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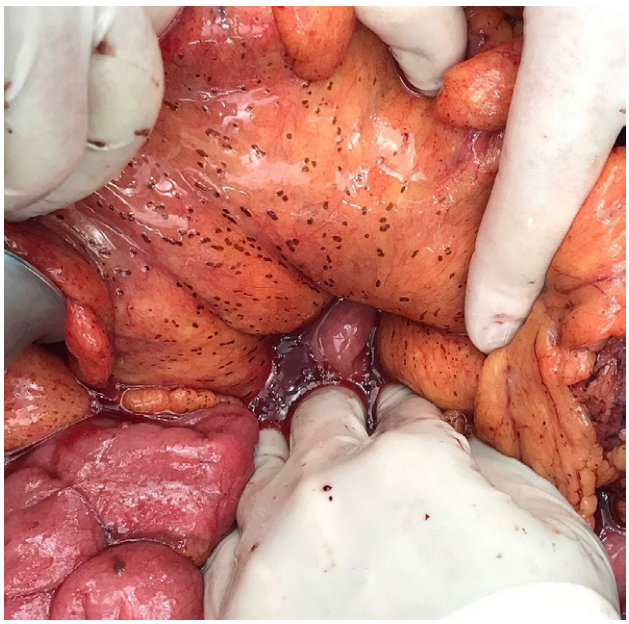

Multiple small blackish spots on the peritoneum: what is your diagnosis?

Influenza POCT and clinical pathway

MenW causes massive diarrhoea and sepsis

Transient thyroiditis after parathyroid surgery

A puzzling haptoglobin level

Successful treatment of aplastic anaemia

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EDITORIAL

Improving influenza care

P.L.A. van Daele

Although the influenza epidemic in the Netherlands was relatively mild with considerably less mortality as compared with previous years, this winter was long. Normally the influenza epidemic lasts about nine weeks. This year, it was prolonged by five weeks (source: RIVM report March 2019).

As mentioned by Lankelma et al. in this issue, the seasonal influenza epidemic poses a significant burden on hospitals in terms of capacity and costs.[1] It is known that patients suspected of suffering from influenza may be admitted to the hospital and cared for in isolation. This is done with the hope of reducing the risk of hospital transmission while awaiting results of respiratory sample testing. For a significant number of these patients, isolated care proves unnecessary.

Unfortunately, centralized laboratory testing of respiratory samples takes time. Accelerating diagnosis using point-of-care (POC) testing may prevent unnecessary isolation procedures. In recent years, rapid, sensitive and reliable POC molecular assays have been developed, reducing the time from sample collection to results.

Earlier this year, Ramahat-Langendoen et al. published a paper in which they described how using such a rapid POC molecular assay can reduce time-to-diagnosis, hospital stay and, thereby, in-hospital costs. This study was performed in a large university hospital in the Netherlands between December 2016 and April 2017. Both routine and rapid POC testing were performed and it was calculated that a reduction in-hospital costs by € 300-1000 per patient suspected of infection with influenza could have been achieved if decision on admission would have been based on the results of the latter test.[2]

Additionally, using a POC influenza testing led to a more accurate prescription of antivirals and antibacterial medication in another recent publication.[3]

In the study by Lankelma et al. in this issue, a similar, although not identical clinical pathway was actually implemented using the same commercially-available PCR-based test as was used in the previously mentioned studies. Their study was performed during the influenza epidemic in 2017-2018. POC testing was performed by trained emergency room nurses and even by receptionists who have first contact with patients, thereby further speeding up the time to diagnosis. Patients who were diagnosed with influenza were admitted to a separate ward for influenza patients. The authors estimated that by using this approach they saved an estimated total of € 400,000.[1] In the Netherlands, there are about 80 general hospitals. Using a similar approach throughout the country could theoretically lead to a reduction in over € 20 million on influenza-related costs. In fact, several other hospitals have already adapted and implemented this POC testing approach (https://www.zorgvisie.nl/ikazia-beperkt-opnamedruk-door-griep/).

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ORIGINAL ARTICLE

Diagnosing and treating antiphospholipid syndrome: a consensus paper

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KEYWORDS

Antiphospholipid syndrome, antiphospholipid antibodies, thrombosis, pregnancy morbidity, catastrophic antiphospholipid syndrome, treatment

ABSTRACT

Introduction. The antiphospholipid syndrome (APS) is defined by the occurrence of venous and/or arterial thrombosis and/or pregnancy-related morbidity, combined with the presence of antiphospholipid antibodies (aPL) and/or a lupus anticoagulant (LAC). Large, controlled, intervention trials in APS are limited. This paper aims to provide clinicians with an expert consensus on the management of APS.

Methods. Relevant papers were identified by literature search. Statements on diagnostics and treatment were extracted. During two consensus meetings, statements were discussed, followed by a Delphi procedure. Subsequently, a final paper was written.

Results. Diagnosis of APS includes the combination of thrombotic events and presence of aPL. Risk stratification on an individual base remains challenging. 'Triple positive' patients have highest risk of recurrent thrombosis. aPL titres > 99th percentile should be considered positive. No gold standard exists for aPL testing; guidance on assay characteristics as formulated by the International Society on Thrombosis and Haemostasis should be followed. Treatment with vitamin K-antagonists (VKA) with INR 2.0-3.0 is first-line treatment for a first or recurrent APS-related venous thrombotic event. Patients with first arterial thrombosis should be treated with clopidogrel or VKA with target INR 2.0-3.0. Treatment with direct oral anticoagulants is not recommended. Patients with catastrophic APS, recurrent thrombotic events or recurrent pregnancy morbidity should be referred to an expert centre.

Conclusion. This consensus paper fills the gap between evidence-based medicine and daily clinical practice for the care of APS patients.

Introduction

The antiphospholipid syndrome (APS) is defined by the occurrence of venous and/or arterial thrombotic events and/or pregnancy-related morbidity (≥ 3 unexplained consecutive spontaneous abortions < 10 weeks with exclusion of chromosomal causes, foetal death or severe pre-eclampsia before 34th week of gestation), combined with the presence of circulating antiphospholipid antibodies (aPL) and/or a lupus anticoagulant (LAC),

Table 1. *Classification criteria for the antiphospholipid syndrome*[1]
A patient can be classified as having the antiphospholipid syndrome when at least one clinical and one laboratory criterion is present. We consider arterial thrombosis in the eye as a defining clinical event for antiphospholipid syndrome; venous thrombosis of the eye is not considered a defining event. We prefer to use the 99th percentile cut-off value for anticardiolipin antibodies and do not use the > 40 GPL-cut-off.

Clinical criteria	
1. Vascular thrombosis (confirmed by imaging studies or histopathological studies)	a. One or more clinical episodes of arterial, venous or small-vessel thrombosis, in any tissue or organ
2. Pregnancy morbidity	a. Three or more sequential spontaneous abortions before 10th week of gestation; or b. Unexplained foetal death of a morphologically normal foetus after 10th week of gestation; or c. Early birth before 34th week of gestation of a morphologically normal foetus due to eclampsia, severe pre-eclampsia or confirmed placental failure
Laboratory criteria	
	a. Lupus anticoagulant (LAC) present in plasma, confirmed on minimally two occasions with an interval of at least 12 weeks b. Anticardiolipin-antibodies (aCL), IgG- or IgM-isotype, present in serum or plasma, with elevated titre (> 99th percentile), confirmed on minimally two occasions with an interval of at least 12 weeks c. Anti-β2 glycoprotein-I-antibodies, IgG- or IgM-isotype, present in serum or plasma (with titre > 99th percentile), confirmed on minimally two occasions with an interval of at least 12 weeks

see table 1.[1] Formally, LAC is the result of aPL binding to plasma proteins, mainly β2-glycoprotein, that have affinity for the negatively-charged phospholipids; therefore, the pathologic auto-antibodies are not directed against phospholipids. In this paper, the term 'aPL' refers to both LAC and anticardiolipin (aCL)/anti-β2-glycoprotein-I (anti-β2GPI) antibodies, following clinical practice and literature. APS is considered a primary autoimmune disease, but is often diagnosed as being secondary to other auto-immune diseases; 30-40% of patients with systemic lupus erythematodes (SLE) also have APS, and APS can be diagnosed secondary to rheumatoid arthritis, systemic sclerosis, dermatomyositis or other autoimmune diseases.[2] Large, controlled, randomised clinical trials for interventions in APS are limited, and the quality of current data is not sufficient to develop a structured guideline or assess evidence-based management strategies. However, clinically-relevant questions about diagnostic criteria and treatment of APS patients arise on a daily basis.
We aim to provide clinicians with an expert consensus on the management of APS, with a focus on classification, diagnostics, risk stratification, and treatment.

Methods

A literature review was performed (KdL and ML) with the following Pubmed search terms: 'antiphospholipid syndrome', "Antiphospholipid Syndrome"[Mesh], 'antiphospholipid antibodies', "Antibodies, Antiphospholipid"[Mesh], 'obstetric antiphospholipid syndrome', 'catastrophic antiphospholipid syndrome', 'laboratory diagnostics', 'Clinical Laboratory Techniques"[Mesh] 'diagnosis', "Diagnosis"[Mesh], 'treatment' and "Therapeutics"[Mesh]; papers focusing on diagnostics and/or treatment for APS were included. Non-English papers and papers published before 2000 were excluded. The literature search was performed on April 3rd, 2018; papers published after that date but with high impact according to the writing committee were included until September 1st, 2018. Statements on APS diagnostics and treatment were extracted from the papers selected, and a first draft of the consensus paper was written (KdL and ML). This draft was circulated amongst all authors and comments were

Table 2. *Non-criteria clinical manifestations of antiphospholipid syndrome*

Livedo reticularis/racemosa
Heart valve lesions/Libman-Sacks endocarditis
Thrombocytopenia
Superficial venous thrombosis
Nephropathy
Migraine
Chorea
Epilepsy
Myelitis transversa
'SLE-like' symptoms (e.g. alopecia, aphthous ulcers)

SLE = systemic lupus erythematosus

collected. On June 6th, 2018, a first consensus meeting was held in Utrecht, The Netherlands. Based on the outcomes of this meeting, a second draft of the paper was written (JS, ML) and circulated again for comments. On November 5th, 2018, a second consensus meeting was held in Utrecht, The Netherlands. Degree of consensus on statements was assessed by a Delphi procedure and a final report was written afterwards (see table 3).

Diagnosis, classification, risk stratification

Diagnosis of APS

No *diagnostic* criteria for APS exist. If a patient meets the classification criteria – developed for research purposes – for APS (e.g., a thrombotic event and/or pregnancy morbidity, combined with repeated presence of antiphospholipid antibodies (aPL); see table 1), most likely a clinical diagnosis of APS will be made, although thrombotic and pregnancy complications are not necessarily causally related to circulating aPL.

In addition to the thrombotic or pregnancy-related events listed in the classification criteria, APS may be associated with a variety of *non-criteria manifestations*, such as superficial vein thrombosis, thrombocytopenia, renal microangiopathy, heart valve disease, livedo reticularis or racemosa, migraine, chorea, seizures and myelitis; see table 2. As a result, a *clinical* diagnosis of APS can be made in patients who do not fulfil the classification criteria.[3]

An even more complicating factor is the concept of seronegative APS, a term coined to include patients with clinical (criteria and non-criteria) features suggestive of APS, but who are persistently negative for aPL.[4] The existence of seronegative APS is a point of international discussion among experts. If the suspicion of seronegative APS arises, we suggest referral to an expert centre.

