care residents, we combined both our own ambition to have staff and residents trained and the obligation to have Dutch residents in internal medicine trained in POCUS. Our aim is to

have residents trained in POCUS before they start their intensive care rotation. Residents in internal medicine or its subspecialties in Rijnstate rotate through intensive care in their second year of residency and this rotation lasts 4-6 months. There are also residents in the Rijnstate Intensive Care Department who are not in training but do the same work as residents in training; on average, residents not in training stay in the department for one year. Residents not in training also participate in the POCUS course and are encouraged to use POCUS regularly.

In the Rijnstate Hospital, the POCUS course is scheduled three times per year with the possibility to train 10 candidates each time. We started our course in 2017 and until now, have trained 64 residents, all courses are fully booked.

We decided that not only internists in training can be candidates for the course, and also ask residents who have an obligatory intensive care rotation (such as cardiology and pulmonology residents) to participate. This means that a far larger number of residents need to be trained. In Rijnstate, each year, five physicians start their internal medicine training program but the number of residents from other specialties is about five times higher.

Key issues of POCUS curricula are becoming more clear but evidence about the precise content and duration of a training program is limited.[26,27] In our view, only POCUS of the heart and lungs is insufficient as intensivists and internists are also confronted with acute abdominal pathology.[28,29] We decided to combine basic thoracic and abdominal POCUS, and our view on the components of basic POCUS was recently published.[13]

Table 1. *Components of POCUS training*

Image generation	
General introduction	The student will learn the basics of ultrasound (knobology, pitfalls, etc.) The student will learn to perform ultrasound exams using established protocols The student will learn basic ultrasound; no colour Doppler The student will learn when ultrasound can be of added value and when more expertise is warranted
Cardiac POCUS	Basic image generation: PLAX, PSAX, A4C, SC, SC-IVC
Lung POCUS	Determine the presence or absence of lungsliding Recognize A & B lines Recognize pleural fluid
Abdominal POCUS	Recognition of normal anatomy (liver, gallbladder, kidneys, spleen, pancreas, large vessels and movement of the bowels Recognition of normal anatomy in the pelvic region (bladder, prostate, uterus, adnex Recognition of intra-abdominal fluid The e-FAST exam (focused assessment by sonography in trauma)
Vascular POCUS including neck	Recognition of large vessels Correct use of ultrasound in performing vascular cannulation Normal anatomy of neck

A4C = apical 4 chamber view; PLAX = parasternal long axis; POCUS = point-of-care ultrasound; PSAX = parasternal short axis; SC = subcostal view; SC-IVC = subcostal inferior vena cava

3. TRAINING PROGRAM

The Rijnstate POCUS course for residents consists of three key areas,[8] which will be described hereafter: a. image generation, b. image interpretation, and c. clinical integration.

3.a. Image generation

After a general lecture on the theoretical background of ultrasound and possible pitfalls, the course participant is trained in acquiring the pre-defined appropriate images (table 1).

Short tutorials on every component of POCUS are followed by hands-on sessions under supervision in which the candidates use each other as mannequins. The morning sessions are under supervision of the radiology department and during morning hours, abdominal ultrasound is the main topic. The afternoon sessions are under responsibility of the intensive care and cardiology departments and during afternoon hours, the focus is thoracic ultrasound (heart and lungs).

During the hands-on sessions, the number of candidates per ultrasound machine should be limited. In our experience, the optimal number of candidates per ultrasound machine and tutor is 3:1. The tutors should be experienced and qualified ultrasound experts.

The Rijnstate basic POCUS course consists of four days (Monday, Tuesday, Thursday, and Friday). Residents often have other educational obligations on Wednesdays so we have no fixed program on that day. We divided the several POCUS items over four days in a way we found appropriate for every POCUS item in terms of importance and or learning difficulty on the basis of available literature. Learning basic lung ultrasound is the quickest;[30] learning cardiac and abdominal POCUS requires more time, but all elements of basic POCUS can be trained in a limited period of time.[27,31,32] In table 2, the time and number of test questions per POCUS item is shown. A two-day multi-organ POCUS training was efficient for intensive care fellows;[33] others advise one day per application,[34] but one-day courses are also described.[35] Our four-day course

gives ample time to soundly train POCUS and from a practical point, it means that residents have to be taken off rotation for one week.

Table 2. *Components of POCUS training and testing*

Component of POCUS	Hours (%)	No questions (%)
General introduction	2 (6,25)	3 (6)
Cardiac POCUS	14 (43,75)	22 (44)
Lung POCUS	2 (6,25)	3 (6)
Abdominal POCUS	12 (37,5)	19 (38)
Vascular POCUS incl. neck	2 (6,25)	3 (6)
Total	32 (100)	50 (100)

POCUS = point-of-care ultrasound

3.b. Image interpretation

During the course, the use of young healthy mannequins attributes to the element of image generation but the changes of finding pathology (image interpretation) are very low. Therefore, course participants learn to recognise normal ultrasound images and are instructed to be alert when images in patients are different from the normal images. During the introduction talks for each component, examples of ultrasound abnormalities are shown and the characteristics of ultrasound pathology discussed (table 3).

In the coming years, we foresee a bigger role for simulation education for ultrasound training as already has been described in literature,[36] although simulation-only education is probably insufficient and hands-on training remains important.[37] In the Rijnstate course, we use the Sonosim which is a computer-based platform in which ultrasound studies with real pathological situations are installed. Attached to the computer is an ultrasound probe with movement detection. By moving the ultrasound probe, different views are simulated. Candidates are therefore confronted with real ultrasound pathology. The candidates are stimulated to use the Sononsim during quiet hours. On the last day of the course, the candidates (in pairs) have to assess five Sonosim scenarios: cholethiasis, severe right and left ventricle dysfunction, E-fast protocol showing a pneumothorax on the right side, massive pulmonary embolism, and right kidney hydronephrosis. In the near future, we will explore whether we can optimise the use of ultrasound simulation.

For the insertion of central lines, we use a vascular mannequin (Blue Phantom) on which the technique of ultrasound-guided catheterisation of the internal jugular vein can be practiced. In our department, residents are trained to insert central venous catheters into the internal jugular vein with ultrasound guidance, as endorsed in literature.[38] This technique is part of the Rijnstate course but is rehearsed at the beginning of the intensive care rotation.

3.c. Clinical integration

Clinical integration of ultrasound findings is, in our view, the most difficult part. There are reports that physicians do not adequately maintain ultrasound competency after a basic course,[39] and it is challenging to obtain specific recommendations from literature on maintenance of competency.[19] The NVIC has designed a 'consolidation course', which includes, in addition to a two-day refresher of basic skills, the evaluation of 40 ultrasound examinations performed by the candidates within a period of nine months. These 40 thoracic ultrasound examinations are to be described according to the intracavitary ultrasound protocol (www.nvic.nl/consolidatiecursus).

In the near future, ultrasound portfolios for residents will be in place in our hospital, in which 40 ultrasound examinations (thoracic and abdominal) will be reviewed during a one-year period after the course. There is discussion on the exact number of ultrasound exams needed to reach acceptable competency,[31] and for residents in internal medicine, an exact number will be replaced

Table 3. *Image interpretation*

Image interpretation	
Cardiac POCUS	Left ventricle is enlarged yes/no Left ventricle function: normal, moderately diminished, severely diminished Right ventricle is enlarged yes/no Right ventricle function assessed by TAPSE Pericardial fluid present yes/no, signs of tamponade yes/no Width of IVC, variation during respiration in cms
Lung POCUS	Signs of pneumothorax PLAPS yes/no
Abdominal POCUS	Kidney size in cms left and right, signs of obstruction Major liver and gallbladder abnormalities Spleen size and aspect Abdominal aorta aneurysm Bladder abnormalities Abdominal free fluid and were to look for it
Vascular POCUS	Femoral and popliteal thrombosis

PLAPS = posterolateral alveolar and/or pleural syndrome; POCUS = point-of-care ultrasound; TAPSE = tricuspid annular plane systolic excursion; IVC = inferior vena cava

Table 4. *Checklist POCUS imaging process*

	Speed (min:sec)	Image quality (good/moderate/bad)	Ergonomics adequate/inadequate
Assessor (initials) FB MB			
Candidate:			
Date:			
Lung: Blue 1 right			
Lung: Plaps right			
Heart: PLAX			
Heart: PSAX (2 levels): Aortic valve Papillary muscle			
Heart: A4C			
Heart: IVC			
Abdomen: Aorta - transversal - sagittal			
Abdomen: Kidney right side Kidney length			
Abdomen: Spleen Spleen length			
Total score:			

A4C = apical 4 chamber; Blue 1 = upper blue point; PLAPS = posterolateral alveolar and/or pleural syndrome; PLAX = parasternal long axis; POCUS = point-of-care ultrasound; PSAX = parasternal short axis; IVC = inferior vena cava; min = minutes; sec = seconds

soon by the concept of entrustable professional activities (EPAs).[11]

Every Thursday afternoon at 3:00 p.m., there is an ultrasound round on the intensive care and general wards. Patients with interesting ultrasound findings are asked to participate and are examined by ultrasound by attending residents and one ultrasound supervisor.

By designing a basic POCUS course in combination with a one-year portfolio, the possibility to store exams digitally, weekly ultrasound rounds, and easy access to ultrasound supervision, we try to optimise the acquisition and retention of ultrasound skills. We fully endorse and emphasise the need to warn our residents that in the wrong hands, POCUS can be dangerous, and that it is essential to know one's limits and to call for expert help if needed.[3,4,24]

Residents stay in Rijnstate for a maximum of one to three years, and after this period, they continue their training elsewhere. It will be up to them to maintain their POCUS skills and hopefully they will join a department with a positive POCUS attitude and program. The NVIC notices that just a small percentage of candidates from the basic

course joins the consolidation course (data from NVIC, personal correspondence), meaning that most colleagues either stop performing POCUS after the basic course or continue with a personalised form of POCUS education (possibly 'learning on the job' without formal training).

3.d. Testing

The candidates are tested in theoretical and practical knowledge. An online theoretical multiple-choice test consisting of easy and more difficult questions with proportional percentage of questions for each component of POCUS (table 1) was developed. This test is taken shortly before the course to assess basic knowledge and candidate preparation, on the last day of the course to assess possible acquisition of knowledge, and after three months to assess whether the trained skills are retained by the candidates (learning retention). The questions and order of answers are changed digitally to prevent possible foreknowledge.

A practical exam is taken on the last afternoon of the course. The candidates are asked to show appropriate images of two lung, four heart, and four abdominal views in 10 minutes. They are evaluated in terms of speed, imaging quality, and ergonomics (table 4). This practical test is also rehearsed after three months to assess whether practical skills are retained. For intensive care fellows, a two-day multi-organ ultrasound course was found to improve ultrasound proficiency after three months.[33] In a recent study on medical students, there was a difference in decay of motor and cognitive skills for pleural and cardiac images,[40] meaning that we have to be aware that learning and retaining POCUS skills might be different for each component. We are planning to evaluate the results for our resident training program in 2020: Does our course improve ultrasound knowledge and skills, are knowledge and skills retained after three months, and is there a difference between retention of motor and cognitive skills?