Catastrophic antiphospholipid syndrome (CAPS) is the most extreme APS variant that includes simultaneous multiple organ thrombosis and develops in a short period of time with a high mortality rate. Although strongly associated with the presence of LAC, no other laboratory or clinical determinants are known to be associated with CAPS.[2]

Risk stratification in APS

Several assessment tools to risk-stratify patients have been proposed, mainly focusing on presence and levels of aPL and/or on clinical parameters. For aPL, the presence of LAC is the strongest risk factor for both arterial and venous thrombosis in APS.[5,6] For aCL and anti-β2GPI, the association between (levels of) antibodies and thrombosis is less clear. It has been suggested that anti-β2GPI-dependent LAC has a strong association with thrombotic risk.[7] In several studies, it has been demonstrated that the risk of arterial and venous thrombosis increases with the number of positive tests for aPL, with the highest risks in patients with both LAC, aCL and anti-β2GPI antibodies, so-called 'triple positive patients'.[6,8] In clinical practice, risk stratification does not affect treatment decisions in most situations. The antiphospholipid score (aPL-S) has been developed to predict the risk of APS-related clinical events in patients with APS and other autoimmune diseases (such as SLE, rheumatoid arthritis, and Sjögren's syndrome) based on the presence of aPL.[9] The global APS score (GAPSS) is another clinical score, including both aPL and conventional cardiovascular risk factors, predicting the risk of thrombotic events in patients with SLE.[10] The GAPSS has been validated in a cohort of APS patients, and a correlation between higher GAPSS values and recurrence of thrombotic events was observed.[11] However, these scores are not sufficient to design treatment strategies for the individual patient. We consider triple positive patients to be at highest risk for recurrent thrombosis.

Laboratory diagnostics in APS

The classification criteria for APS indicate three different antibody subsets of aPL. For two of these, the antigen is well-defined: aCL antibodies recognize the plasma glycoprotein β2GPI in complex with the anionic phospholipid cardiolipin, and anti- β2GPI antibodies recognize the protein β2GPI in the absence of cardiolipin. Both antibody subtypes can be detected with quantitative solid phase assays in which the antigen is immobilized on a surface. The third aPL subtype, known as LAC, is detected with a functional assay: these antibodies manifest as phospholipid-dependent inhibitors of *in vitro* coagulation. They are detected with phospholipid sensitive coagulation assays. Although the exact antigen to which LAC are directed is currently unclear, there is ample evidence that antibodies against β2GPI as well as antibodies against prothrombin can induce the LAC phenomenon.[12,13]

The diagnosis of APS is made in cases of persistent presence of aPL (titre > 99th percentile), assessed in two separate samples taken with an arbitrarily defined interval of at least twelve weeks. This is an important distinction, as several aPL occur transiently in relation to viral and bacterial infections and are of uncertain clinical relevance.[14] Moreover, since aPL is prevalent (1-5%) in the general population,[15] aPL status should only be tested in patients considered at risk of having APS, such as those < 50 years of age, unprovoked arterial or venous thrombosis, thrombosis at an unusual site, recurrent thrombosis, and thrombotic/pregnancy complications with or without association with a systemic autoimmune disease.[16-18]

Unfortunately, gold standards for aPL detection are lacking, although aCL assays based on pooled human serum have been in use for over 20 years.[19] Reports have

been published of new standards based on human(ized) monoclonal antibodies against β2GPI and purified patient-derived polyclonal antibody preparations, but these are not yet available.[20] No such standards exist for LAC-positive plasmas. For further harmonization of results between diagnostic laboratories, centres performing these tests participate in diagnostic surveys as part of laboratory accreditation.

Measurement of anticardiolipin and anti-β2-glycoprotein I antibodies

The classification criteria for APS specify that both immunoglobin G (IgG) and IgM class immunoglobulins against cardiolipin or β2GPI should be measured. Several commercial entities supply kits to measure these antibodies and many laboratories have developed their own solid phase assays. To minimize the effect of the lack of gold standards and the large number of assays in use for detection of aPL on assay standardization, guidance on assay characteristics has been provided by the Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis.[16] Detection of aCL and β2GPI antibodies can be performed in both trisodium citrate anticoagulated plasma and in serum. Since aCL antibodies associated with APS are β2GPI-dependent, diagnostic laboratories should use assays in which cardiolipin is saturated with human β2GPI. Samples should be considered positive when the value obtained in these assays exceeds the 99th percentile of the normal population, rather than antibody levels exceeding 40 arbitrary units as indicated in the classification criteria, as this appears to be more specific for APS.[21] We recommend that the laboratory report mentions both a cut-off value (< 99th or > 99th percentile, e.g., negative or positive) and a continuous numeric value.

Detection of lupus anticoagulant

LAC are phospholipid-dependent coagulation inhibitors and are detected with sensitive coagulation assays in trisodium citrate anticoagulated plasma. Plasma samples should be double centrifuged to minimize contamination with platelets, as they are a major source of phospholipid and might therefore interfere with LAC detection.[17,18] LAC can be detected with any phospholipid-dependent coagulation assay, however, no gold standard for LAC testing exists. For this reason, it is warranted to perform two tests based on a different assay principle for LAC detection, preferably a dilute Russell's viper venom time (dRVVT) and a LAC-sensitive activated partial thromboplastin time (APTT).[17] In order to be deemed LAC-positive, a sample should have a prolonged clotting time when a reagent with a low phospholipid content is used (screening test), which should correct when a reagent with a high phospholipid content is used (confirmatory test), indicating phospholipid-dependence of the prolongation. The presence of a coagulation inhibitor as the cause of the prolongation should be shown with a mixing test, in which patient plasma is mixed with an equal volume of pooled normal plasma. This will normalise any coagulation factor deficiencies that are present, and any remaining prolongation of the clotting time is therefore caused by an inhibitor. Cut-off values for LAC should be determined locally in each diagnostic laboratory, based on the 99th percentile of the local normal population or alternatively, on the mean + 2 standard deviation (SD) of the clotting time of the normal population. The strength of the LAC should be expressed as a ratio between screen and confirm clotting times, preferably normalized on the mean of the normal population, according to the following equation:

$$\text{normalized LAC ratio} = \frac{\text{Screen(patient)/Screen(normal)}}{\text{(Confirm(patient)/Confirm(normal)}}$$

Samples are deemed positive for LAC when one or both tests for LAC detection (APTT and dRVVT-based tests) indicate the presence of LAC.

The use of anticoagulant drugs interferes with detection of LAC, possibly resulting in false-positive test results. Samples for LAC-detection should therefore be collected before treatment with anticoagulants has started, or sufficiently long after cessation of treatment to minimize confounding effects. However, it should be avoided to use samples obtained in the acute phase after a thrombotic event or during infection, as this is associated with high Factor VIII levels, which might interfere with LAC detection by APTT-based assays. Although LAC can be determined in samples from patients receiving vitamin K antagonists when they are mixed with an equal volume of pooled normal plasma, the outcome of LAC tests in samples with an INR within therapeutic range (INR 2-3) should be interpreted with caution and measurement of LAC in samples with an international normalised ratio (INR) > 3 is not recommended. Mixing antagonists with normal plasma dilutes the titre of LAC and thus reduces the sensitivity of the assay. On the other hand, the mixing test may not completely correct the clotting time for samples in the high INR range and may lead to false-positive interpretation. Temporary discontinuation of vitamin K antagonists (or co-administration of vitamin K and continuing vitamin K antagonists) and bridging with low molecular weight heparin is possible. Unfractionated heparin, however, is incompatible with LAC testing, as is the use of direct oral anticoagulants, even at trough levels of factor Xa or thrombin inhibitors, with factor Xa inhibitors producing false-positive LAC.[22] No alternatives exist for LAC detection in samples containing direct

thrombin inhibitors. A possible means to detect LAC in samples containing rivaroxaban is the Taipan snake venom time/Ecarin clotting time combination, as these tests are insensitive to factor Xa-inhibitors.[23] More studies on the specificity and sensitivity for LAC of this test combination are required before these tests will be widely adopted for LAC detection.

Non-criteria aPL

There are several reports on the association between various non-criteria aPL subtypes and thrombosis. Amongst these are IgA anti-β2GPI antibodies,[24-26] antibodies against the phospholipid phosphatidylethanolamine (PE),[27] antibodies against the complex between the phospholipid phosphatidylserine, and the coagulation factor prothrombin (aPS/PT).[28] Currently, however, there is insufficient evidence of their clinical relevance to warrant routine detection of these antibodies.

Treatment

Venous thrombosis in APS

A first venous thrombotic event (VTE; amongst others including deep vein thrombosis and pulmonary embolism, abdominal vein thrombosis, cerebral vein thrombosis) should be treated according to the current guidelines for treatment of VTE; no routine testing for aPL is indicated in the general population. In cases of recurrent thrombosis (both provoked and unprovoked), or patients with a pre-existing autoimmune disease (and in particular, SLE), additional testing for aPL should be performed.

Low molecular weight heparin (LMWH) in therapeutic doses and subsequent vitamin K antagonists (VKA) are first-line treatments for a first or recurrent APS-related venous thrombotic event (VTE). Treatment with direct oral anticoagulants (DOACs; see separate section below) is not recommended. For APS patients with a first VTE, life-long anticoagulation is recommended. After treatment with LMWH in the acute phase, treatment will be switched to VKA, with an INR target range of 2.0-3.0 for venous events.[29,30] High-intensity treatment with an INR ≥ 3.0 after a first VTE is not recommended.[31,32]

Arterial thrombosis in APS

Optimal long-term treatment for arterial thrombosis (other than cerebral arterial thrombosis; see below) is still a matter of debate; either anti-platelet therapy such as aspirin or clopidogrel, VKA with an INR target range of 2.5-3.5 or combined therapy with VKA with an INR target range of 2.0-3.0 and anti-platelet therapy has been recommended.[30] As combined therapy, VKA and anti-platelet therapy has not been shown to be superior to anti-platelet therapy alone, and since more major bleeding complications were observed in the combination group,[33] we do not recommend up-front combined treatment with both VKA and anti-platelet therapy. Based on expert opinion and in slight contrast with international recommendations, we prefer treatment with either clopidogrel or VKA with an INR target range of 2.0-3.0 in these patients.[33,34]

In patients with a cerebral ischemic event (transient ischemic attack (TIA) or ischemic stroke) as clinical manifestation, there is no evidence supporting one therapy over the other. A prospective, comparative study in aPL-positive stroke patients showed no benefit of warfarin over aspirin (325 mg/day) on recurrent events; more (minor) haemorrhagic complications in the warfarin group were observed. However, these patients did not necessarily fulfil APS criteria.[35] A small (n = 20), randomized, controlled trial in APS patients with ischemic stroke compared VKA and low-dose aspirin with low-dose aspirin alone, and demonstrated less recurrent stroke in the combined-therapy group.[36] In APS patients with a first ischemic stroke or TIA without any cause other than APS on work-up, we propose treatment with either VKA with an INR target range of 2.0-3.0 or clopidogrel (since this is superior to aspirin for stroke prevention in a general population suffering from atherosclerotic cerebrovascular disease).[37]

Position of direct oral anticoagulants in APS

DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban, were shown to be non-inferior to VKAs for treatment and secondary prevention of venous thromboembolic events and prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[38] Furthermore, these drugs have some advantages compared to VKAs as it is a fixed dose, no monitoring is required, interaction is limited, and there is a lower risk of intracranial and other major bleeding. Nonetheless, few studies are published concerning the use of DOACs in known APS. A recent review summarised the available data, including one randomized controlled trial (RAPS trial) and case series.[39]

From all available case series and case reports, 122 patients were analysed.[39] High-risk APS patients with triple positivity or with several clinical criteria for definite APS, developed recurrent thrombosis more frequently while on DOACs in comparison to warfarin. The RAPS trial, comparing 54 APS patients treated with rivaroxaban to 56 APS patients treated with warfarin, demonstrated that the *in vitro* anticoagulant effect of rivaroxaban may be inferior to that of warfarin.[40] A randomized controlled clinical trial in triple positive patients, comparing VKA treatment with rivaroxaban, was terminated early due to more thrombotic events in the rivaroxaban-arm, with particularly more ischemic strokes in the DOAC group.[41]

At this moment VKAs, compared to DOACs, remain the standard of care in the treatment of APS, especially in high-risk APS patients. DOACs might be an alternative

treatment modality for only those patients with instable INR or poor adherence to INR monitoring, and we anticipate more data from future trials using DOACs in thrombotic APS.

Recurrent venous thrombotic events while using anticoagulation therapy

Recurrent thrombosis in APS patients, despite adequate anticoagulation therapy (INR target range, 2.0-3.0) is common and occurs in up to one-third of all patients.[2] However, recurrent thrombosis is uncommon in APS patients with a higher INR target range of 2.5-3.5 and most patients treated with a VKA with recurrent thrombosis, appear to have an INR target < 3.0.[42] Therefore, anticoagulation therapy should be intensified with a INR target range of 2.5-3.5 in case of a recurrent venous event despite adequate INR. When a recurrent venous thrombosis is diagnosed with a suboptimal INR (< 2.0), therapeutic LMWH should be given for a period of two weeks and the INR treatment range should not be changed. Note that the INR value can be underestimated due to interference of thromboplastin and LAC, although this is mostly problematic with higher INR values, i.e. > 4.0.[43]

If the target INR cannot be reached and/or maintained with VKA, referral to an expert centre is recommended.

Based on expert opinion, in patients with recurrent venous thrombosis, despite an adequate INR target range of 2.5-3.5 and after two weeks of therapeutic LMWH, additional long-term use of aspirin can be recommended, or intensifying of VKA therapy with to an INR target range of 3-4. Alternatively, a permanent switch to therapeutic LMWH can be considered.

Combining VKA with hydroxychloroquine may also decrease the risk of recurrent venous thrombosis, although randomized studies with hydroxychloroquine in APS are still lacking.[44,45]

Until now, no clinical support for the use of statins in patients with recurrent venous thrombosis despite anticoagulation exists. However, based on *in vitro* work and surrogate endpoints, a beneficial role of statins has been suggested.[46,47]

Recurrent arterial thrombotic events while using anticoagulation therapy

No consensus on treatment of recurrent arterial thrombosis was reached at the last meeting of the APS task force.[30] Optimal treatment strategies for recurrent arterial thrombotic events have not been studied. In recurrent arterial thrombosis, including TIA or ischemic stroke, despite treatment with clopidogrel, we suggest switching treatment to VKA with an INR target range of 2.0-3.0.

If recurrent arterial thrombosis occurs despite adequate treatment with VKA, referral to an expert centre is recommended.

We do not recommend to routinely perform brain magnetic resonance imaging (MRI) in APS patients with an ischemic stroke. However, some experts believe that if neurological symptoms, including migraine or cognitive performance, deteriorate, a repeat brain MRI is indicated and new white matter abnormalities may lead to intensifying treatment. The possible benefits of this strategy have not been confirmed in clinical studies, and for patients with deterioration of neurological symptoms, referral to an expert centre is recommended.

Catastrophic antiphospholipid syndrome (CAPS)

CAPS is a rare complication of APS and occurs in approximately 1% of APS patients. CAPS is a severe condition, including massive (mostly arterial) thrombosis of small vessels, causing multi-organ failure. Mortality in CAPS is high, up to 50%. Adequate and fast treatment initiation slightly improves clinical outcomes (mortality 20-40%) and treatment should be carried out in an expert centre.[48,49] A combination of anticoagulant drugs (mostly unfractionated heparin with APTT ratio 2-2.5), intravenous corticosteroids (methylprednisolone 500-1000 mg/day for 3-5 days), therapeutic plasma exchange (TPE) and/or intravenous immunoglobulins (IVIG) (1 g/kg, for a time period of 3 days) is associated with highest survival rates. Combination of heparin-corticosteroids-plasmapheresis with or without additional IVIG results in 69-78% patient survival.[50-52] TPE should be started when the clinical suspicion of CAPS arises, within a minimum of 5 days.[52] Clinical response dictates the duration of TPE and no single clinical or laboratory parameter is used to determine when to discontinue treatment.

For patients with CAPS and underlying SLE, treatment with cyclophosphamide (750 mg/m^2 monthly) has been proposed.[48,53] Rituximab (anti-CD20) has been administered to patients with refractory CAPS and may be of adjunctive value in a selected population of patients. Eculizumab (anti-complement 5) has been reported in case reports as a last resort, and could be considered in those patients refractory to all other therapies.[54,55]

Pregnancy and antiphospholipid antibodies

Pregnancy complications of APS include recurrent first trimester pregnancy loss, intrauterine growth restriction (IUGR), preeclampsia (PET), premature birth, and intrauterine death (IUD). Early miscarriages are reported in 26-35% and aPL-related PET, premature birth or foetal death are seen in 10–20% of APS pregnancies.[2,56]

Women with positive aPL do not all carry the same obstetric risk. The following parameters are associated with an increased risk: the presence of LAC, more than one

aPL (especially triple positivity), IgG aPL (instead of IgM), previous thrombosis, previous pregnancy complications, associated autoimmune condition, and hypocomplementemia.[57] At present, however, risk stratification does not direct different treatment strategies.

The current standard treatment, based on low-dose aspirin and LMWH, increases the percentage of a successful pregnancy from 20% to 54-80%.[58] In patients with obstetrical APS, aspirin and a prophylactic dose of LMWH should be administered. Depending on the context (concurrent SLE, maternal age, non-criteria clinical features), treatment of patients with fewer than three miscarriages, and therefore, formally not classified as having APS, can be considered. To prevent overtreatment in these cases, confirmation of miscarriage by ultrasound is recommended. During pregnancy, regular clinical pregnancy follow-up is sufficient; only in specified subpopulations (e.g. patients with SLE, chronic kidney disease, morbid obesity, triple positive antibody profile, and patients with a thrombotic event during pregnancy), follow-up (of foetal growth and hypertensive pregnancy complications) should be intensified. Platelets should be checked at least once every 10-14 days after starting LMWH to exclude heparin-induced thrombocytopenia. If pregnancy complications (foetal death or miscarriage) still occur despite combined treatment with low-dose aspirin and prophylactic dose of LMWH, the dose of LMWH can be increased to a therapeutic dose; reverting back to a prophylactic dose of LMWH after 36 weeks of gestation can be considered.

Based on expert opinion, patients with APS who already use therapeutic anticoagulation before pregnancy, should be switched to therapeutic dose of LMWH and low-dose aspirin should be added. Anti-factor Xa levels should be periodically monitored (at least once every trimester) in patients receiving therapeutic doses of LMWH, depending on the context.

If this strategy fails, further treatment should take place in an expert centre. The recommendations are again based on expert opinion and retrospective cohort studies and include, for example, the addition of hydroxychloroquine or intravenous immunoglobulins. This should however, be confirmed in randomized controlled trials.[59-61]

In the postpartum period there is an increased risk for thrombosis. Patients with APS with an indication of therapeutic anticoagulation before pregnancy, should be switched to VKA or continue with therapeutic LMWH. Obstetrical APS patients should receive prophylactic or intermediate doses (a randomized clinical trial to investigate optimal dosing is currently underway[62]) of LMWH during a period of six weeks postpartum.[57]

Withdrawal of antithrombotic treatment in APS

As mentioned above it is recommended to treat thrombotic APS patients lifelong. However, as long-term anticoagulation therapy is associated with haemorrhagic complications, the question arises whether it is possible to withdraw this therapy in selected patients, especially those who have a long-term event free period or who no longer have positive aPL, also called seroconversion. Only a few (uncontrolled and small) studies have addressed this question. Criado-Garcia *et al* described the effects of anticoagulation withdrawal in six primary APS patients in whom aPL had disappeared.[63] None of these patients experienced a thrombotic event during a follow-up of 21 ± 4.9 months. It should be mentioned, however, that these patients were at low risk for recurrence, as they only had a venous thrombosis history. Similar results were found by Coloma Bazan *et al*, who reported no thrombotic recurrences after anticoagulation withdrawal durign a median follow-up of 20 months in 11 primary APS patients (seven with history of venous thrombosis and four with obstetrical APS).[64] However, in a more recent study, 30 APS patients with anticoagulation withdrawal were compared to a thrombotic APS control population without withdrawal. During a median follow-up of 51 months, anticoagulation withdrawal was associated with a higher risk of thrombotic relapse (HR 4.82). Predictive factors were male gender, anti-β2GPI-positivity and triple positivity at onset as well as persistence positivity over time. Predictive factors for low risk of relapse were aspirin prescription and aPL disappearance during follow-up.[65]

In conclusion, data is insufficient to draw firm conclusions concerning anticoagulation withdrawal in APS patients. The available data suggests that anticoagulation could be withdrawn in APS patients with a single provoked venous thrombotic event in the presence of a known transient precipitating risk factor (such as smoking, disease activity, oral contraceptive use) together with disappearance of aPL. In all other situations, the high risk of thrombotic relapse favours the continuance of anticoagulation treatment. Randomized studies with larger sample sizes are still needed to confirm these statements.[66,67]

The decision to withdraw anticoagulation in APS patients should be made in an expert centre.

Position of rituximab, hydroxychloroquine, intravenous immunoglobulins

Several immunomodulatory drugs are suggested for the treatment for patients with APS, although their exact use in the treatment of APS is unclear; these include. rituximab, hydroxychloroquine (HCQ), and IVIG. Most evidence is based on cohort studies, case series or expert opinion. Only a few randomised controlled trials (RCTs) are published. Furthermore, their application is strongly dependent on the different clinical situations. For example, in secondary APS in SLE patients, HCQ is strongly recommended, as it has been shown that HCQ has 'thrombo-protective' effects, resulting in fewer

venous and arterial thrombotic events.[68] In primary APS, limited data is available. One retrospective cohort study demonstrated strong reduction of aPL titres and a decrease in the incidence of arterial thrombosis recurrence by using HCQ.[69,70] One RCT randomizing 40 APS patients to VKAs versus VKAs with HCQ showed a protective effect of adding HCQ upon venous thrombotic events.[45] At this moment, HCQ is not included in standard care of primary APS, but refractory cases, including refractory obstetrical APS, might benefit from this treatment. Treatment with HCQ (200-400 mg per day) is safe during pregnancy and lactation.

Rituximab and IVIG may be used in difficult-to-treat APS patients, especially in those with CAPS or recurrent haematological non-criteria manifestations as thrombocytopenia, but not as standard of care of APS.[71,72]

Prophylaxis in aPL-positive patients without earlier events

The question remains whether patients with obstetric APS or individuals with positive aPL without thrombotic events should be treated to prevent thrombosis (primary thromboprophylaxis). At present, there is insufficient evidence to support prophylactic treatment for all of these patients.[8,73] However, in patients with more risk factors for thrombosis (such as obesity, smoking, higher age) and/or high-risk aPL profile (e.g., triple positive), low dose aspirin might be beneficial. In any case, attention should be paid to avoid or to treat any associated cardiovascular risk factors, e.g. using antihypertensives or cholesterol-lowering agents and avoidance of smoking, etc. Also, the administration of oral contraceptives should be used with caution and with counselling.[74] Lastly, prophylaxis of venous thrombosis using LMWH is required for patients in situations associated with increased risk of thrombosis, such as surgical procedures, plaster casts, and those requiring bed rest.

Box 1. *Recommendations for consultation and/or referral of patients to an APS expert*

- Recurrent thromboembolic events despite adequate treatment with VKA and/or anti-platelet therapy
- Recurrent obstetric events despite therapy with low dose aspirin and LMWH in prophylactic dose
- Strong suspicion of APS with negative aPL
- Positive aPL but only non-criteria manifestations
- APS-patients with deterioration of neurological symptoms
- (Suspected) CAPS
- Withdrawal of anticoagulation in APS patients

VKA = vitamin K antagonists; LMWH = low molecular weight heparin; APS = antiphospholipid syndrome; aPL = antiphospholipid antibodies; CAPS = community-acquired pneumonia

Conclusion

APS is a rare and heterogeneous disease and as a result, well-designed and well-conducted clinical trials are scarce and the development of a formal guideline is difficult. However, by combining data from completed clinical intervention trials together with observational data and data from research in other thrombotic and/or inflammatory conditions, recommendations for clinical practice can be formulated. Current national and international initiatives – such as the Dutch Arthritis Research and Collaboration Hub (ARCH) and the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN-ReConnet) – are aiming to structure the care for APS patients to offer a unique future opportunity to collect longitudinal clinical data on APS treatment and outcomes. Until a formal guideline has been made, this consensus paper fills the gap between evidence-based medicine and daily clinical practice for the care of APS patients.