FINAL REMARKS

Although there is lack of hard evidence that ultrasound saves lives,[41] we do strongly believe that POCUS is a very important new development in intensive care and emergency medicine. We are convinced that using it 'as the new stethoscope' leads to safer, better, and cheaper patient care. There is ample circumstantial evidence indicating that the use of POCUS leads to more accurate diagnosis,[42-52] has therapeutic implications,[42,46,48,49,51-53] leads to lesser use of other medical resources,[48,49,51,54,55] and probably leads to lower mortality.[53,56] Furthermore, the use of POCUS may reduce uncertainty in the diagnostic process.[49] From our experiences in our own clinical day-to-day work, we have encountered many situations in which the use of POCUS resulted in significant diagnostic and therapeutic alterations. Recently, we admitted a 45-year-old woman who suffered from a severe carbon monoxide (CO) intoxication. After several hours, her haemodynamic status deteriorated. POCUS not only showed a severe CO-related cardiomyopathy, but also showed a 20- week-old pregnancy, sadly without heart activity. We are sure that like us, colleagues who embrace POCUS will pass or have passed that point of no return when not using POCUS is just unimaginable.

In this paper, we describe our stepwise approach to implementing the integral use of POCUS and we also describe how a POCUS training program for residents could be designed. Of course, these topics are dynamic and require regular evaluation, improvements, and adjustments. By sharing our implementation and training experiences, we want to contribute to the spread of POCUS and be of help to colleagues who wish to implement POCUS into their intensive care departments.

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ORIGINAL ARTICLE

Urea for hyponatraemia due to the syndrome of inappropriate antidiuretic hormone secretion

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ABSTRACT

Background: Hyponatraemia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) can pose a therapeutic challenge. After fluid restriction, urea is recommended as a second-line treatment by Dutch and European treatment guidelines. Data on this practice are still scarce. We introduced urea for the treatment of SIADH in our hospital and prospectively collected data on its effectiveness and tolerability.

Methods: In hospitalised patients with a serum sodium level ≤ 129 mmol/l due to SIADH, urea in a dosage of 0.25-0.50 g/kg/day was indicated if prescribed fluid restriction had no effect or could not be applied. Measurement of serum sodium was performed at baseline, after the first and second day of urea therapy and at the end of the first inpatient treatment episode (EIT). The primary outcomes were normonatraemia (serum sodium level 135-145 mmol/l) at EIT and discontinuation of urea due to side effects.

Results: Thirteen patients were treated with urea over a median of 5 days (range 2-10 days). The median serum sodium level at baseline was 124 mmol/l (IQR 122-128), which increased to 128 mmol/l (IQR 123-130) (p = 0.003) after the first dose of urea and to 130 mmol/l (IQR 127-133) (p = 0.002) after the second dose of urea. Normonatraemia at EIT was observed in 8 (62%) patients. Seven (54%) patients reported distaste. In one of these patients, urea was discontinued because of nausea. Overcorrection was not observed.

Conclusion: Our data show that urea is an effective treatment for hospitalised patients with SIADH. Distaste was a frequent side effect, but usually did not lead to early treatment discontinuation.

KEYWORDS

Hyponatraemia, SIAD, SIADH, urea

INTRODUCTION

Hyponatraemia, which is defined as a serum sodium concentration < 135 mmol/l, is estimated to occur in up to 30-40% of hospitalised patients.[1-3] Hyponatraemia can pose a therapeutic challenge, and this condition is often accepted, despite an association with poor outcomes. The 2015 multinational Hyponatraemia Registry showed that almost half of 3087 patients with hyponatraemia were discharged from hospitals with a serum sodium level of 130 mmol/l or less.[1] Patients with chronic hyponatraemia (existing > 48 hours) often appear asymptomatic, but chronic hyponatraemia has been associated with cognitive deficits, an increased risk of falling, bone fractures and osteoporosis, and an increased risk of mortality.[4-10]

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a common cause of hyponatraemia, although clear prevalence data are lacking, possibly partly due to failures in diagnostic procedures.[1,2] Hyponatraemia in SIADH is the result of increased retention of water due to excess antidiuretic hormone (vasopressin), and hence fluid restriction is an effective and widely accepted first-line treatment strategy.[11,12] However, in patients with a high level of antidiuretic activity, strict fluid restriction may not be sufficient or cannot be applied due to another prescribed therapy or poor patient adherence. Urea is recommended as a second-line treatment for SIADH by the 2014 European Renal Best Practice (ERBP) guideline and the 2017 Dutch Practice Guideline 'Het Acute Boekje'.[11,12]

In the kidney, urea plays an important role in concentrating urine and acts as an osmotic diuretic. Since the diuretic property of urea is its main pharmacokinetic mechanism, it might be possible to estimate the serum sodium level after a urea dose using a patient's urine osmolality level and total body water (TBW).[13] For example, in a patient with a urine osmolality of 750 mOsm/l, 500 mmol of urea (30 g) leads to 0.66 l of electrolyte-free water excretion. If the patient

has a TBW of 20 l, the new TBW is 19.34 l. The new serum sodium value can then be calculated using the formula:

$$\text{new serum sodium} = \text{baseline serum sodium} \times \frac{\text{baseline TBW}}{\text{new TBW}}$$

In 1980, Decaux and colleagues were the first to report the use of urea as a treatment for hyponatraemia due to SIADH.[14] In the years following, they published several case series and observational studies showing that urea can be successfully used for both rapid correction of acute hyponatraemia and long-term maintenance therapy for chronic hyponatraemia.[15-18]

Although incorporated into the European and Dutch guidelines, experience with urea therapy for SIADH is limited in the Netherlands. In this case series, our primary aim was to present data on the effectiveness and tolerability of urea as a second-line treatment in hospitalised patients with SIADH. As secondary aim, we determined whether the serum sodium levels after a dose of urea can be accurately estimated.

MATERIALS AND METHODS

This study was conducted in the Medical Centre of Leeuwarden, a 700-bed teaching hospital in the Netherlands, from December 2017 to February 2019. Formal approval was waived by the local ethical committee according to national guidelines.

In December 2017, we implemented an inpatient SIADH management protocol including urea as a second-line treatment strategy. Treating physicians from the departments of internal medicine and geriatrics were informed about the protocol and asked to report patients in need of second-line treatment to the coordinating investigator (JW). Furthermore, this investigator screened all hospitalised patients with moderate to profound hyponatraemia (serum sodium ≤ 129 mmol/l) using a notification system built into our Electronic Patient Record. In possible cases, study criteria were assessed by the coordinating investigator in collaboration with the treating physician.

Study population

Patients included in this case series were aged 18 years or older and had moderate to profound chronic hyponatraemia (serum sodium ≤ 129 mmol/l, existing for more than 48 hours) due to SIADH. A diagnosis of SIADH was made if patients met the diagnostic criteria as stated in the European guideline.[11] Diagnostic procedures therefore included measurements of serum osmolality, serum glucose, urine osmolality, urine sodium, serum cortisol, serum thyroid-stimulating hormone (TSH), serum creatinine, and assessment of volume status and diuretic use by the treating physician.

Patients eligible for treatment with urea included those in whom fluid restriction was not or was minimally effective and/or in whom further restriction of fluid intake was not possible. Contra-indications for urea were moderate to severe renal impairment (chronic kidney disease stage 3b or higher) and liver failure. Patients were excluded from this case series if they received other treatment for hyponatraemia (e.g., hypertonic saline, loop diuretics combined with sodium chloride tablets), if they did not receive urea for at least two subsequent days, if they were in the intensive care unit, or if they had severe symptoms of hyponatraemia (e.g., seizures, coma) or SIADH with an expected fast-resolving cause (e.g., after discontinuation of causal medication).

The dosage of urea was determined using the guidelines' dosage recommendation of 0.25-0.50 g/kg/day.[11,12] Urea was prescribed in one dose per day or two doses when receiving 40 g/day or more. We used a urea formulation recipe known as 'Brussels Champagne' consisting of the following ingredients in addition to 10 g of urea: sodium bicarbonate 2 g, citric acid 1.5 g, and saccharose 200 mg. This formulation is diluted in 50-100 ml of water and can be taken orally.[11,19] The previously prescribed fluid restriction was maintained in patients able to tolerate the restriction. The duration of urea therapy and continuation after discharge were determined per case, for example, by taking into account the severity and underlying cause of SIADH.

Data collection

In patient treatment

After inclusion, we documented the baseline clinical and treatment characteristics of patients. The presumed cause of SIADH was reviewed and agreed upon by the treating physician and coordinating investigator. Serum sodium concentrations were measured at admission and at the following time points in relation to the start of urea therapy: Day-2, Day-1, baseline, Day+1, Day+2, and at the end of inpatient treatment (EIT). Serum urea, creatinine, and uric acid levels were measured at baseline, Day+2 and EIT. The occurrence of side effects and overcorrection, defined as an increase in serum sodium > 8 mmol in 24 hours, were monitored. The duration of treatment and changes in urea dose were recorded. The EIT was considered to occur either at discharge or when a patient discontinued urea therapy during hospitalisation. In the case that a patient had multiple inpatient treatment episodes, only the first episode was included for this analysis.

Follow-up

If a patient was discharged with urea treatment, we asked the attending physician to perform follow-up evaluations of serum sodium levels at two and six to eight weeks after discharge. The duration of ambulatory treatment and changes in urea dose were also recorded. Restart of urea therapy during the study period was documented, both during (re)admission and ambulatory care, after reporting by the attending physician and/or by the notification system of our Electronic Patient Record.

Estimating serum sodium

We estimated serum sodium levels for the time points Day+1 and Day+2 using the formula mentioned in the introduction section. Baseline TBW was assessed with Watson's formula, which includes body height, weight, age, and sex.[20] For the Day+2 estimation, the measured serum sodium level at Day+1 was used as the baseline serum sodium level; the baseline TBW was not adjusted.

Endpoints

The main outcomes were normonatraemia (serum sodium 135-145 mmol/l) at EIT and discontinuation of urea due to side effects. Secondary outcomes were the number of patients experiencing side effects and overcorrection. In the analysis of serum sodium estimation, the endpoint was agreement between the estimated and measured serum sodium levels, which was defined as a maximal difference of 1 mmol/l.

Data analysis

We describe continuous variables as medians and ranges or interquartile ranges (IQRs), and the Wilcoxon signed rank test was performed to compare laboratory values before and after the start of urea treatment. P-values are two-tailed, and the significance level was set at 0.05.