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DISCLOSURES

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Table 3. *Degree of consensus according to Delphi procedure outcome. 1 Denotes 'totally disagree', 10 denotes 'fully agree'*

Nr	Statement	Average	Range
1	Seronegative APS is acceptable as a clinical entity	6.1	3 - 10
2	Triple positive patients have highest risk of recurrent thrombosis	9.3	8 - 10
3	Non-citeria aPL should not be tested routinely	8.3	1 - 10
4	Low molecular weight heparin (LMWH) in therapeutic doses and subsequent vitamin K antagonists (VKA) is first-line treatment for a first or recurrent APS-related thrombosis	9.3	7 - 10
5	Treatment with direct oral anticoagulants is not recommended for APS patients	8.5	6 - 10
6	For APS patients with a first thrombotic event, life-long anticoagulation is recommended	7.4	1 - 10
7	For APS patients with 1st VTE, VKA with INR 2-3 is recommended	9.5	7 - 10
8	For APS patients with 1st VTE, high-intensity treatment with an INR ≥ 3.0 is not recommended	9.8	9 - 10
9	For APS patients with first arterial event including TIA or ischemic stroke, treatment with either VKA with target INR 2.0-3.0 or clopidogrel is recommended	8.1	3 - 10
10	Anticoagulation therapy should be intensified with a target INR between 2.5-3.5 in case of a recurrent venous event despite adequate INR (2.0-3.0)	9.6	8 - 10
11	If the target INR cannot be reached and/or maintained with VKA in patient with recurrent VTE, continuous treatment with therapeutic dosing of LMWH can be considered	8.6	8 - 10
12	In patients with recurrent VTE despite an adequate target INR 2.5-3.5, after two weeks of therapeutic LMWH, additional long-term use of aspirin can be recommended, or intensifying of VKA therapy to a target INR 3-4	8,5	3 - 10
13	In recurrent arterial thrombosis, including TIA or ischemic stroke, despite treatment with clopidogrel, we suggest switching treatment to VKA with a target INR 2.0-3.0	9.3	7 - 10
14	If neurological symptoms – including migraine or cognitive performance – in APS patients deteriorate, repeating brain MRI is indicated and new white matter abnormalities may lead to intensifying treatment	7.7	2 - 10
15	For the treatment of CAPS, a combination of heparin/methylprednisolone/PE and/or IVIG is recommended	9.2	8 - 10
16	In patients with obstetrical APS, aspirin and prophylactic dose of LMWH should be given	8.7	3 - 10
17	For pregnant patients with APS, regular clinical pregnancy follow-up is sufficient; follow-up should be intensified only in specified subpopulations (patients with chronic kidney disease, morbid obesity, triple positive antibody profile and patients with a thrombotic event during pregnancy)	7.2	3 - 10
18	If pregnancy complications still occur despite treatment with low dose aspirin and prophylactic LMWH, the dose of LMWH can be increased to a therapeutic dose	8.7	6 - 10
19	Patients with primary or secondary APS who already use therapeutic anticoagulation before the pregnancy, should be switched to therapeutic dose of LMWH and low-dose aspirin should be added	8.9	3 - 10
20	Obstetrical APS patients should receive prophylactic LMWH during a period of 6 weeks, post-partum	9.5	8 - 10
21	Anticoagulation could be withdrawn in APS patients with only a single venous thrombotic event in the presence of a known transient precipitating risk factor (e.g., smoking, disease activity, oral contraceptive use) together with disappearance of aPL	7.9	4 - 10
22	Patients with seronegative APS with recurrent thrombosis need long-term anticoagulation therapy	8.6	1 - 10
23	Women with seronegative APS and recurrent pregnancy complications should receive the same treatment as established APS patients	6.6	1 - 10
24	In patients with more risk factors for thrombosis and/or high-risk aPL profile (e.g., triple positive), low dose aspirin might be beneficial as primary prophylaxis	7.8	6 - 10
25	Prophylaxis of venous thrombosis using LMWH is required for aPL positive individuals in situations associated with increased risk of thrombosis, such as surgical procedures, plaster casts, those requiring bed rest	9.2	7 - 10

APS = antiphospholipid syndrome; aPL = antiphospholipid antibodies; LMWH = low molecular weight heparin; VKA = vitamin K antagonists; VTE = venous thromboembolism; INR = international normalized ratio; TIA = transient ischemic attack; MRI = magnetic resonance imaging; PE = plasma exchange; IVMP = intravenous methylprednisolone

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ORIGINAL ARTICLE

Implementation of point-of-care testing and a temporary influenza ward in a Dutch hospital

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ABSTRACT

Background. The seasonal influenza epidemic poses a significant burden on hospitals, both in terms of capacity and costs. Beds that are occupied by isolated influenza patients result in hospitals temporary being closed to admissions and elective operations being cancelled. Improving hospital and emergency department (ED) patient flow during the influenza season could solve these problems. Microbiological point-of-care-testing (POCT) could reduce unnecessary patient isolation by providing a positive/negative result before admission, but has not yet broadly been implemented.

Methods. A clinical pathway for patients with acute respiratory tract infection presenting at the ED was implemented, including a PCR-based POCT for influenza, operated by nurses and receptionists. In parallel, a temporary ward equipped with 15 beds for influenza-positive patients was established. In this retrospective observational study, we describe the results of implementing this pathway by comparison with the previous epidemic.

Results. Clinical performance of the POCT within the clinical pathway was good with strongly decreased time from ED presentation to sample collection (194 vs 47 min) and time from sample collection to result (1094 vs 62 min). Hospital patient flow was improved by a decreased percentage of admitted influenza-positive patients (91% vs 73%) and shorter length of subsequent stay (median 5.86 vs 4.61 days) compared to the previous influenza epidemic. In addition, 430 patient-days of unnecessary isolation have been prevented within a time span of 18 weeks. Roughly estimated savings were almost 400,000 euros.

Conclusion. We recommend that hospitals explore possibilities for improving patient flow during an influenza epidemic.

KEY WORDS

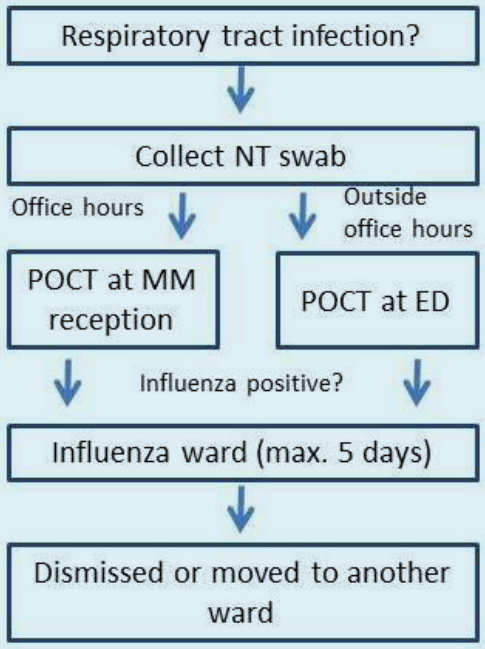
Clinical pathway, emergency department, epidemic, influenza, point-of-care-testing

BACKGROUND

Influenza viruses cause acute respiratory infection (ARI), which is self-limiting in most patients but can cause severe illness in high-risk populations. The seasonal influenza epidemic poses a significant burden on hospitals, both in terms of capacity and costs.[1] A major concern during the peak season is isolation of influenza-suspected or influenza-positive patients in single rooms, as prescribed by infection control guidelines.[2] Shortening test turnaround time could decrease unnecessary isolation measures and improve emergency department (ED) and hospital patient flow. Clinical chemistry point-of-care testing (POCT) was shown to reduce ED patient time and treatment delays and increase patient discharge rates.[3] However, microbiological POCT has not yet been broadly implemented. The first clinical studies on influenza POCT have recently been published, reporting safety and reproducibility.[4-7] To increase efficiency of patient care, we decided to implement a temporary clinical pathway during the 2017-2018 influenza season at the Jeroen Bosch Hospital (JBH), 's Hertogenbosch, The Netherlands (figure 1A). A polymerase chain reaction (PCR)-based POCT for influenza A/B with a turnaround time of 20 minutes was placed at the ED and microbiology laboratory reception desk and operated by nurses and receptionists. In parallel, a separate ward with 15 beds for influenza-positive patients was established to increase efficiency of infection control by enabling cohort nursing and thus, more efficient

medical care. In this article we aim to describe our experience in implementing this clinical pathway.

Figure 1A. *Clinical pathway for influenza-suspected patients.*



NT swab = nose-throat swab; POCT = point-of-care-test; MM = medical microbiology; ED = emergency department

MATERIALS AND METHODS

Ethical approval

Due to the retrospective and anonymous nature of this study, ethical review was waived by the Ethical Committee Brabant (no. NW2018-15).

Setting

The JBH is a teaching hospital with 575 beds. The ED is equipped with 12 beds that are suitable for influenza-suspected patients. In the Netherlands, free influenza vaccination is available for people over 60 years of age, people with chronic diseases, and health care workers. Vaccine coverage was and 15% and 19% for healthcare workers in the JBH during the epidemics of 2016-2017 and 2017-2018, respectively.[8]

PCR tests

The Cobas Liat system is a PCR-based test for a single sample with a turnaround time of 20 minutes and approximately two minutes hands-on time (Cobas Liat, Roche Molecular Diagnostics, Mannheim, Germany). We used the combined influenza A/B/RSV assay; RSV is not included in the present study. Prior to commissioning the test, a laboratory validation process was performed using 14 clinical samples and 10 samples from a proficiency testing panel. The test results were compared to a Panther Fusion influenza A/B/RSV test (Hologic, Zaventem, Belgium) as well as in-house PCRs. Both commercial systems were more sensitive compared to the in-house PCRs (in-house 72%, Panther 83%, Liat 94% of positive test samples detected; see *Supplementary Materials*)*. During the 2016-2017 influenza epidemic, the standard of care was a laboratory-developed real-time PCR to detect influenza A/B on the BD MAX System (Becton Dickinson, Erembodegem, Belgium).

Clinical implementation and training

Six key users (three microbiology technicians and three ED nurses) were trained by Roche, after which ED nursing staff (n = 50) and receptionists (n = 5) were trained by the technician key users. Training included a Microsoft PowerPoint presentation, a pipetting exercise, running a demo sample, and a clinical sample. Further details are provided in the *Supplementary Materials*.

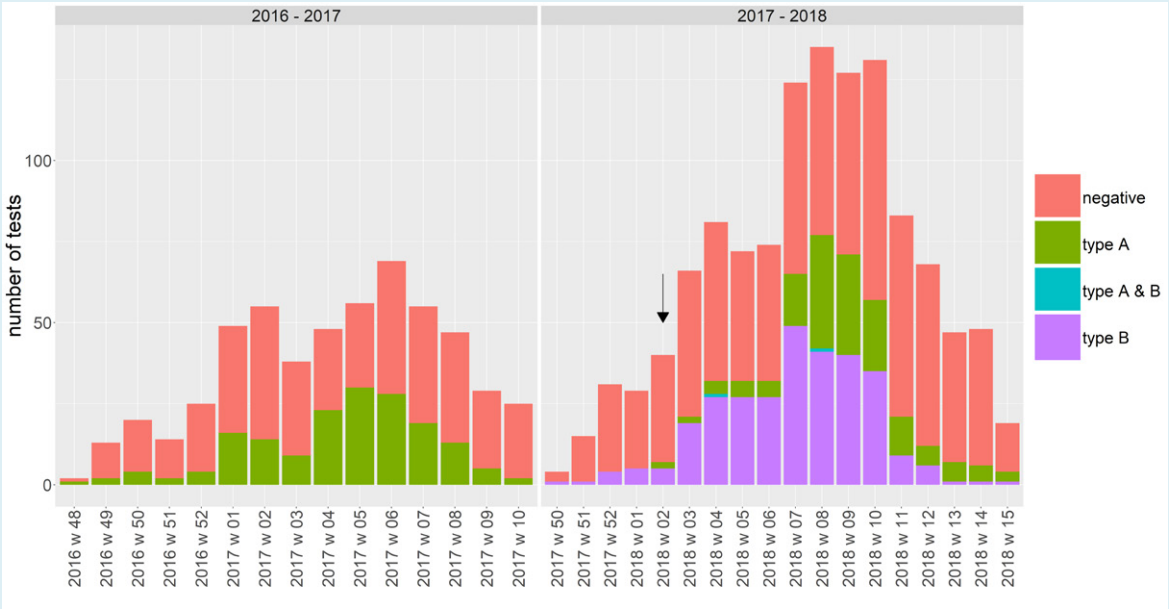
Samples

Two nose-throat (NT) swabs in Eswab medium (Copan Diagnostics, Brescia, Italy) were collected from each ED patient fulfilling the case definition: temperature ≥ 38.0 °C and symptoms of acute respiratory tract infection. One swab was used for POCT at the microbiology reception desk or ED, depending on time and day: during office hours, influenza testing was performed by laboratory receptionists; during weekends and nightshifts, ED nurses performed the test. The second NT swab was used for a confirmatory Panther Fusion test at the laboratory. Samples were stored at room temperature until collection during the next day of business. We considered the sensitivity of the PCR test to detect respiratory viruses using NT swabs as compared to nasopharyngeal swabs acceptable based on a number of studies including hundreds of patients.[9-11] As available literature did not report inferior test performance of the Cobas Liat POCT in daily hospital practice,[5] we decided to perform pairwise testing on a limited number of samples, followed by random pairwise testing (total n = 121). In case of a discrepant test result (one NT swab positive, while the other NT swab from the same patient was negative), the two swabs were reciprocally tested.

Temporary influenza ward

A separate ward was set up for all influenza-positive patients, except for those requiring special care at another ward (e.g., intensive care, cardiac care, haematology, oncology, or children's ward; other types of patients were eligible for admission to the influenza ward). A capacity of

Figure 1B. *Number of influenza tests at the JBH per week during the epidemics of 2016-2017 and 2017-2018, according to national crossings of epidemic threshold. Arrow indicates introduction of POCT*



15 beds was calculated based on numbers of the 2016-2017 influenza season. Patients were admitted into single rooms if available; if not, they were admitted in cohort nursing according to influenza type A or B. In accordance with the number of days that patients have to be nursed in isolation, these patients were either dismissed or moved to another ward after five days, a rule that was strictly adhered to. A weekly multidisciplinary gathering (attending geriatrics doctor, ward nurse, planning nurse, manager, pulmonologist, internal medicine specialist, clinical microbiologist, infection control nurse) was set up to evaluate the process and adjust if necessary. The pathway including POCT and influenza ward was operational as soon as logistically possible after the start of the influenza season, which was on January 8th, 2018.

Statistics

Data were retrospectively collected for the influenza epidemics of 2016-2017 and 2017-2018 according to the national crossing of epidemiologic thresholds (week 48, 2016 - week 10, 2017 and week 50, 2017 - week 15, 2018). Data were gathered from the electronic patient record system Hix (ChipSoft), and the laboratory information system MOLIS (CompuGroup Medical). Only patients admitted via the ED were included in the analyses. Data including all patients is presented in the *Supplementary Materials*. Analyses were performed using R studio built under R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). A p-value of < 0.05 was considered to be statistically significant. Normal distribution of each data set was evaluated using a Shapiro-Wilk test. All data was nonparametric and analysed using a Mann-Whitney U-test; results are presented as median [interquartile range (IQR)].

Cost analysis

A rough estimate of the costs of this clinical pathway is based on the costs of laboratory and clinical aspects as well as costs based on the of length of stay, the number of hospitalisations of influenza-positive patients and the number of unnecessary isolations during the 2017-2018 season compared to the previous. Details are provided in the *Supplementary Materials*.

RESULTS

The Dutch National Institute for Public Health and the Environment (RIVM) reported an influenza epidemic lasting 15 weeks in 2016-2017 and 18 weeks in 2017-2018, with a 20-year average of nine weeks in the Netherlands.[12] During the entire 2016-2017 season, influenza A(H3N2) dominated and influenza A(H1N1)pdm09 and B were only sporadically detected. The 2017-2018 epidemic was dominated by influenza B (Yamagata lineage) with an increase in influenza A (H3N2) and (H1N1)pdm09 during the second half of the epidemic (table 1 and figure 1B): in our hospital 100% influenza A was detected in 2016-2017 vs 36% influenza A in 2017-2018. Vaccine effectiveness was comparable in 2016-2017 and 2017-2018 (47% vs

Table 1. *Comparison of patients admitted via the ED during influenza seasons 2016-2017 and 2017-2018 at JBH*

	2016-2017 (15 weeks)	2017-2018 (18 weeks)	p-value
ED visits (n, [patients/day])	8979 [87]	11406 [92]	0.004
Leading to hospital admission (n, %)	3480 (39%)	4328 (38%)	0.23
Influenza tests (n, [no./day])	591 [5]	1546 [11]	< 0.0001
Positive test result (n, %)	189 (32%)	624 (40%)	0.0003
Time from ED presentation to sample collection (minutes, median [IQR])	194 [136-539]	47 [21-124]	< 0.0001
Time from sample collection to result (minutes, median [IQR])	1094 [782-1317]	62 [49–120]	< 0.0001
Time on ED, all patients (hour, median [IQR])	2.65 [1.7-3.78]	2.73 [1.77-3.9]	0.0005
Time on ED, all influenza-tested patients (hour, median [IQR])	3.75 [3.03-4.67]	3.72 [2.97-4.72]	0.51
Time on ED, all influenza-positive patients (hour, median [IQR])	3.83 [3.15-4.57]	3.63 [2.9-4.55]	0.028
Influenza-positive patients (n)	189	624	0.0003
Age (median, IQR)	76 [67-84]	72 [58-82]	0.0001
Admitted to hospital (n, %)	172 (91%)	455 (73%)	< 0.0001
• Admitted to influenza ward (n, %)	N/A	221 (49%)	N/A
• Admitted to ICU (n, %)	11 (6%)	21 (5%)	0.37
Length of hospital stay (days, median [IQR])	5.86 [4.01-11.27]	4.61 [2.72-7.96]	< 0.0001
Bacterial or fungal superinfection (n, %)	21 (10%)	81 (14%)	0.17
Influenza A-positive patients (n, %)	189 (100%)	224 (36%)	
Admitted to hospital (n, %)	172 (91%)	156 (70%)	< 0.0001
• Admitted to influenza ward (n, %)	N/A	77 (49%)	N/A
• Admitted to ICU (n, %)	11 (6%)	5 (3%)	0.18
Length of hospital stay (days, median [IQR])	5.86 [4.01-11.27]	3.91 [2.61-7.48]	< 0.0001
Bacterial or fungal superinfection (n, %)	21 (10%)	26 (12%)	0.55
Admitted influenza-positive patients that received one or more doses antibiotics* (n, %)	99 (58%)	206 (45%)	0.006
Of which, received at the ED (n, %)	71 (41%)	157 (35%)	0.11
Admitted influenza-negative patients that received one or more doses antibiotics* (n, %)	229 (61%)	364 (49%)	0.0001
Of which, received at the ED (n, %)	162 (43%)	287 (39%)	0.14
Admitted influenza-positive patients that received one or more doses oseltamivir* (n, %)	15 (9%)	50 (11%)	0.40
Of which, received at the ED (n, %)	11 (6%)	45 (10%)	0.17
Admitted influenza-negative patients that received one or more doses oseltamivir* (n, %)	20 (5%)	4 (0.6%)	< 0.0001
Of which received at the ED (n, %)	16 (4%)	3 (0.4%)	< 0.0001

Data are analysed using a Mann-Whitney U-test for nonparametric data. During influenza season 2016-2017, only influenza A was detected. *Antibiotics include only amoxicillin and cefuroxime, the empiric antibiotics for community-acquired pneumonia in our hospital.
ED = emergency department; IQR = interquartile range; ICU = intensive care unit

44%, respectively).[12,13] During the 2017-2018 influenza season, a high number of elderly people with pneumonia was registered nationally as compared to the previous year, as well as a sharp increase in mortality.[14] Six percent more patients were seen at the ED in 2017-2018 compared to 2016-2017 (87 vs 92/day, respectively; p = 0.004, table 1). When compared with 2016-2017, a higher number of influenza tests was performed in the 2017-2018 season, with a higher proportion of influenza-positive results (32% vs 40%, respectively; p = 0.0003) in younger patients (76 vs 72 years, respectively; p = 0.0001, table 1).

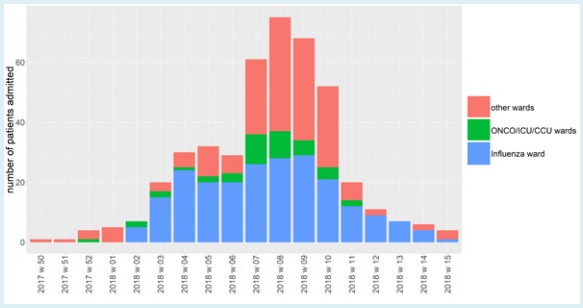
Clinical performance of POCT

Overall rate of agreement between the Cobas Liat and Panther Fusion assay was 100% for influenza A and 98.3% for influenza B (*Supplementary table 2*). Reciprocal testing showed that the only two discrepancies (one NT swab tested positive, while the other NT swab from the same patient tested negative) were due to differences in influenza load between the first and second NT swab and/or low RNA load (cycle threshold value of 44.0). As expected, turnaround times were sharply decreased compared to the 2016-2017 epidemic: time from ED presentation to sample collection (194 in 2016-2017 vs 47 min in 2017-2018, p < 0.0001) and time from sample collection to result (1094 in 2016-2017 vs 62 min in 2017-2018, respectively; p < 0.0001) were both significantly shorter (table 1). ED patient-time was increased for all patients in 2017-2018 compared to 2016-2017 (2.65 vs 2.73 hours, respectively; p = 0.0005), but was lower for influenza-positive patients (3.83 vs 3.63 hours, respectively; p = 0.028).

Patient treatment and hospital flow

A significantly lower percentage of influenza-positive patients was admitted from the ED to the hospital when comparing 2016-2017 to 2017-2018 (91% vs 73%, respectively; p < 0.0001; including influenza A-positive patients only, 91% vs 70%, respectively, table 1). This was also true for patients who were tested influenza-negative (93% vs 80%, respectively; p < 0.0001) but not for all ED patients (39% vs 38%, respectively; p = 0.23). Compared to 2016-2017, length of stay of influenza-positive patients was shorter in 2017-2018 (5.86 vs 4.61 days, respectively; p < 0.0001; for influenza A-positive patients only, 5.86 vs 3.91 days, respectively; p < 0.0001). A significantly longer length of stay was observed for all admitted influenza-positive patients in 2016-2017 compared to patients initially on the influenza ward in 2017-2018 (5.86 vs 4.43 days, respectively; p < 0.0001), but no difference was observed between patients on the influenza ward and those on other wards in 2017-2018 (4.43 vs 5.09 days, respectively; p = 0.32). During weeks 7-10 of 2017-2018, the 15-bed capacity of the influenza ward was insufficient (figure 1C). The average time from hospital admittance to test result was 16.15 hours in 2016-2017. Since 635 patients were tested negative for influenza and admitted subsequently in 2017-2018, 427 patient-days of unnecessary isolation were prevented (636*16.15 = 10,255 hours). The POCT result was known, on average, 49 minutes before admission, due to several aspects of the clinical pathway, including 1) faster sample collection at the ED, 2) shorter test turnaround time, and 3) no extra time for communicating the result from the laboratory to the clinician.

Figure 1C. *Influenza-positive patients admitted to the influenza ward and other clinical wards during 2017-2018 epidemic.*



ICU = intensive care unit; CCU = cardiac care unit; ONCO = oncology

Antibiotic use was significantly reduced in 2017-2018 compared to 2016-2017, at a similar rate for both influenza-positive and -negative patients (table 1). Oseltamivir use however was significantly lower for admitted influenza-negative patients (5% in 2016-2017 vs 0.6% in 2017-2018, p < 0.0001), most of which was accounted for by oseltamivir that was started in the ED (4% in 2016-2017 vs 0.4% in 2017-2018; p < 0.0001). For influenza-positive patients, no significant difference in oseltamivir use was observed between the 2016-2017 and 2017-2018 seasons (9% vs 11%, respectively; p = 0.4). The rate of bacterial or fungal superinfection (defined as positive culture of respiratory tract material or positive pneumococcal antigen test) was not significantly different either in admitted influenza patients during the 2016-2017 and 2017-2018 seasons (10% vs 14%, respectively; p = 0.17; for influenza A-positive patients only, 10% vs 12%, p = 0.55).

The vaccination rate of employees on the influenza ward was 74%, whereas the same department (then Geriatrics) in 2016 had a vaccination rate of 47%. During weekly gatherings, all disciplines involved declared to endorse the implementation of the clinical pathway.