To analyse the agreement between the method of estimating serum sodium and the gold standard of measuring serum sodium, a Bland-Altman plot was constructed, showing differences between the estimated and measured serum sodium levels plotted against the measured serum sodium level. The mean difference and 95% limits of agreement (mean difference ± 1.96 SD of the differences) were calculated using the one-sample T-test. Based on the researchers' opinion, the maximum allowed upper and lower limits of agreement were defined beforehand as ≤ 3 mmol/l and ≥ -3 mmol/l, respectively.

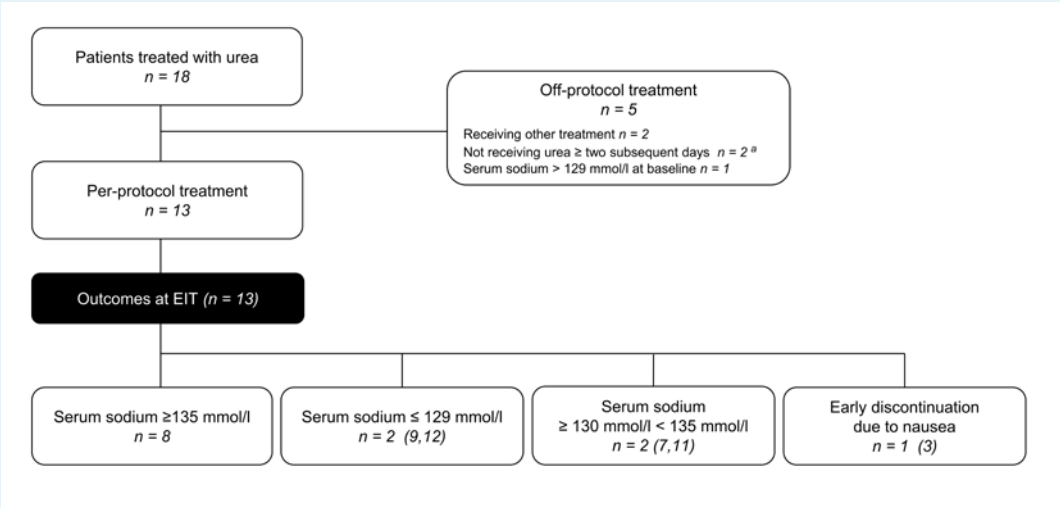
We used SPSS Statistics version 25 (IBM, New York, United States) and Microsoft Office 2010 (Microsoft, Redmond, United States) to analyse and display our data.

RESULTS

Study population

During the study period, 18 patients were treated with urea, of whom, 13 met the inclusion criteria (figure 1). The described diagnostic procedures for the diagnosis of SIADH were completed in all patients except for patients

Figure 1. *Flow chart showing patients treated with urea, with outcomes for end of inpatient treatment (EIT)*



[a] In one patient, this was due to a one-day interruption of treatment because of distaste, and in one patient, this was due to temporary problems in the supply of urea.

Table 1. *Baseline clinical and treatment characteristics of 13 patients treated with urea for SIADH*

Patient	Sex	Age (years)	Presumed cause of SIADH	Serum sodium (mmol/l)	Urine osmolality (mOsm/kg)	Urine sodium (mmol/l)	Weight (kg)	Urea dose (g)	Duration of clinical treatment (days)
1	F	75	Pulmonary infection (viral)	119	440	70	74	30	5
2	M	79	Pulmonary infection (viral)	129	436	90	85	30	5
3	F	68	Pulmonary infection (aspergillosis)	121	503	177	58	30	4
4	F	48	Medication (valproic acid)	128	509	65	76	30	10
5	F	77	Lung carcinoma	123	880	31	60	30	4
6	F	68	Unknown	128	553	41	49	10	3
7	M	67	Pulmonary infection (tuberculosis)	120	499	136	42	15	6
8	F	85	Cerebrovascular event	127	616	33	85	20	5
9	M	90	Unknown, possible pain	126	732	89	75	30 - 40	7
10	F	85	Post-operative and/or pain	124	458	56	68	20	5
11	F	67	Ovarian carcinoma	124	654	130	55	15	2
12	F	70	Medication (bortezomib)	123	754	91	49	15 - 30	6
13	M	65	Lung carcinoma	124	813	76	77	30	4

F = female; M = male; SIADH = syndrome of inappropriate antidiuretic hormone secretion

1 and 2, for whom serum osmolality data were missing. The clinical and treatment characteristics of our 13 patients are listed in table 1. Their median age was 70 years (range 48-90) and nine patients were female (69%). Pulmonary infection was the most common presumed cause of SIADH (n = 4), followed by cancer (n = 3). One patient with pulmonary infection and one patient with medication as identified causes of SIADH were also diagnosed with cancer. Patients with medication-induced SIADH were unable to discontinue the causative agents e.g., valproic acid and bortezomib.

The median serum sodium level at baseline was 124 mmol/l (IQR 122-128) and the median urine osmolality at baseline was 553 mOsm/kg (IQR 478.5-743). Moderate to severe hyponatraemia was already present at admission in 11 of 13 patients, and the serum sodium levels at admission ranged from 110 to 136 mmol/l (median 125 mmol/l, IQR 117.5-126.5). Patients were treated with urea for a median of 5 days (range 2-10) in doses ranging from 10-40 g. The prescribed fluid restriction varied from 750 to 2000 cc/day. In four patients, with a fluid restriction of 1500 - 2000 cc/day, the inability to further restrict fluid intake was the main reason that urea treatment was started. Two of these patients were undergoing tube feeding for poor nutritional status.

Outcomes

Inpatient treatment

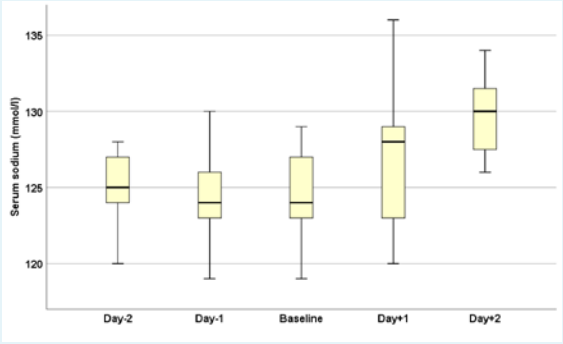
The median serum sodium level at baseline did not significantly differ from the median serum sodium level on Day-2 (124 mmol/l (IQR 122-128) versus 125 mmol/l (IQR 123-128), p = 0.53), and the level increased to 128 mmol/l (IQR 123-130) (p = 0.003) after the first day and to 130 mmol/l (IQR 127-132) (p = 0.002) after the second day of urea therapy (table 2, figure 2). During the first two days of urea treatment, the average increase in serum

Table 2. *Laboratory parameters at baseline and during inpatient treatment*

Parameter	Baseline	Day+1	Day+2	End of inpatient treatment
Serum sodium, mmol/l [n = 13]	124 [122-128]	128 [123-130] p = 0.003	130 [127-132][b] p = 0.002	135 [130-137] p = 0.002
Urea, mmol/l [n = 12]	6.1 [4.0-7.6]		9,0 [8.0-11.4][b] p = 0.003	10.4 [7.8-11.8] p = 0.004
Creatinine, µmol/l [n = 12]	44 [30-73]		51 [31-65][b] p = 0.96	46 [35 - 79] [c] p = 0.59
Uric acid, mmol/l [n = 11, a]	0.16 [0.13-0.18]		0.18 [0.14-0.25] [b] p = 0.043	0.16 [0.13-0.27] p = 0.034

Data are presented as median [interquartile range]. Statistics: Wilcoxon signed rank test.
n = number of patients
[a] In patient 3, the serum uric acid level was consistently < 0.05 mmol/l and could not be included for analysis.
[b] One missing value.
[c] Two missing values.

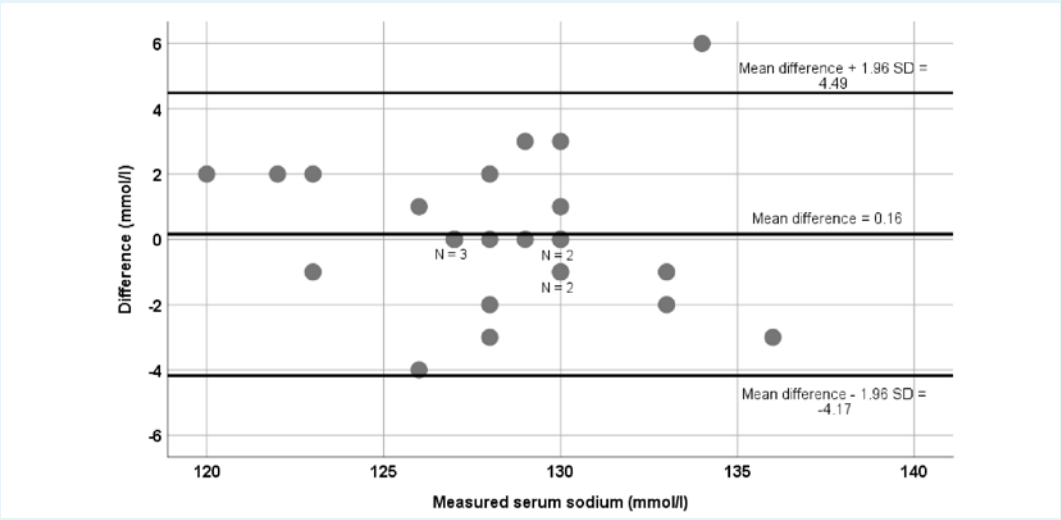
Figure 2. *Boxplots showing serum sodium levels before and after the start of urea treatment*



sodium was 2.9 mmol/day. The median serum urea level was 6.1 mmol/l (IQR 4.0-7.6) at baseline and 10.4 mmol/l (7.8-11.8) (p = 0.004) at EIT. Serum creatinine levels at both baseline and EIT were available for 10 patients and did not significantly differ (table 2).

At EIT, normonatraemia was observed in 8 of 13 patients (62%). Two patients (15%) had a serum sodium level between 130 and 135 mmol/l, and two patients (15%) had a serum sodium level of ≤ 129 mmol/l. In patient 3, urea was discontinued due to nausea after four days of therapy, and at that time, the patient had a serum sodium level of 129 mmol/l (figure 1). Six patients reported light to moderate intake difficulties due to the taste of urea, and one of these patients also reported light nausea that was

Figure 3. *Bland-Altman plot showing differences between estimated and measured serum sodium plotted against measured serum sodium as the gold standard (n = 25)*



SD = standard deviation

likely related to urea. All of these patients were able to continue urea therapy. Overcorrection was not observed.