Costs

Estimated costs of the laboratory aspects of the clinical pathway are 73,822 euros (personnel 43,822; technical

30,000) and estimated costs of the clinical aspects are 27,367 euros (ED 3,367; other staff 24,000), leading to a total of 101,189 euros (for details see *Supplementary Materials*). Estimated savings due to shorter length of stay are 257,644 euros, those due to decreased hospital admissions 234,125 euros, and savings due to fewer unnecessary isolations 6,450 euros, leading to a total estimated saving of 498,219 euros. Subtracting the costs from the savings gives an estimated saving of 397,030 euros for influenza season 2017-2018.

DISCUSSION

Overall, our hospital had a positive experience with the implementation of the clinical pathway for influenza. Test performance was good and turnaround times significantly reduced. Comparing the epidemics of 2016-2017 and 2017-2018, ED patient-time was slightly decreased for influenza-positive patients, even while an increase for all ED patients was observed. A lower percentage of influenza-positive patients was admitted, which was also true for patients with a negative influenza test, but not for all ED patients. Increased ED discharge rates could be due to faster influenza test results, available for a larger proportion of presenting patients; the prevailing viruses are unlikely to be responsible, since the 2017-2018 season appeared to be more severe with a higher incidence of pneumonia compared to the previous year and higher mortality was observed. Length of stay of both influenza A and B-positive patients was shorter compared to the previous season, which could be related to more efficient clinical decision making and the short-stay nature of the influenza ward. A strong reduction in unnecessary isolation was accomplished, which is an important factor in improving hospital patient flow.

The reductions in admissions, length of stay, and unnecessary isolation combined were roughly estimated to have saved 397,030 euros. To gain better insight into the costs and savings from a healthcare provider perspective, a more sophisticated analysis including costs associated with additional or avoided diagnostics is required. We do not expect this to strongly alter the result: the number of additional tests related to respiratory tract infection was not significantly different in 2016-2017 compared to 2017-2018 (sputum culture in 31% vs 30% of patients and *Legionella* and *Streptococcus pneumoniae* antigen tests both in 4% vs 4% of patients, respectively). Our data do not indicate that a more severely ill selection of influenza-positive patients was admitted in 2017-2018 compared to 2016-2017: The percentage of superinfections and ICU admissions was not different; a lower percentage of patients received antibiotics and the length of stay was shorter.

In setting up a clinical pathway for influenza, several aspects should be considered. The single-sample capacity of the POCT can be a disadvantage if many patients with respiratory disease present at once. It proved useful to transfer the second POCT from the microbiology reception desk to the ED during peak moments. Near the end of the epidemic, it was considered better to not include fever criterium into the case definition, but only acute respiratory tract infection, since cases might be missed. Retrospectively, the 15-bed influenza ward should have been twice as large during the peak season. The estimation of the required capacity was calculated based on previous season's numbers: the discrepancy could be due to both a different algorithm for and way of testing, and the epidemic in general being more severe compared to the previous year.

Few studies have been published on PCR-based influenza POCT in daily practice. Gibson et al. found 99.6% and 99.3% percent positive agreement for the Cobas Liat Influenza test compared to another PCR-based test in 1361 nasopharyngeal swabs (both primary care and ED).[5] Trabattoni et al.[7] used the Alere i Influenza A&B POCT in 132 ED patients and found reduced hospitalization rates and a reduced number of additional diagnostic tests compared with routine testing, but no differences in prescription of antibiotics. In contrast with the modest reduction in ED patient-time we observed, this study found a strong reduction from approximately six hours to four hours; however, in our study ED patient-time was already four hours before implementation of POCT. Brendish et al.[4] performed the only randomized controlled trial so far, using the FilmArray Respiratory Panel, which includes 17 viruses and 3 bacteria. They found a reduced length of hospital stay for patients assigned to POCT (n = 362, mean 5.7 days) versus routine care (n = 358, mean 6.8 days). This observation was most pronounced among patients with exacerbations of airway disease, in whom also a significant reduction of antibiotic duration was reported. Patient time in ED was not reported; mean POCT turnaround time was 2.3 hours. Influenza POCT was shown to provide overall cost savings due to changes in physician decision making.[15,16]

To the best of our knowledge, this is one of the first reports on implementation of a clinical pathway for influenza, focusing not only on the POCT itself but on all aspects involved in clinical care for influenza patients during an epidemic. This study has a number of limitations. Due to its retrospective nature, no causal relationships can be inferred. Circulating viruses and severity of both epidemics could affect many of the reported values. The slightly younger age of influenza-positive patients could be a confounder. While in 2017-2018, the case

definition for testing was strictly adhered to, it is possible that in 2016-2017 some influenza-positive admitted patients remained undetected, rendering our comparison incomplete.

Overall, implementation of the clinical pathway for influenza patients proved a success in terms of practical and logistical execution in a multidisciplinary setting. Based on our results, the clinical pathway has likely improved patient flow, possibly leading to a lower percentage of admissions and shorter length of stay. Moreover, it has likely led to a significant reduction in costs. We would recommend hospitals with settings similar to ours to explore possibilities in improving patient flow during the influenza epidemic. Our data may not be applicable to, for example academic hospitals, which have a very different type of patient population, when commissioning a different POCT, when plenty of single rooms are available, or when the laboratory is open 24/7. Further research is needed to dissect the full impact of implementing an influenza clinical pathway, but the first results are promising.

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PREVIOUS PRESENTATION OF DATA

Part of the data from this paper was presented as a poster at the Scientific Spring Meeting of the Dutch Society for Microbiology (NVMM/KNVM), Papendal, The Netherlands, March 2018. In addition, part of the data was published as a short, non-scientific report in Dutch in *Medisch Contact*, section 'Beleid', October 31st, 2018.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

* For the *Supplementary Materials*, please contact the corresponding author.

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CASE REPORT

Massive diarrhoea and sepsis due to an infection with *Neisseria meningitidis* serogroup W

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ABSTRACT

Invasive meningococcal disease is associated with significant mortality. Classic presentation consists of high fever, headache and neck stiffness. *Neisseria meningitidis* serogroup W may present with atypical symptoms, which complicates recognition. Furthermore, it is associated with a high case fatality rate.

KEY WORDS

Invasive meningococcal disease, *Neisseria meningitidis* serogroup W, diarrhoea, gastroenteritis.

What was known on this topic?

Neisseria meningitidis is known to cause meningitis, sepsis, and rarely, shock or multiple organ dysfunction syndrome. Classical signs and symptoms are high fever, neck stiffness, headache, and confusion. Even when treated promptly, these infections are correlated with high morbidity and mortality.

What does this add?

This case of an infection caused by *Neisseria meningitidis* serogroup W, presenting with massive diarrhoea without meningeal symptoms, clearly illustrates the atypical clinical presentation of this serotype. Timely recognition and prompt treatment of this serious infection is warranted. Invasive infection with Neisseria meningitidis serogroup W should be included in the differential diagnosis of every patient presenting with a septic shock and gastrointestinal complaints.

INTRODUCTION

Bacterial meningitis in adults is associated with significant morbidity and mortality. The most common causative agents are *Streptococcus pneumoniae* and *Neisseria meningitidis*. The classic clinical presentation of bacterial meningitis includes high fever, neck stiffness, headache and confusion. Even when diagnosed early and treated adequately, morbidity and mortality of bacterial meningitis remain high.[1-4]

Thirteen subtypes of *Neisseria meningitidis* have been identified, based on the antigenic structure of their polysaccharide capsule. The most prevalent serogroups in the Netherlands include B, C, W, and Y. Patients with meningitis caused by *Neisseria meningitidis* serogroup W (MenW) may have an atypical presentation with gastrointestinal complaints including profound vomiting and diarrhoea.[5,6]

Several countries have reported an increasing incidence of MenW carriage and infections.[4,5,7-9] In this case report, we present a patient with a severe infection due to MenW with massive diarrhoea as the main presenting symptom.

CASE REPORT

A 23-year-old previously healthy female presented with complaints of nausea, vomiting, profound diarrhoea and generalised pain and cramps in her legs, especially on the soles of her feet, two days prior to her visit. On the second day of complaints, she became seriously ill and was admitted at the emergency department. Physical examination in the emergency department showed a

pulse rate of 140 beats per minute, a blood pressure of 93/73 mmHg, a temperature of 35.8 °C, a respiratory rate of 38 breaths per minute, and an oxygen saturation of 95% with 3 liters of oxygen per minute by nasal canula. She was initially lethargic, with a Glasgow Coma Scale score of E4M4V1 without signs of neck stiffness. Her legs were cold and mottled without petechial rash. A chest X-ray showed no abnormalities. Laboratory results revealed lactic acidosis (lactate 9.0 mmol/l, pH 7.04, pO2 4.9 kPa, bicarbonate 10.0 mmol/l), leukopenia ($0.8*10^9$/l), elevated CRP (332 mg/l), thrombocytopenia ($5*10^9$/l), and signs of disseminated intravascular clotting (DIC; platelet count $8*10^9$/l, PT 29.3 sec., D-dimer 10 mg/l, Fibrinogen 3.8 g/l). The differential diagnosis consisted of gastroenteritis with sepsis (after eating fish soup), atypical meningitis, or a toxic shock syndrome. A lumbar puncture was not performed because of severe thrombocytopenia and, according to the neurologist, her case presentation not being primarily neurological. Antibiotic treatment containing ceftriaxone (2 g IV twice a day) and dexamethasone (10 mg IV four times a day), was switched to a broader regimen consisting of meropenem (2 g IV twice a day), clindamycin (600 mg IV four times a day), and intravenous immunoglobulins (50 g IV once a day) because of deterioration within hours into a septic shock, for which noradrenalin and vasopressin infusion was required.

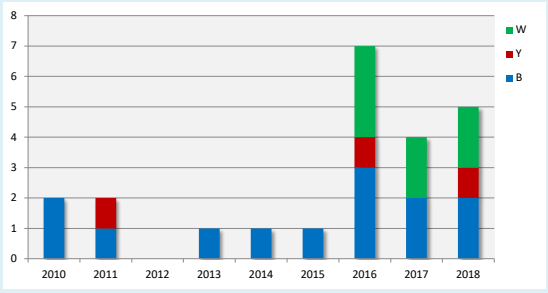
Ultimately, she developed multiple organ dysfunction syndrome (MODS), with mechanical ventilation because of exhaustion; septic cardiomyopathy, confirmed by transthoracic echocardiography for which inotropic agents were initiated; and fulminant DIC with petechiae on the extremities and haematemesis. In addition, because of acute kidney injury, renal replacement therapy was started. After two days of antibiotic treatment, blood cultures showed *N. meningitidis*, and subsequently antibiotic therapy was switched to benzylpenicillin (2 million IV six times a day). Our patient stabilised and inotropic agents could be decreased within the next days. She was weaned off the ventilator after a tracheostomy was placed. The antibiotic treatment with benzylpenicillin was continued for a total duration of one week. The Netherlands Reference Laboratory for Bacterial Meningitis determined that the isolated *N. meningitidis* was serogroup W.

After initial good clinical improvement, our patient unfortunately developed gradual demarcation of the lower extremities due to sepsis and DIC. After an ICU period of 22 days, she was discharged to the general surgery ward for a bilateral lower leg and right thumb amputation. She rehabilitates with orthopaedic prostheses.

Table 1. *Characteristics of invasive meningococcal infections at Erasmus University Medical Centre between January 2010 and October 2018*

	Number of patients	Percent (%) of patients
Total number of patients	**23**	**100%**
Age of the patients (years)		
< 5	8	35%
5-14	2	9%
15-24	4	17%
25-44	3	13%
45-64	5	22%
> 65	1	4%
Culture sample positive for *N. meningitidis*		
Blood	22	96%
Cerebrospinal fluid	4	17%
Serogroup		
B	13	57%
W	7	30%
Y	3	13%
Outcome		
Dead	5	22%
Alive	18	78%

Figure 1. *Number of patients with invasive meningococcal disease in the Erasmus University Medical Centre between January 2010 and October 2018 differentiated by serogroup*



X-axis denotes year of invasive *N. meningitidis* infection; y-axis denotes number of meningococcal infections.
* The year 2018 consists of data up to October.

DISCUSSION

We present a case of a young patient who developed septic shock and MODS due to an invasive infection with *Neisseria meningitidis*, for which the isolate was determined to belong to serogroup W (MenW). The initial presenting symptom of our patient was massive diarrhoea.

The incidence of invasive MenW infections is increasing worldwide, which is consistent with the increasing numbers in our academic hospital. The characteristics and subtypes of invasive meningococcal disease, defined as *N. meningitidis* isolated from blood and/or cerebrospinal fluid (CSF) at our medical centre are illustrated in table 1 and figure 1. MenW infections are associated with a high case fatality rate,[6] which was also seen in our centre. In the last eight years, 23 patients were identified, of which five patients (22%) died as a result of the infection (serogroup W:2, serogroup B:1, serogroup Y:1).

The introduction of a vaccine against *N. meningitidis* serogroup C (MenC) in 2002 resulted in a rapid decline of the incidence of MenC in the Netherlands.[10] The growing number of MenW infections urges the need for vaccination against MenW. In 2018, the MenC vaccine, as part of the national vaccination program, will be replaced by the quadrivalent MenACWY-vaccine in the Netherlands.[11]

In summary, *Neisseria meningitidis* is known for causing sepsis and meningitis. Currently, the incidence of infections due to MenW is increasing in the Netherlands as it is worldwide. This serogroup can present atypically, as this case also illustrates, with massive diarrhea,[5,6] and highlights the difficulty of timely recognition of the disease which is pivotal for guidance of prompt treatment. Invasive infection with *Neisseria meningitidis* serogroup W should be included in the differential diagnosis of every patient presenting with a severe septic shock and gastrointestinal complaints.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received.

ACKNOWLEDGEMENTS

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CASE REPORT

Transient thyroiditis after parathyroidectomy for tertiary hyperparathyroidism

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ABSTRACT

Thyrotoxicosis due to thyroiditis is predominantly caused by infection or autoimmune disease of the thyroid. Parathyroid surgery however, is a lesser known cause of thyroiditis, due to thyroid manipulation. We treated a patient who developed transient symptomatic thyroiditis following parathyroid surgery for tertiary hyperparathyroidism. Therefore, the differential diagnosis for patients with symptoms after parathyroid surgery should include transient thyroiditis.

KEY WORDS

Parathyroidectomy, transient thyrotoxicosis, thyroiditis, post-surgery

What was known on this topic?
Transient thyrotoxicosis after parathyroid surgery for hyperparathyroidism is a relatively unknown condition, most likely with a higher incidence than is currently assumed. Transient thyrotoxicosis occurs within two weeks after surgery and resolves spontaneously in the following weeks.

What does this add?
This case report enhances the clinical awareness of transient thyrotoxicosis after parathyroidectomy for hyperparathyroidism. Symptoms compatible with thyrotoxicosis, especially after difficult and extensive exploration, should raise awareness in clinicians of the possibility of thyroiditis.

INTRODUCTION

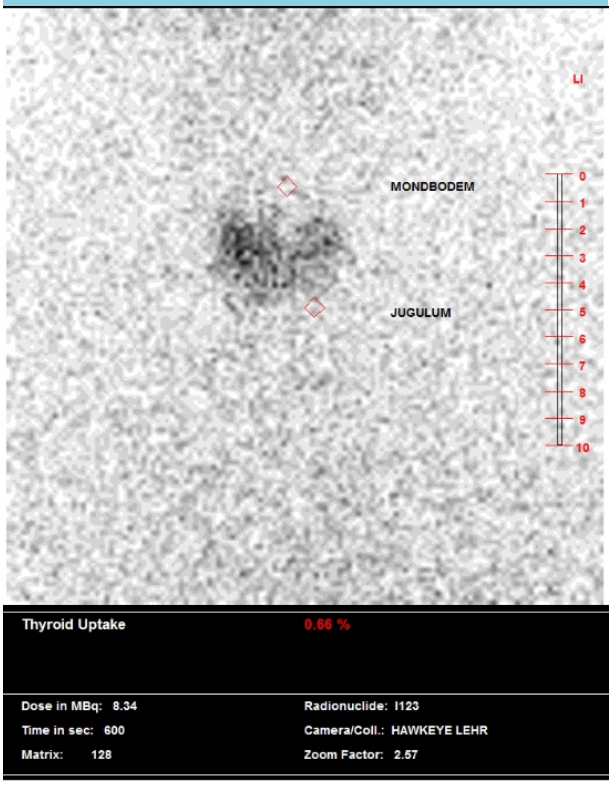
Chronic renal disease could by characterized by the development of hyperparathyroidism. In patients with severe hyperparathyroidism who do not respond to medication, parathyroid surgery is recommended. Post-operative hypocalcaemia and local surgical problems are the most frequent complications and are usually well-anticipated.
In this paper, we report a patient with tertiary hyperparathyroidism, who developed symptomatic transient thyrotoxicosis in the post-operative period after parathyroidectomy. The pathogenesis appeared to be thyroiditis, induced by thyroid surgical manipulation.

CASE REPORT

A 32-year-old man was hospitalized for planned parathyroidectomy. He suffered from Townes Brock syndrome, a congenital condition associated with kidney hypoplasia, but not from thyroid abnormalities. He had developed severe tertiary hyperparathyroidism (iPTH: 111.6 pmol/l; n = 1.6-6.9 mmol/l) due to chronic renal failure and possibly poor adherence to active vitamin D supplementation. Despite treatment with high dose cinacalcet (90 mg/day), parathyroidectomy was indicated in preparation of pre-emptive kidney transplantation. There was no personal or family history of thyroid disease. Preoperative thyroid function tests were normal. No imaging with iodinated contrast were performed before surgery. A surgical neck exploration was performed with removal of three parathyroid glands. The fourth parathyroid gland was not detected despite

thorough exploration and palpation of the operation area. Post-operative nadir serum calcium concentration was 2.01 (n = 2.20-2.60 mmol/l) while albumin level was 29 g/l (n = 35-55 g/l). Calcium suppletion was started as a preventative. The following day, the patient felt restless and noted palpitations. Pain in the neck was absent. Physical examination demonstrated an agitated patient with a pulse rate of 108 beats/min and a temperature of 36.8 °C. Routine blood analysis showed an increased C-reactive protein (147 mg/l, n = < 10mg/l). No clear source for an infection was found. In addition, the surgical wounds healed well. Further examination showed a thyroid-stimulating hormone (TSH) level of 0.4 mU/l (n = 0.3-4.2 mU/l) and a free thyroxine (fT4) level of 64.3 pmol/l (n = 12-24 mU/l) on the third post-operative day. Thirteen days post-operative, a blood test showed a TSH of 0.03 mU/l (n = 0.3-4.2 mU/l) and a fT4 of 46.1 pmol/l (n = 12-24 mU/l). An iodine-123 scan showed a remarkably low uptake of 0.7% after six hours and 1.2% after 24 hours, compatible with thyroiditis. As clear signs of an infectious or autoimmune cause were absent, it was hypothesized that surgical manipulation was responsible for the clinical manifestations. Beta blockade was started and the patient gradually recovered. Thyroid function normalized after six weeks and remained normal during two years of follow-up.

Figure 1. *Iodine-123 scan: 6 hours*



DISCUSSION

The described patient developed thyrotoxicosis due to thyroiditis after parathyroid surgery. Postparathyroidectomy transient thyrotoxicosis is a relatively unknown condition and not widely acknowledged among parathyroid/endocrinologic surgeons or consulting internists.

Several studies report transient thyrotoxicosis after parathyroid surgery for primary hyperparathyroidism in 20-30% of patients[1-5], but the percentage of occurrence after total parathyroidectomy for secondary and tertiary hyperparathyroidism is unknown.

Four cases of acute thyroiditis after parathyroidectomy for secondary or tertiary hyperparathyroidism in chronic renal failure patients are described.[3,6,7] All patients had normal preoperative thyroid function tests. In two cases, in which manipulation of the thyroid gland during parathyroidectomy was minimal, the patients developed elevated thyroid hormone levels without typical symptoms.[3] In the other two cases, the patients developed symptoms consistent with thyrotoxicosis on the second and third post-operative day. These patients had symptoms such as fever with profuse sweating, restlessness, agitation, intractable nausea, and palpitations. In both patients, thyroid antibodies were negative.[6,7] A pertechnetate isotope thyroid scan was performed in one patient and revealed low uptake.[7]

In two of the four cases, the thyroid hormone levels were followed over time. The maximal increased fT4 and fT3 values occurred at days three to seven post-operatively and returned to normal within 14 days. Their TSH decreased to undetectable values and returned to normal within two to three months.[3]

Iatrogenic thyroiditis is reported after use of lithium, amiodarone or immunotherapy. In addition, radioiodine ablation, external irradiation and (incidentally after) manipulation of the thyroid gland during operative procedures, or trauma may cause thyroiditis (table 1).[4,8]

After surgery, a non-thyroidal illness syndrome can be observed. A parallel decrease of TSH and peripheral hormones fT3 and fT4 can be detected. This phenomenon may be induced by an acute phase response.[5] Anaesthesia, on the other hand, can cause an elevation of fT4 levels, with a peak in the first hour after induction. Levels normalize within 24 hours post-operatively.[9]

Trauma and palpation of the thyroid gland may cause a subacute thyroiditis with release of preformed hormone into the circulation and as result development of transient thyrotoxicosis.[8] Palpation of the normal thyroid parenchyma causes so-called palpation thyroiditis, a non-specific multifocal granulomatous folliculitis.[10-11] The incidence of post-operative thyrotoxicosis seems to be higher after bilateral neck exploration compared to

Table 1. *Causes of acute thyroiditis*

Thyroid pain and tenderness	Subacute thyroiditis	Granulomatous
		Nonsuppurative
		De Quervain tenosynovitis
	Infectious thyroiditis	
	Radiation-induced thyroiditis	
	Palpation-induced thyroiditis	(Parathyroid) surgery
	Trauma-induced thyroiditis	
No thyroid pain and tenderness	Painless thyroiditis	Silent thyroiditis
		Subacute lymphocytic thyroiditis
		Postpartum thyroiditis
	Associated with drugs	Interferon-alpha
		Interleukin-2
		Lithium
		Tyrosine kinase inhibitors
		Cytotoxic T lymphocyte-associated antigen 4
		Immunotherapy
		Amiodaron
	Chronic lymphocytic thyroiditis	Hashimoto's thyroiditis
	Fibrous thyroiditis	Riedel's thyroiditis
		Invasive thyroiditis

unilateral neck exploration or removal of solitary thyroid adenoma.[3] Incidence depends on the degree of exploration, variation in size/shape of the thyroid and amount of intra-operative trauma.[3,5]

The expected progress of post-operative thyrotoxicosis is an increase of T4 within the first week. Due to a half-life of T4 of one week and resolution after five to six half-life times, persistence of hyperthyroxinaemia can last for up to six weeks after the operation. Spontaneous resolution will therefore occur in most patients within six weeks, confirming manipulation of the thyroid gland as a contributing factor in the transient thyrotoxicosis.[4]

CONCLUSION

Thyrotoxicosis may occur after parathyroidectomy. This condition is more likely when extensive palpation and mobilization of the thyroid gland leads to manipulative trauma. In patients with symptoms like tachycardia, agitation, palpitation, and heat-intolerance after parathyroidectomy, post-operative thyroiditis should be included in the differential diagnosis. Symptomatic treatment with beta blockers should be started for temporarily relieve while thyrotoxicosis spontaneously resolves within weeks after surgery.