Follow-up

In patients 5 and 8, urea was restarted during admission because of a decline in serum sodium. In patient 11, urea was restarted during readmission for hyponatraemia. A total of eight patients received ambulatory urea treatment with a duration ranging from 13 days to > 5 months. This included patients 5, 8, and 11. In the five other patients, urea was directly continued after the first inpatient treatment episode, including both patients with serum sodium levels ≤ 129 mmol/l at EIT. Both patients received a higher dose during ambulatory treatment and showed normalisation of serum sodium during follow-up. The median serum sodium level at two weeks of follow-up was available for six patients and was 134 mmol/l (range 132-141). The median serum sodium level at six to eight weeks of follow-up was available for five patients and was 134 mmol/l (range 128-140).

Estimating serum sodium

Serum sodium levels were estimated for 25 measurements, with one missing value for Day+2. The Bland-Altman plot shows the differences between the estimated and measured serum sodium levels (figure 3). Thirteen of 25 (52%) estimated serum sodium levels were in agreement with the measured serum sodium level. The upper limit of agreement was 4.49 mmol/l, and the lower limit of agreement was -4.17 mmol/l, hence exceeding the defined maximum allowed limits of ≤ 3 mmol/l and ≥ -3 mmol/l.

DISCUSSION

We introduced urea as second-line treatment for hyponatraemia due to SIADH and found it to be an effective inpatient treatment strategy; most patients showed a direct increase in serum sodium after urea commencement, and 8 of 13 patients achieved normonatraemia at the end of inpatient treatment. Tolerability can be reduced due to an unpleasant taste of urea, but in most patients, this did not lead to discontinuation. Serious side effects were not observed.

In many hospitalised patients with hyponatraemia due to SIADH, effective management is not achieved.[1] Fluid restriction, in addition to treating the underlying condition, is the first-choice treatment; however, fluid restriction may not be sufficient, cannot always be applied due to the use of other therapy, or fails due to poor adherence. Pharmacotherapeutic interventions for SIADH may have disadvantages such as cost and lack of outpatient reimbursement (tolvaptan), concerns regarding side effects (tolvaptan, demeclocycline), or very limited evidence on their efficacy (oral sodium chloride combined with loop diuretics).[11,21,22] Urea recently attracted global interest due to evidence of its efficacy and safety from several observational studies.[23-25] Despite the inclusion of urea in treatment guidelines,[11,12] urea remains an intervention that is not formally registered based on an adequate balance of benefits and risks. Structured reports on the efficacy and safety of urea in SIADH are therefore necessary to obtain a better estimation of its added therapeutic value.

All of our patients had moderate to profound hyponatraemia (median serum sodium at baseline 124 mmol/l) and were not effectively treated with fluid restriction alone, as reflected in the median serum sodium level of 125 mmol/l at two days prior to baseline. We observed an average increase in serum sodium of 2.9 mmol/day during the first two days of urea treatment, which is consistent with findings in American and Australian observational studies of hospitalised patients with hyponatraemia.[23,24] It cannot be fully ruled out that recovery of the underlying cause of SIADH also improved serum sodium levels, for example, in patients with pulmonary infection. However, we believe that this was not a major factor in serum sodium increase, since all of these patients showed no increase in serum sodium in the 48 hours before initiation of urea therapy. We found a higher proportion of patients with normalisation of serum sodium than among the urea-only treated American patients (8 of 13 (62%) versus 4 of 12 (33%), respectively).[23] Distaste was also frequently reported in our population in 7 of 13 patients (54%), whereas Lockett et al. reported distaste in 7 of 69 patients (10.1%).[24] The higher proportion of both efficacy and tolerability outcomes in our case series, as compared to the recent observational studies, can possibly be explained by our prospective design, in which serum sodium and side effects were actively monitored.

Despite the use of the more palatable 'Brussels Champagne' formulation,[11,19] distaste was still frequently reported. Urea was discontinued early in one patient due to nausea. She weighed 58 kg and received a dosage of 30 g/day, which is on the upper limit of the dosing directive, possibly contributing to intolerance. It is possible that tolerability can further be improved by splitting the dose, by diluting urea in orange juice and by taking urea after a meal.

Urine osmolality (mOsm/kg) is a parameter of antidiuretic activity and is useful in the management of SIADH.[26,27] For example, Winzeler et al. found that urine osmolality and urine sodium were significantly associated with nonresponse to fluid restriction. Optimal cut-off values predictive for nonresponse were ≥ 500 mOsm/kg for urine osmolality and ≥ 130 mmol/l for urine sodium.[26] Most of our patients had a urine osmolality level ≥ 500 mOsm/kg. In two of our patients with a very high urine osmolality level of ≥ 700 mOsm/kg, urea dosage had to be increased

to 0.5g/kg/day to increase serum sodium. During urea therapy, fluid restriction was continued in patients able to be restricted. This was done because our patients were considered to have more severe SIADH as reflected by a high urine osmolality level and prior nonresponse to fluid restriction alone. Most of our patients had a moderate fluid restriction of 1000-1250 cc/day. In our hospital, a severe fluid restriction is not often prescribed, due to poor patient acceptance and also healthcare providers' unfamiliarity with the management of more severe SIADH. Nervo et al. successfully treated ambulatory patients with urea as single therapy without fluid restriction. Most of their patients received a higher urea starting dose of 30 g and their patients had a lower mean urine osmolality level (452 mOsm/kg vs 604 mOsm/kg in our population).[25]

In the management of hyponatraemia, particular attention is also necessary to prevent an excessively rapid correction and thereby osmotic demyelination syndrome, a rare but feared complication. Soupart et al. showed in animal models that urea therapy may additionally protect from osmotic demyelination.[28] Overcorrection during urea treatment has been observed in patients in intensive care units receiving a high dosage of urea (0.5-1.0 g/kg/day),[16,17] but not in our study or in other recent studies.[23-25] To further guide dosing, the ability to estimate the effect of urea on serum sodium might be helpful. As described by Sterns et al., urea mainly acts as an osmotic diuretic and serum sodium levels were estimated based on this property.[13] Thirteen of 25 (52%) estimated serum sodium values were in agreement with the measured serum sodium level. However, the 95% limits of agreement did not meet our defined criteria of ≤ 3 mmol/l and ≥ -3 mmol/l, hence, we cannot conclude that this method is accurate. A major limitation of this analysis was the small sample size; therefore, additional data are needed. We had a possible outlier (6 mmol/l difference) that we could not readily explain, but even after excluding this outlier from the analysis, the limits of agreement were not met. The method might be oversimplified; it has been shown that urea not only promotes water excretion, but also decreases natriuresis.[13,29] Furthermore, the method assumes stable fluid and food intake, which were not fully controlled for in this study and are also not fully controlled in real-life practice, which may limit the use of this method.

The main limitations of this study are its small sample size and uncontrolled design. The strengths of our study are the prospective nature of data collection, patient follow-up in a real-life practice setting, and applying strict diagnostic criteria for SIADH.

In conclusion, this study adds to the evidence that urea is an effective second-line treatment strategy for hospitalised patients with hyponatraemia due to SIADH. Distaste and nausea were reported side effects in our population, but, for the most part did not lead to early discontinuation. After the inclusion of urea treatment in the 2014 European and the 2017 Dutch practice guidelines, these are the first data from the Dutch population, and to our knowledge, this is only the second study on this subject to perform prospective evaluation of data. Additional data are needed to assess the long-term effectiveness and tolerability of urea treatment.

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PREVIOUS PRESENTATION OF THE DATA

31th Annual Meeting of The Netherlands Association of Internal Medicine, 24 April 2019, Maastricht, the Netherlands. Abstract O4.06 'Urea as second-line treatment for hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion: a case series involving 13 in-hospital patients'.

Scientific Spring Meeting of Dutch Society for Clinical Pharmacology and Biopharmacy, 12 April 2019, Rotterdam, the Netherlands. No abstract available online.

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CASE REPORT

FSGS tip lesion in polyautoimmunity including Sjögren's syndrome

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ABSTRACT

We present a case with five auto-immune phenomena, including Sjögren's syndrome, for which we also diagnosed a tip lesion of focal segmental glomerulosclerosis (FSGS). About one-third of Sjögren's syndrome patients have renal involvement, but FSGS is rarely reported. FSGS is thought to involve T-cell dysfunction and in this patient with multiple auto-immune phenomena, it may reflect a severe dysregulation of cellular immunity.

KEYWORDS

Focal segmental glomerulosclerosis, multiple autoimmune disease, polyautoimmunity, Sjögren's syndrome

What was known on this topic?
About one-third of patients with Sjögren's syndrome have renal involvement, characterised by tubulointerstitial nephritis in three-quarters of cases. FSGS is rarely reported, and may reflect an expression of dysregulation of cellular immunity.

What does it add?
To the best of our knowledge, this is the first case report of a FSGS tip lesion in Sjögren's syndrome with multiple autoimmune phenomena, possibly reflecting a more severe dysregulation of cellular immunity. This may 1) help unravel the complex immunological pathophysiology of both phenomena and 2) remind us that it remains essential to perform a renal biopsy to establish the correct diagnosis.

INTRODUCTION

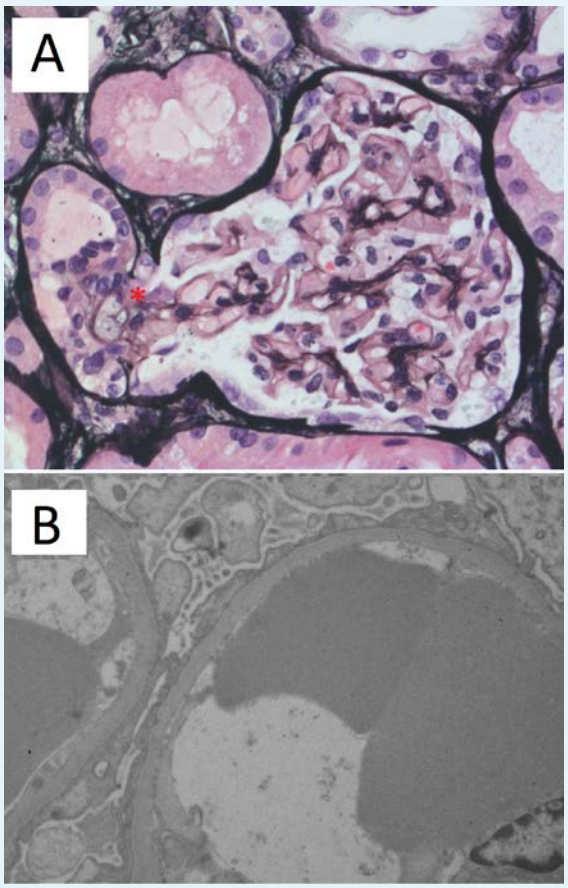
Sjögren's syndrome is a rare autoimmune condition characterised by lymphocytic infiltration of salivary and lacrimal glands associated with anti-SSA (Ro) or anti-SSB (La) autoantibodies. Extra-glandular manifestations are frequently observed and often include renal involvement.[1] Sjögren's syndrome-associated renal disease usually consists of tubulointerstitial nephritis (75% of patients) and glomerulopathy, such as membranous proliferative glomerulonephritis.[1-3]. Focal segmental glomerular sclerosis (FSGS) as a dominant pathological finding is found rarely in patients with Sjögren's disease (2/24, 3/103, 0/25 of renal biopsies[1-3] and three case reports, respectively).[4-6] We present a case with multiple autoimmune phenomena, including Sjögren's syndrome with a FSGS tip lesion and discuss possible immunological phenomena involved.

CASE REPORT

A 57-year-old non-smoking woman had developed celiac disease and autoimmune hypothyroidism in 1990, and autoimmune gastritis, autoimmune thrombocytopenia, and Sjögren's syndrome in 2010. Sjögren's syndrome was diagnosed based on the combination of sicca syndrome, due to chronic sialo-adenitis, arthralgia, and positive anti-extractable nuclear antigen antibodies consisting of anti-SSA (> 240 U/ml) and rheumatoid factor (6.1 IU/ml) with diffuse hypergammaglobulinemia [(immunoglobulin G (IgG) 16.3 g/l (ref: 7.0-16.0 g/l); IgA 5.2 g/l (ref: 0.7-4.0 g/l); IgM 1.16 g/l (ref: 0.4-2.3 g/l)]. Treatment with hydroxychloroquine was discontinued after half a year because of side effects, followed by intramuscular triamcinolone acetonide injections (80 mg every six weeks) with a good result.

One year after cessation of the triamcinolone acetonide treatment in 2017, thrombocytopenia was progressive (33 x 10^9/l) and she developed a nephrotic syndrome with diffuse oedema and a 14 kg weight gain, hypoalbuminemia (albumin 22 g/l), heavy proteinuria (total protein 8.6 g/10 mmol creatinine), and an increase in creatinine from 81 to 105 µmol/l within two weeks. Serum complement levels were normal (C3 1.16 g/l, C4 0.35 g/l) and anti-phospholipase-A2-receptor (anti-Pla2R) was negative. Renal biopsy revealed a tip lesion variant of FSGS with negative immunofluorescence (IgA, IgG, IgM, kappa, lambda, C1q, C3, and Congo red) and no evidence of thrombotic microangiopathy (figure 1). The patient was treated with furosemide, angiotensin-converting enzyme inhibitor perindopril, and prednisolone (1 mg/kg). Within two weeks, the patient lost 12 kg, albumin levels increased to 24 g/l, protein excretion decreased to 1.7 g/10 mmol creatinine, and creatinine normalised. During the tapering of prednisone to 40 mg, protein excretion increased to 2.7 g/10 mmol creatinine. Because of side effects of long-term corticosteroid usage, rituximab was given as a corticoid-sparing agent. Five months later, kidney function normalised (creatinine 62 µmol/l; albumin 37 g/l; urinary total protein 0.09 g/10 mmol creatinine).

Figure 1. *(A) H&E with silver staining of a glomerulus and adjacent tubules. The asterisk indicates a segmental tip lesion with foamy changes without global glomerulosclerosis, characteristic for focal segmental glomerulosclerosis. (B) Electron microscopy of the glomerular base membrane with diffuse extensive obliteration of podocytes.*



H&E = haematoxylin and eosin

DISCUSSION

We report a patient with at least five auto-immune phenomena, including Sjögren's syndrome, who developed a nephrotic syndrome due to a FSGS tip lesion. A FSGS tip lesion often responds better to glucocorticoid therapy than other histological variants of FSGS. Approximately three-quarters of FSGS variants are 'not otherwise specified' according to the Colombia classification and reach complete remission in 13-24% after 1-2 years of follow up. The 'collapsing' variant (4-12% of cases) is the least favourable, with complete remission rates from 8-14%, followed by the 'perihilar' variant, with rates around 10%; the rare 'cellular' variant (1-3% of cases) and more common tip lesion (10-14% of cases) achieve remission more often: 33-39% and 50-61%, respectively.[7]

Although FSGS has rarely been reported in Sjögren's syndrome[1-3] we consider Sjögren's syndrome as the most likely cause and, to the best of our knowledge, this is the first case report of a FSGS in association with Sjögren's syndrome that is classified as a tip lesion. In autoimmune hypothyroidism there have been anecdotical reports of FSGS.[8] However, since autoimmune hypothyroidism is a common disorder, these might be unrelated phenomena and represent the distribution of this renal pathology in the general population. The other autoimmune phenomena present in our patient – celiac disease, atrophic gastritis, and thrombocytopenia – have not been associated with FSGS.

Although it is not possible to prove a causal link between polyautoimmunity and a FSGS tip lesion with certainty in our patient, both disease entities involve dysregulation of the immune system. The exact cause of FSGS remains unclear, but is thought to involve a glomerular permeability factor. This factor would affect the glomerular capillary wall and thereby lead to podocyte fusion and proteinuria. Additionally, since the monoclonal antibody rituximab agent (that depletes the CD20 B-cell population) appears effective as a corticoid-sparing agent in glucocorticoid-sensitive FSGS, B-cells may play a role in the pathophysiology.[9] Similarly, in nearly all autoimmune diseases, dysfunctional T-cells play a key role: CD4-positive T-lymphocytes lose immunological tolerance to self-antigens and B-cells produce a spectrum

of more or less specific auto-antibodies. Ciclosporin, which mainly inhibits T-cells, has also been successful in treating FSGS in Sjögren's syndrome in a few cases.[4,6] Interestingly, diffuse epithelial foot process effacement has also been described in systemic lupus erythematosus (SLE) without immune complex deposition, occurring more commonly with a disease flare.[10] One may speculate that activated T-cells are implicated in the pathogenesis of this so called 'lupus podocytopathy'.

Since our patient presented with at least five autoimmune phenomena, this may represent more severe dysregulation of the immune system and, although this is highly speculative, leaving her more prone to FSGS. One-third of patients with Sjögren's syndrome has polyautoimmunity and 9% has three or more autoimmune phenomena, most commonly hypothyroidism.[11] Autoimmune diseases are linked to genetic and environmental factors, both may contribute to polyautoimmunity. Since various renal pathology has been reported in Sjögren's syndrome that have varying prognoses and require different treatment, we consider it essential to perform a renal biopsy to establish the correct diagnosis. In conclusion, polyautoimmunity including Sjögren's syndrome may be associated with a FSGS tip lesion.

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CASE REPORT

Case series of three adult patients with exceptional clinical presentations of haemophagocytic lymphohistiocytosis

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ABSTRACT

Macrophage activation syndrome (MAS) is a secondary form of haemophagocytic lymphohistiocytosis (HLH). MAS-HLH is an underrecognised and life-threatening condition associated with a heterogeneous group of diseases including connective tissue disease and inflammatory disorders. Here, we report three cases of adult patients with MAS-HLH triggered by different entities, including systemic lupus erythematosus, Griscelli syndrome type 2, and Adult onset Still's disease.

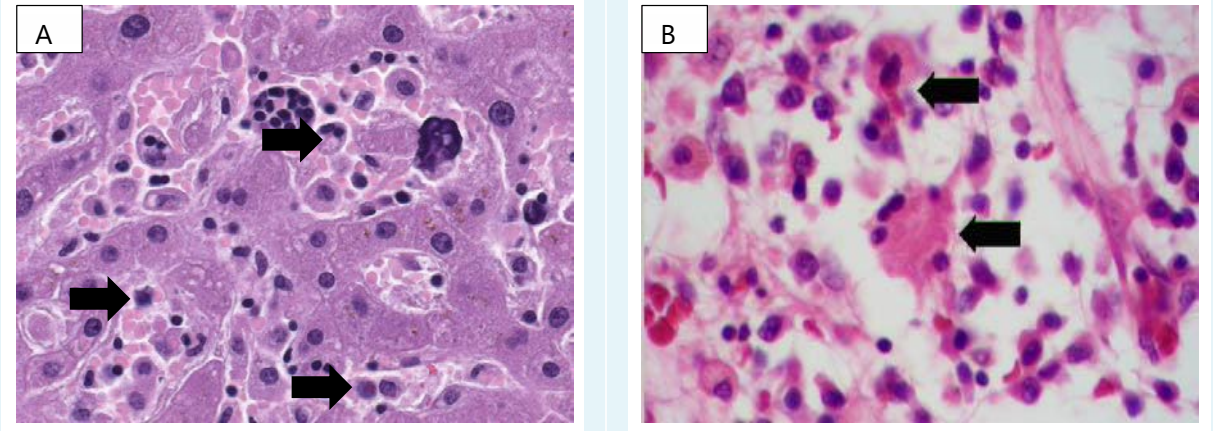
KEYWORDS

Adults Still's disease, Griscelli syndrome type 2, haemophagocytic lymphohistiocytosis, macrophage activation syndrome, systemic lupus erythematosus

BACKGROUND

Macrophage activation syndrome (MAS), a secondary form of haemophagocytic lymphohistiocytosis (HLH), is an underrecognised and life-threatening condition associated with a heterogeneous group of diseases including

Figure 1. *(A) HE staining, 400x magnification. Liver biopsy of patient 1 with haemophagocytosis (arrows). (B) HE staining, 200x magnification. Bone marrow biopsy of patient 3 with haemophagocytosis (arrows).*



HE = Haemotoxylin and eosin

Table 1. *Virological tests*

	Case 1	Case 2	Case 3
Viral pathogens			
Cytomegalovirus PCR	Negative	Negative	Negative
Ebstein-barr virus PCR	Negative	Negative	Negative
Human immunodefiency virus serology	Negative	Negative	Negative
Hepatitis A serology Heptitis B-C-E PCR	Negative (all)	Negative (all)	Negative (B and C)
Parvovirus-B19 serology	ND	Negative	ND
Human herpes virus type 6 and 8 PCR	ND	Negative	ND
Varicella zoster PCR	ND	Negative	ND

ND = not determined.

connective tissue diseases (CTD), cancer, infections, and exposure to drugs.[1]

Both MAS and HLH are characterised by inappropriate survival of histiocytes, cytotoxic CD8+ T cells, and macrophages, leading to a massive cytokine release, hyperinflammatory state and haemophagocytosis.[2,3] Clinically, patients with MAS-HLH present with persistent fever, hepatosplenomegaly, cytopenia, hyperferritinaemia, coagulation disorders, elevated inflammatory markers (C-reactive protein (CRP) and soluble interleukin-2 receptor (sIL2R)), hypertriglyceridaemia, and histopathological evidence of haemophagocytosis and multi-organ failure.[4]

Recognition of MAS-HLH may be challenging since clinical features can mimic other conditions such as sepsis, shock, and underlying active systemic disease.[5] MAS-HLH occurs more frequently in children than in adults, however, reporting in adults is increasing.[1]

Despite several studies reported on MAS-HLH and its association with different triggers and underlying diseases, the mortality remains high with rates of up to 80%, possibly also due to diagnostic delay.[1,6,7] In this report, we describe three adult cases with different presentations of MAS-HLH and their clinical features and outcomes, aiming at improving early identification and treatment of MAS-HLH.

Case 1

A 40-year-old female with a previous history of mild subacute cutaneous lupus erythematosus (SCLE) for the past 16 years, presented with fever, malaise, photosensitivity, and SCLE flare. Treatment with prednisone 60 mg daily initially resulted in improvement of cutaneous lesions. However, the patient developed jaundice and laboratory tests revealed deteriorated cholestatic liver tests with elevated transaminases, as well as haemolytic anemia (11 g/dl), thrombocytopenia (86 cells/ul), leucopenia (3600 cells/ul), and hyperferritinaemia (807 ng/ml). Physical examination revealed a fever of up to 40°C and diffuse macular erythematous rash. Autoantibody, viral screens, blood and urine cultures were negative (table 1).

Abdominal ultrasound examination showed hepatosplenomegaly without biliairy obstruction. A skin biopsy revelaed erythema multiform, however, SCLE flare could not be ruled out. The liver biopsy was initially interpreted as drug-induced liver injury.

During follow-up, her clinical condition worsened with respiratory insufficiency, progressive haemogram, and liver test disturbances (see table 2 for maximum values). The patient was admitted to the intensive care unit (ICU). Progressive loss of renal function with concurrent haematuria and proteinuria developed. Complement 3 and 4 levels were decreased. Revision of the liver biopsy showed signs of haemophagocytosis (figure 1). Bone marrow biopsy revealed neither malignant cells nor haemophagocytosis. Renal biopsy showed acute tubulus injury and bile cast nephropathy.

A diagnosis of MAS-HLH secondary (19 days after initial presentation) to SLE was established and treatment with ciclosporin and pulse methylprednisolone was initiated. Ciclosporin was discontinued due to nephrotoxic effects and treatment with anakinra was started. After initiation of anakinra, liver tests improved and ferritin levels decreased. However, the patient remained respiratory insufficient with progressive renal failure. Synchronising therapy with plasmapheresis, rituximab, and cyclophosphamide was started for treatment of the underlying severe SLE and anakinra was discontinued. Due to subsequent insufficient control of inflammation, therapy was switched to the HLH-2004 protocol. Yet due to several complications, treatment with etoposide was discontinued and anakinra was started again without any clinical response. The patient died within seven weeks after admission.

Table 2. *Patient Characteristics with MAS-HLH (minimum and maximum values)*

	Case 1	Case 2	Case 3
Clinical features			
Sex	F	M	M
Age (years)	40	26	63
Fever ≥ 38.5°C	Yes	Yes	Yes
Splenomegaly	Yes	Yes	
Haemophagocytosis	Liver	Bone marrow	Bone marrow
Underlying disorder	SLE	GS type 2	Flare of AOSD and erysipelas
Laboratory			
Haemoglobulin g/dl	4.0	6.1	7.6
Platelets cells/µl	6000	28000	77000
Neutrophills cells/µl	< 500	< 500	< 500
Ferritin ng/ml	48810	17156	48238
sIL2R pg/ml	43900	50294	ND
Triglycerides mg/dl	778	407	ND
Fibrinogen mg/dl	280	280	ND
NK-cell activity	Normal	Normal	ND
FHL genetic screen	ND	RAB27A	ND
CRP mg/l	147	230	330
LDH U/l	2695	2360	1847
Autoantibodies			
ANA	Positive (anti SSa/SSb/ RNP)	Negative	Negative
anti-dsDNA	Negative	Negative	Negative
ANCA (PR3 and MPO)	Negative	Negative	Negative
anti-AMA	Negative	Negative	ND
anti-SMA	Negative	Negative	ND
RF IgM	ND	Negative	Negative
ACPA	ND	ND	Negative

ACPA = anti–citrullinated protein antibody; AMA = anti-mitochondrial antibody; ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibody; anti-dsDNA = anti-double stranded DNA; AOSD = Adult-onset Still's disease; CRP = C-reactive protein; F = female; FHL = aamilial haemophagocytic lymphohistiocytosis; GS = Griscelli syndrome; IgM = immunoglobulin M; LDH = lactate dehydrogenase; M = male; ND = not determined; NK = natural killer; RF = rheumatoid factors; sIL-2R = soluble interleukin-2 receptor; SMA = smooth muscle antibody

Case 2

A 26-year-old male, originally from Eritrea, presented with a right-sided peripheral facial nerve palsy suspected for Bell's palsy after a cold and a tick bite. Treatment with prednisone was started. Two days after the first visit, the patient experienced numbness, tingling, and progressive muscle weakness of the lower limbs, resulting in left-sided foot drop. A presumed diagnosis of Guillan-Barre Syndrome was made and intravenous immunoglobulins (IVIG) were started. He showed initial improvement after the first cycle of IVIG therapy. However, 14 days later, he developed a left-sided facial and bilateral abducens nerve palsy, difficulty with speaking and swallowing, symmetric paraparesis of the upper and lower limbs, areflexia, sensibility loss with numbness from the knees down, and also fever. Electromyography and magnetic

resonance imaging of the brain were normal. A lumbar tap (2x) was performed without the presence of infectious or malignant cells. Based on clinical course, the diagnosis of polyradiculitis was established and a second IVIG cycle was started. During follow-up, the patient developed respiratory insufficiency, bowel complaints, fever (up to 39.5°C), abnormal liver tests, and decreased haptoglobulin and pancytopenia were observed (table 2). In addition, soluble interleukin-2 receptor (sIL2R), ferritin, and triglycerides levels were raised. Cytotoxic natural killer (NK)-cell function was normal. Renal function and C-reactive protein (CRP) were unremarkable. Blood, urine, spinal fluid, and fecal cultures were negative.

Additional imaging diagnostic tests were normal, except for the splenomegaly (17 cm). Bone marrow biopsy revealed haemophagocytosis and hyperinfiltration of T cells, and the patient fulfilled the criteria for MAS-HLH. Treatment with dexamethasone was started as initial treatment for MAS-HLH. Etoposide was considered at this time, but withheld due to concern of ongoing infection. Although some improvement in pancytopenia was observed, the patient suddenly went into cardiopulmonary arrest and was resuscitated. Despite achieving spontaneous cardiac output, post-anoxic coma developed with a poor prognosis. The patient died approximately seven weeks after his first presentation, despite initiation of etoposide treatment after resuscitation.

Interestingly, post-mortem, a genetic test revealed a homozygote RAB27A mutation. This mutation lead to Griscelli syndrome (GS) type 2, a rare autosomal recessive disorder, which is associated familial/primary HLH. Additional tests on the bone marrow biopsy also revealed an abnormal T-cell population, potentially compatible with T-cell malignancy.

Case 3

A 63-year-old male presented with a two-year history of uveitis anterior, thrombophlebitis, episcleritis, arthritis, auricular perichondritis, pharyngitis and otitis, as well as macular skin lesions and livid macular lesions on the lower extremities. He had developed relapsing and remitting fevers, and neutrophilic dermatosis (Sweet syndrome). PET scan showed flurodeoxyglucose (FDG)-positive consolidations within the lung parenchyma, reactive mediastinal lymphadenopathy, and splenomegaly with diffuse increased uptake in bone marrow with reactive findings on bone marrow biopsy. Repeated infections were ruled out by bronchoalveolar lavage. Intially considered as aspecific inflammatory syndrome, the patient was treated with different disease-modufying anti-rheumatic drugs and prednisone, but tapering of prednisone was followed by disease flares with fever, and eventually skin rash; pancytopenia; raised inflammatory markers (CRP 8.9 mg/dl and erythrocyte sedimentation rate 64 mm/hr), ferritin (up to 2040 ng/ml), and sIL2R (6025 U/ml) levels. He had normal triglycerides, and liver and renal function most compatible with AOSD with concurrent flare of Sweet syndrome. Anakinra was administered, but due to severe injection-site reactions this was switched to canakinumab and with disease control and the patient was dismissed.

In the meantime, myelodysplastic syndrome type EB-1 (excess blast-1) was considered based on revised bone marrow examination and he was referred for consideration for an allogeneic stem cell transplant.

However, 10 weeks later, the patient presented at the emergency department with bullous skin lesions on the left lower leg, a fever of up to 38.5°C, high CRP (14 mg/dl), normocytic anaemia (93 g/l), leucocytosis (15300 cells/uL), and a normal platelet count. The patient was diagnosed with erysipelas and intravenous antibiotic was initiated. Blood cultures revealed gram-positive bacteria and *Pseudomonas species* were cultured from the skin lesion.

Nevertheless, progressive necrosis developed in the left foot. The patient was transferred to the intensive care unit because of haemodynamic instability. Despite surgery, the patient's condition deteriorated with a fever of up to 41°C with progressive pancytopenia and abnormal liver tests (AST 1155 U/l). Moreover, ferritin levels were elevated, yet sIL2R and triglycerides were not tested (table 2). Septic shock was assumed as clinical condition, and only by the time of ongoing deterioration, was MAS-HLH considered provoked by a flare of AOSD due to infection. The patient died within 10 days after admission to the hospital. Post-mortem analysis of bone marrow showed an increase in the number of macrophages and focal haemophagocytosis (figure 1), consistent with MAS-HLH.

DISCUSSION

Here we present three adult patients with MAS-HLH with various active underlying diseases, which illustrate the different faces of MAS-HLH. The clinical and laboratory features in all our patients met the requirements for MAS-HLH according to the HLH-2004 guidelines, yet concurred with delayed treatment. Measurent of serum ferritin early in disease course and monitoring for dynamics is inexpensive and may be instrumental in earlier recognition of MAS-HLH.[8]

Although MAS-HLH is well-recognised in paediatric systemic juvenile idopathic arthritis (sJIA), more data on exceptional presentation of MAS-HLH in other CTD/inflammatory diseases in adulthood is useful. The current fatal case series described in our study aims to increase awareness of clinical features and outcome of these exceptional presentations of MAS-HLH in SLE, GS syndrome type 2 with possibly lymphoma and infection-induced AOSD flare.

Macrophage activation syndrome secondary to SLE is rare and the reported prevalence ranges between 0.9 and 4.6%.[3,9,10] Recognition of MAS-HLH in SLE patients is challenging, since it can mimic SLE flare, with delay in initiating appropriate treatment. The presence of unexplained fever, pancytopenia, liver dysfunction, jaundice, and high lactate dehydrogenase and ferritin levels unresponsive to immunosuppressive therapy should raise the suspicion for MAS-HLH.[10-12] Gavand et al. reported MAS occurring in more than half of their cohort after SLE diagnosis was made with a median delay of 106 months (range 49-177).[11] Therefore, the presentation of MAS in our patient at 192 months was relatively late. Indeed, our patient with SLE also presented with these symptoms as first manifestation of MAS-HLH, which was not recognised as such initially, with consequent admission to ICU and delay in treatment. High mortality rates (10-20%) are reported in case series of patients with MAS in studies among SLE patients.[3,13]

Our second patient, presented with neurological symptoms as manifestation of primary HLH. Central nervous system involvement has been reported in 30% of patients with MAS-HLH. In the current case, HLH was associated with GS type 2, which is a rare and fatal autosomal recessive disorder, due to homozygous pathogenic mutations in the RAB27A gene.[5] GS type 2 is associated with impaired pigmentation, primary immunodeficiency due to dysfunction of cytotoxic T cells and NK cells, with subsequent susceptibility to repeated infections and HLH, leading to death without haematopoetic cell transplantation. This patient did not suffer from albinism, which has been described in four patients with the same mutation.[14] Also, similar to our patient, late onset presentation of disease has been reported before, yet is very rare,[15] and may contribute to late recognition of the syndrome. Our patient had normal NK-cell function, unlike the other patients with the same mutation. An explanation for this may be due to somatic reversion leading to selective outgrowth of particular cell subsets, which has been reported in T-cell subsets in, for example, X-linked severe combined immune deficiency,[16] dedicator of cytokinesis 8 deficiency,[17] and Wiskott-Aldrich syndrome,[18] all autosomal recessive primary immunodeficiencies. Interestingly, post-mortem analysis of the bone marrow also revealed an abnormal T-cell population suggestive of a T-cell malignancy. An association between T-cell malignancies and MAS-HLH has been reported in the literature, in particular, with cutaneous T-cell lymphoma and T/NK-cell lymphomas.[19] To the best of our knowledge, there is no correlation reported between GS type 2 and T-cell malignancy.

The third patient had a MAS-HLH associated with infection and a flare of a therapy refractory AOSD all probably due to underlying myelodysplastic syndrome, despite lack of characteristic somatic mutations. Patients with AOSD may experience different life-threatening complications, including MAS, thrombotic thrombocytopenia purpura, pulmonary hypertension, and diffuse alveolar haemorrhage.[20] MAS as a complication of AOSD is reported in 10-25% of adult patients. MAS occurs primarily during the onset of AOSD, but can also develop during the course or a flare-up of AOSD.[20]

Different cytokines are reported to play a role in the pathogenesis of MAS-HLH, however, the involvement of interleukin (IL)-1 seems to play a central role in the pathogenesis, highlighted by the excellent clinical responses to IL-1 blockade in recent studies in sJIA and AOSD-related MAS. Recent observations suggest that initiation of anakinra early in the disease course may improve outcomes of MAS without significant side effects.[4,21,23] Furthermore, IL-1 blockade was associated with less mortality and complications (e.g., sepsis, malignancy) compared to the conventional treatment for MAS without masking clinical and biological features of underlying disease.[22-25]

In addition, a clinical trial is pending on the role of early treatment with IL-1 blockade in patients (both children and adults) with MAS-HLH from the group of Chatman et al. Interestingly, the Food and Drug Administration recently approved the use of emapalumab, an interferon gamma blocking antibody (IFNγ), for the treatment of primary and secondary HLH. Several animal and human studies have reported on elevated IFNγ in MAS-HLH. International phase 2/3 clinical trials are currently ongoing investigating the efficacy, safety, and long-term outcomes in paediatric patients diagnosed with primary HLH and secondary HLH associated with SJIA. Development of more targeted therapeutic options for patients with MAS-HLH may be lifesaving and have fewer side effects and toxicity than the conventional treatment protocol (HLH-2004).[26,27]

CONCLUSION

MAS-HLH is a potentially fatal complication in a heterogeneous group of underlying diseases, ranging from CTD or infectious disease to haematological conditions. Awareness and early treatment is warranted when diagnosis is suspected.

DISCLOSURE

HL attended advisory boards and received speakers fees from Novartis and Sobi.

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PHOTO QUIZ

Splenic incidentaloma

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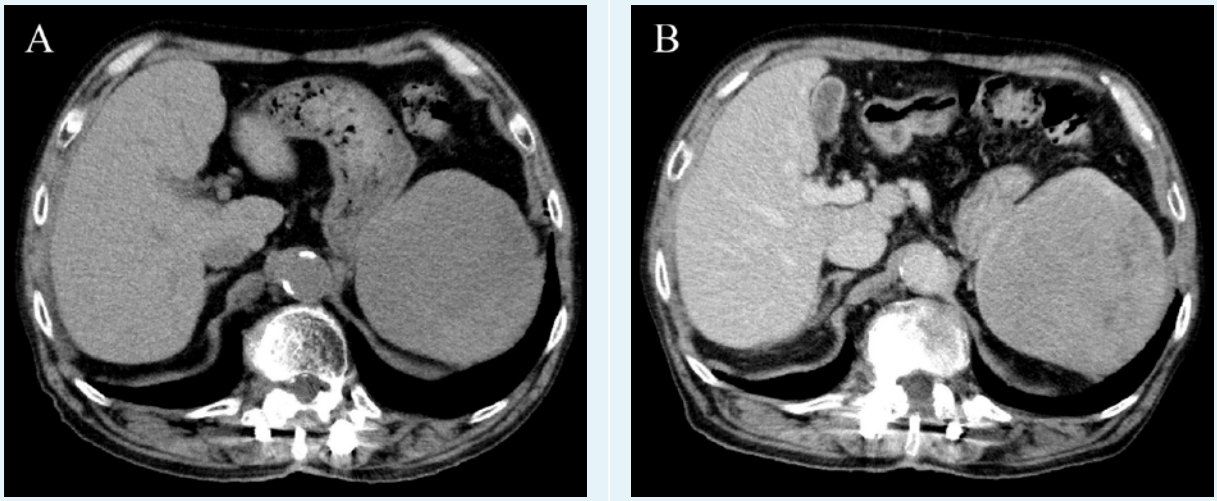
Figure 1. *(A) Non-contrast-enhanced computed tomography of the abdomen, showing an incidental splenic lesion. (B) Contrast-enhanced computed tomography of the abdomen, showing a hypodense and mild contrast-enhancing lesion with a well-defined border in the spleen.*



CASE REPORT

An 83-year-old man with hepatitis C presented to the hospital for follow-up imaging to monitor a thoracic aortic aneurysm. On examination, he was asymptomatic. Laboratory tests showed bicytopenia. Non-contrast-enhanced computed tomography (CT) described no change in size of the thoracic aortic aneurysm but an incidental splenic lesion (figure 1A). Contrast-enhanced CT scan revealed a hypodense, well-defined and mild contrast-enhancing lesion in the spleen (figure 1B).

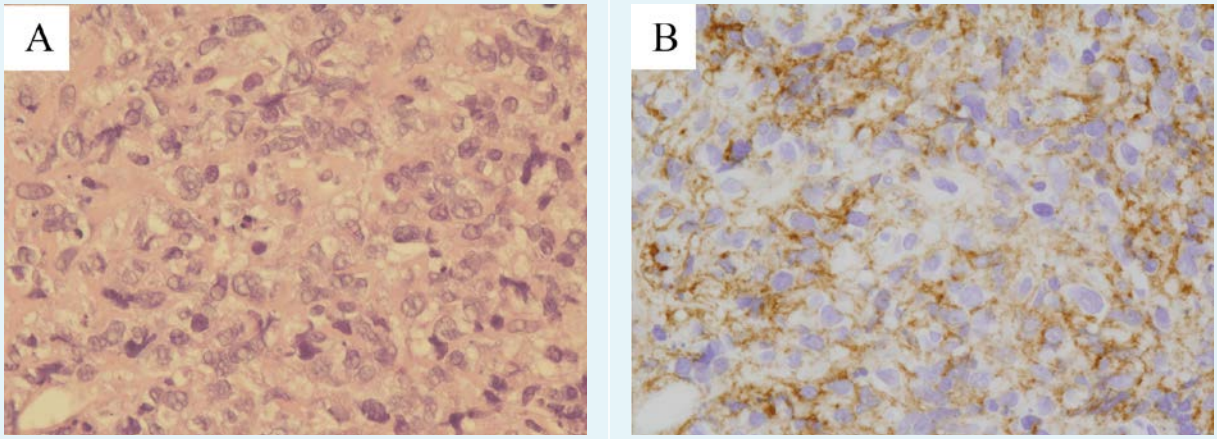
WHAT IS YOUR DIAGNOSIS?

See page 143 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 142)

SPLENIC INCIDENTALOMA

Figure 2. *(A) Histopathological evaluation of the splenic biopsy specimen, showing diffuse proliferation of atypical cells (haematoxylin and eosin stain, original magnification x400). (B) Immunohistochemistry of the splenic biopsy specimen, showing positive CD20 (original magnification x400).*



DIAGNOSIS

The differential diagnosis was angiosarcoma, splenic metastasis, or malignant lymphoma. Ultrasound-guided splenic core needle biopsy led to the diagnosis of diffuse large B-cell lymphoma (figure 2). Positron emission tomography-computed tomography indicated the presence of small lesions in the left scapula and the left ilium; thus the patient underwent chemotherapy with R-CHOP regimen. The patient is in complete remission.

Splenic incidental lesions are often encountered with abdominal CT. Although most of them are benign and are of no clinical significance, clinicians should pay closer attention to certain findings such as presence of solid, contrast-enhancing components and ill-defined borders.[1] These warning findings indicate potentially more relevant diseases including malignancy, abscess, and sarcoidosis. Although splenectomy is generally used for diagnosis, fine needle biopsy and core biopsy are of considerable diagnostic value of suspicious splenic lesions.[2]

Lymphoma represents the most common malignant neoplasm of the spleen. While the spleen is usually involved secondarily in patients with lymphoma, isolated primary splenic lymphoma comprises less than 2% of all lymphomas. Lymphoma of the spleen may present on abdominal CT as splenomegaly without focal lesions, multiple miliary nodules, multiple lesions, or a single solitary mass.[3] Although lymphomatous involvement of the spleen is seldom an incidental finding, it may be seen in patients with vague symptoms including left upper abdominal pain, weight loss, and fatigue. Because early recognition and immediate treatment are crucial for patient prognosis, clinicians should consider lymphoma as a possible differential diagnosis of splenic incidentaloma, especially with warning findings.

DISCLOSURE

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PHOTO QUIZ

A mobile abdominal mass

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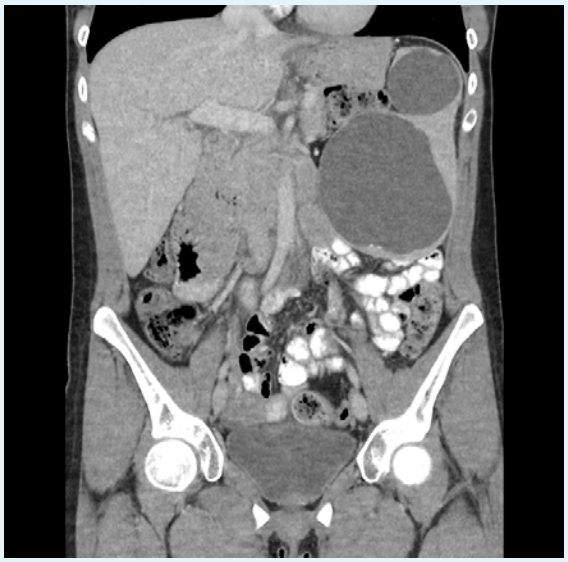
Figure 1. *A contrast-enhanced CT scan of the abdomen, coronal view, showing the enlarged spleen in the left upper abdomen with two cysts*



CT = computed tomography

CASE REPORT

A 22-year-old female was seen at our outpatient clinic because of a palpable mass in the left upper abdomen. She noticed the mass five weeks after she gave birth to a healthy girl after an uncomplicated delivery. She denied abdominal pain, weight loss, fever, or night sweats. She had travelled to Turkey eight years ago and around that time, fell from a horse but without apparent abdominal trauma. Physical examination revealed a palpable firm mass three fingers below the costal margin. Blood tests showed leucocyte count of 7.5 (normal range [NR] 3.5-10.0 x 10^9/l) with a normal differentiation; haemoglobin 8.4 (NR 7.5-9.5 mmol/l); platelets 210 (NR 150-370 x 10^9/l); C-reactive protein 1.9 (NR 0.0-9.0 mg/l); and erythrocyte sedimentation rate (NR 0-19 mm/h).

An ultrasound was performed, which showed an enlarged spleen with two cysts with diameters of 11 and 5.5 cm. A contrast-enhanced computed tomography (CT) scan of the abdomen showed two homogenous hypodense abnormalities in the spleen (figure 1).

The patient returned to the outpatient clinic earlier than planned because she felt pressure in the lower abdomen and experienced pollakisuria without dysuria. Upon physical examination, a mass was palpated in the lower abdomen. Pregnancy test was negative. A new ultrasound was performed, which showed that the spleen (no change in diameter or cysts) was located in the lower abdomen, cranial to the bladder. Serology for *echinococcus granulosus* was negative. In the absence of signs suggestive of malignancy, the cysts were felt to be congenital or post-traumatic.

WHAT IS YOUR DIAGNOSIS?

See page 145 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 144)

A MOBILE ABDOMINAL MASS

DIAGNOSIS

Of more than 3,000 patients undergoing splenectomy, only six were performed for a wandering spleen (*lien mobile*).[1-3] Patients can present with torsion of the splenic vasculature and acute or chronic abdominal pain, or be completely asymptomatic. Torsion can lead to infarction of the spleen, and a wandering spleen can also be complicated by gastric volvulus, bowel obstruction, gastric varices, pancreatitis (due to incorporation of the pancreas' tail in the spleen's vascular pedicle), and traumatic laceration. In cases of chronic or recurrent torsion, venous congestion can lead to splenomegaly.

The aetiology of a wandering spleen can be congenital or acquired. The congenital form is caused by a lack of development of the primary ligamentous attachments of the spleen. The acquired form can be caused by laxity of these attachments, which is thought to be caused by hormonal changes and multiparity. This association with pregnancy can explain the overrepresentation of females in the child-bearing age among adult patients with a wandering spleen. No association has been reported on the presence of cysts and a wandering spleen.

Because of the risk of torsion and other complications, splenectomy or splenopexy is recommended, without evidence on the supremacy of either option. Because the risk of torsion after splenopexy of a spleen this enlarged was deemed high, our patient underwent splenectomy. On pathological examination, two pseudocysts without evidence of malignancy were found (figure 2).

Figure 2. *Resection specimen of the spleen*

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PHOTO QUIZ

White striae and erosions of the oral mucosa, but it is not oral lichen planus

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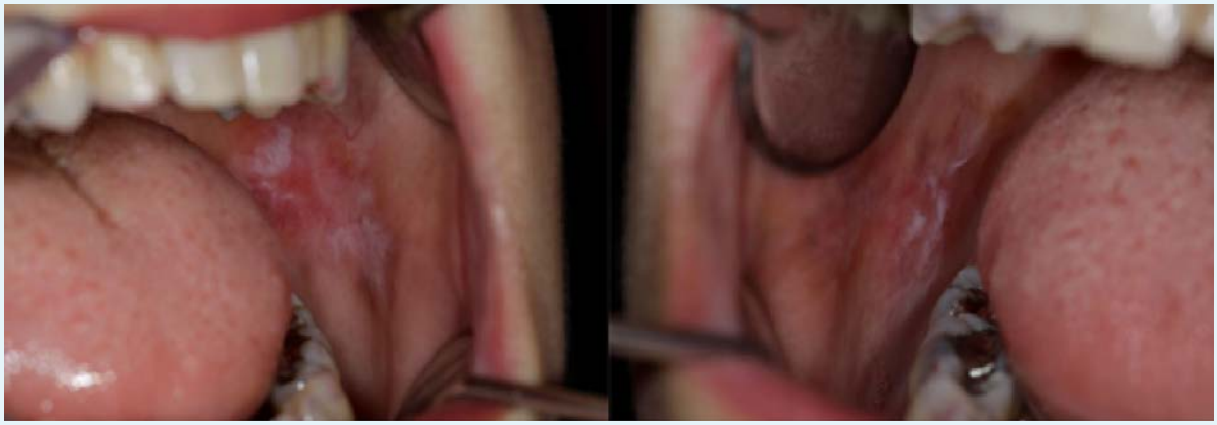
Figure 1. *Clinical aspect of Follicular lymphoid hyperplasia*



CASE REPORT

A 45-year-old female non-smoking patient came to our hospital complaining of relapsing-remitting pain on bilateral buccal mucosa. She was suffering from Hashimoto's thyroiditis, but was not under any replacement therapy. She had bimaxillary orthognathic surgery several years ago.

Clinical examination revealed the presence of bilateral atrophic lesions surrounded by white striae, involving the buccal mucosa (figure 1). The differential diagnosis for reticular changes of the buccal mucosa includes primarily lichen planus, lichenoid drug reaction, and contact allergy. We suspected symptomatic lichen planus and an incisional biopsy of the left buccal mucosa was performed.

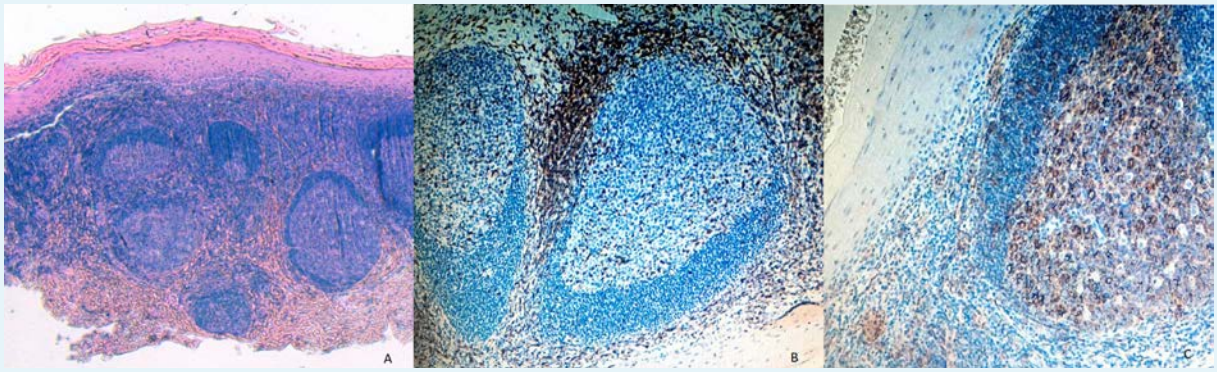
WHAT IS YOUR DIAGNOSIS?

See page 147 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 146)

WHITE STRIAE AND EROSIONS OF THE ORAL MUCOSA, BUT IT IS NOT ORAL LICHEN PLANUS

Figure 2. *Pathological assessment: H&E staining (A: magnification x 4), positive IHC staining for CD3 (B: magnification ×20) and CD20 (C: magnification ×20)*



H&E = haematoxylin and eosin; IHC = immunohistochemistry

DIAGNOSIS

Our pathological assessment showed hyperplastic aspect of the epithelium and the subepithelial tissue contained a dense follicular lymphoid infiltrate. The interfollicular tissue contained small lymphocytes, occasional large lymphocytes, plasma cells, and a few eosinophils (Positive: CD20, CD3; Negative: Bcl2, Bcl6, CD10, Mib1) (figure 2). An incisional biopsy was repeated on the right buccal mucosa with the same pathological assessment. The specimens were analysed by a second pathologist, who confirmed the diagnosis.

To complete the diagnostic process, in agreement with the haematologist, a blood exam, an ultrasonography of the abdomen, a chest X-ray, and protein electrophoresis were performed. The exams ruled out any systemic involvement. The diagnosis of oral lymphoid hyperplasia was concluded from the joint assessment of these results, together with the previous investigations. FLH may also originate from an oral lichen planus (OLP). In fact, OLP is an autoimmune disease that extensively involves the immune system and due to the immune activation, OLP could give rise to lymphoid follicles. The patient has been followed-up for 12 months with no sign of worsening of the lesions, which remained lightly symptomatic.

Follicular lymphoid hyperplasia (FLH) of the oral cavity is a rare lymphoproliferative disorder which may be confused clinically and histologically with malignant lymphoma. The condition has been described in different regions of the body: notably skin, gastrointestinal tract, lungs, nasopharynx, larynx, and breasts. Although rare, the oral cavity may also be involved.[1] The disease occurs in a wide age range, between 38 to 79-year-old patients, and is more common in women.[2] Clinically, the manifestation is a firm, painless, nonulcerated, slowly growing mass or swelling on the one side of the palate. Occasionally, the lesions may be multifocal and the patients may have bilateral involvement.[3] The lymphoid infiltrate may show the features of a benign reactive follicular hyperplasia, causing no difficulties in diagnosis but there is commonly an erroneous diagnosis of follicular lymphoma, with consequent staging procedures and unnecessary treatment. Oral manifestations of FLH have been reported in only approximately 30 cases, which showed the presence of swelling in particular of the hard palate. To the best of our knowledge, this is the first reported case of bilateral buccal mucosa involvement mimicking lichen planus. FLH is a rare and benign lymphoproliferative disorder, and interdisciplinary efforts are crucial to avoid diagnostic time delay.

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