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PHOTO QUIZ

The other cat scratch disease

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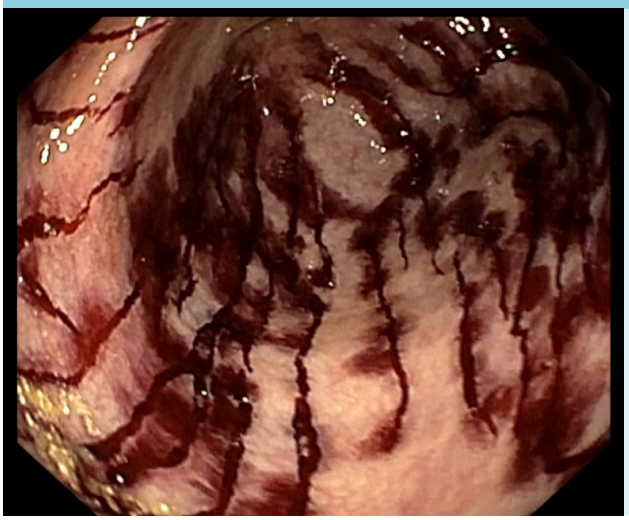
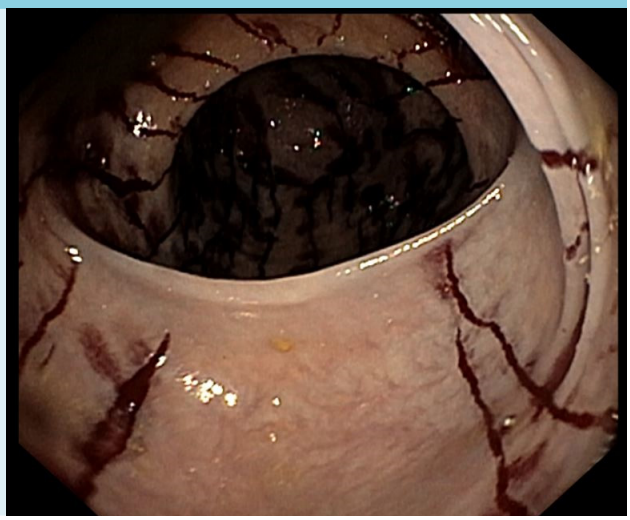
Figures 1 and 2. *Endoscopic view in caecum*





CASE REPORT

We performed a colonoscopy on an 83-year-old female patient presenting with chronic diarrhoea. In the cecum, we observed many superficial tears and spontaneous mild bleeding.

WHAT IS YOUR DIAGNOSIS?

See page 123 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 122)

THE OTHER CAT SCRATCH DISEASE

DIAGNOSIS

From a colonoscopy, we diagnosed the cat scratch phenomenon (CSP), named after the remarkable resemblance to scratches of a cat on bare skin. The rest of the colon showed no macroscopic abnormalities.

Random biopsies were taken to investigate microscopic colitis since the patient presented with chronic diarrhoea. Histology showed collagenous colitis. CSP is rare condition (< 0.5% of all colonoscopies).[1] It is caused by barotrauma (insufflation of air/CO_2) and observed in the right hemicolon. It is mainly seen in older female patients. Although histology is normal in most cases, CSP is associated with collagenous colitis in 14-25% of all patients.[1,2] Collagen deposition in the submucosal layer decreases compliance of the wall. Intraluminal pressure of CO2 may lead to mucosal tears.

Other associations of CSP are made with diversion colitis and ischemic colitis. CSP is considered an innocent finding. In small series of cases, no complications have been noted, although one incidental finding of pneumoperitoneum has been reported elsewhere.[3]

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PHOTO QUIZ

Dark ascites, an ovarian mass and a black dotted peritoneum

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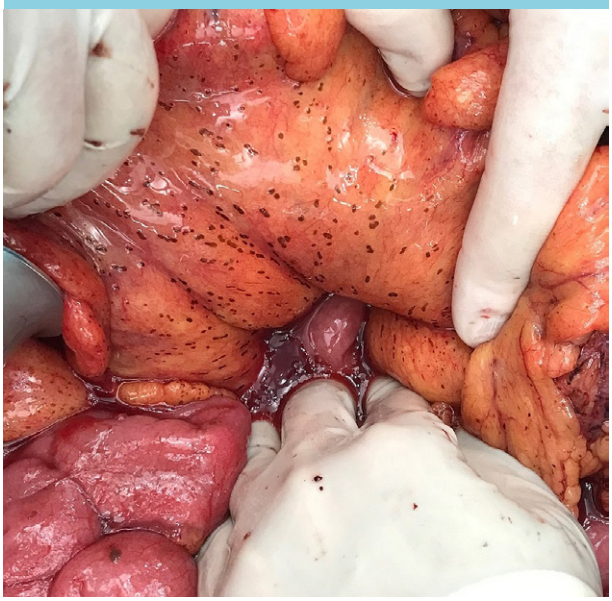
CASE REPORT

A 44-year-old previously healthy woman was admitted to the hospital with complaints of acute abdominal pain, anorexia, and sweating, which started one week prior to admission. An abdominal computerized tomography (CT) scan revealed a mass in the left ovary (10 x 14 cm), a second mass in the left adrenal gland (5 x 6 cm) and massive ascites throughout the abdomen. Laboratory investigations revealed a CA 125 level of 706 U/l (normal < 35 U/l), lactate dehydrogenase (LDH) of 1279 U/l (normal < 250 U/l), and normal haemoglobin, platelets, leukocytes, kidney function, and liver enzymes. Cytology of the ascites showed macrophages loaded with haemosiderin and a few mesothelial cells, lymphocytes and blood cells, but no malignant cells.

Upon laparotomy, there were 3 litres of dark ascites. Multiple, small, non-palpable blackish spots were visible on the peritoneum (figure 1). The left ovary was enlarged (10 x 20 cm) and dark black. We performed a hysterectomy and bilateral salpingectomy, and an omentectomy and biopsies of peritoneum and adrenal gland.

Figure 1. *Multiple small blackish spots on the peritoneum*



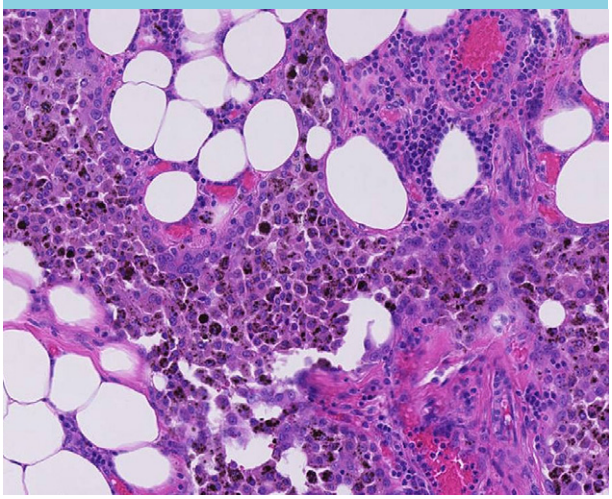
WHAT IS YOUR DIAGNOSIS?

See page 125 for the answer to this photoquiz.

ANSWER TO PHOTO QUIZ (PAGE 124)

DARK ASCITES, AN OVARIAN MASS AND A BLACK DOTTED PERITONEUM

Figure 2. *Histology: Omentum with melanocytes and melanophages (Haematoxylin & Eosin, 250x)*



DIAGNOSIS

Histological examination after surgery demonstrated metastatic melanoma in all specimens (see figure 2). No primary melanoma was found after dermatological consultation. Next generation sequencing showed an NRAS exon 3 mutation. NRAS mutant melanomas can be of cutaneous or mucosal origin and are associated with a poor prognosis.[1] No BRAF mutation was present, precluding targeted therapy with BRAF/MEK inhibitors. Because of the extensiveness and aggressive nature of disease, combination immunotherapy with ipilimumab and nivolumab was started after surgery. Progressive disease was identified at 12 weeks after the start of treatment by CT scan and confirmed six weeks later by a second CT scan; immunotherapy was then stopped. Gradually, the patient's condition deteriorated, prohibiting further study treatment. She died within eight months after first presentation.

Melanoma can originate in the skin, mucosa, or uvea. Metastases can appear in any organ, but are not commonly seen in the ovaries.[2] Even though patients dying of metastatic melanoma have ovarian involvement at autopsy in approximately 20% of cases, diagnosis is rarely made during lifetime.[2] Diffuse melanocytic spread, clinically presenting as melanosis cutis, melanuria, melaloptysis, or black pleural effusion, has been previously reported to be associated with a very poor prognosis.[3] Although pathogenesis is not completely understood, phagocytosis of melanin and melanin precursors that are shed by rapidly dividing melanoma cells seem to play an important role. No melanosis cutis was present in this patient.

Checkpoint inhibitors such as ipilimumab and nivolumab can provide durable disease remission and might even cure patients with metastatic melanoma by unleashing the immune system. Although 58% of advanced melanoma patients respond to combination immunotherapy with ipilimumab and nivolumab,[4] chances of response are generally lower in patients with aggressive disease and high LDH.

In this patient no primary melanoma was identified, which is not uncommon.[5] The primary melanoma may have undergone immune-induced regression or be localized inside the body (e.g. in the case of mucosal melanoma), or the primary melanoma may have been missed or removed without histological examination.

CONCLUSION

As this case shows, metastatic melanoma can mimic primary ovarian malignancies. However, black discoloration of body fluid should prompt suspicion of metastatic melanoma and often is an ominous sign. Looking back, the diffuse spreading, high tumour load and high LDH levels predicted the poor prognosis of this patient.

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LETTER

Successful treatment of aplastic anaemia with cyclosporine during pregnancy

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Dear editor,

Aplastic anaemia in pregnancy is a serious condition for both the mother and child. In the 20th century, maternal morbidity was reported to be 20-60% and termination of pregnancy at early gestation was recommended in pregnant women with aplastic anaemia.[1-4] However, according to recent case series, current maternal and foetal outcome seem to be much better.[5-8] Bone marrow transplantation is the treatment of choice in young patients with aplastic anaemia, but this is contra-indicated during pregnancy due to toxicity for the foetus (table 1).[9] Although guidelines advise treatment with cyclosporine in pregnant woman, only a few transfusion-dependent women with aplastic anaemia received cyclosporine in addition to supportive care.[3,10-12]

We diagnosed a 38-year-old second gravida with pancytopenia at week 12 of gestation (haemoglobin level 6.12 g/dl, (ref: 12-16), white blood cell count 2.3*10^9/l (ref: 4-10), neutrophilic count 0.5*10^9/l (ref: 1.5-3.5), platelet count 9*10^9/l (ref: 150-400), LDH within normal range). In retrospect, she had a platelet count of 57*10^9/l 6 months before presentation as determined by a general practitioner. Bone marrow biopsy revealed aplastic anaemia with a reduced marrow cellularity of 30-40%, without dysplastic signs. Direct antiglobulin test was negative and only a small glucose phosphate isomerase (GPI)-deficient population was found. Anamnesis and virology testing did not indicate another cause for this severe aplastic anaemia other than exacerbation of idiopathic aplastic anaemia by pregnancy. After consultation with a multi-disciplinary team and extensive counselling of the patient, she decided to continue her pregnancy. Initially, she was treated with supportive therapy to keep her haemoglobin level above 10 g/dL and platelet count above 20*10^9/l, and she was administered trimethoprim/sulfametrol as a prophylaxis. Because of a high transfusion need, treatment with cyclosporine was started in week 13 of gestation. After four weeks, transfusion necessity for platelets decreased from twice a week to once a week and her neutrophil count improved. There was no obvious decrease of erythrocyte

Table 1. *Guidelines for treatment of aplastic anaemia (British Journal of Haematology guidelines, 2015)*

	Transfusion	ATG	Cyclosporine	HSCT
NSAA	Platelet count > 10*10^9/l	Recommended for those needing transfusion/ having infections	In combination with ATG	Not recommended
SAA/VSAA < 35 years	Platelet count > 10*10^9/l	Only if HLA-matched sibling is NOT available	In combination with ATG	Recommended if HLA-matched sibling available
SAA/VSAA > 50 years	Platelet count > 10*10^9/l	Recommended	In combination with ATG	Only if no response after 3-6 months ATG
Pregnant woman	Platelet count > 20*10^9/l	Not recommended	Safe, recommended for those needing transfusion	Not recommended

ATG = antithymocyte globulin; HSCT = haemopoietic stem cell transplantation; NSAA = non-severe; SAA = severe; VSAA = very severe; HLA = human leukocyte antigen

transfusion need. She delivered a healthy boy at week 37. Cyclosporine was continued for six months and although pancytopenia persisted, no more transfusions were needed. After cessation of cyclosporine, only mild pancytopenia remained and no further treatment was required.

Based on our experience and review of literature, we do not recommend standard termination of pregnancy at early gestation, although we advise extensive investigation to exclude underlying causes of anaemia, and treatment with supportive care and cyclosporine when necessary.

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LETTER

A puzzling haptoglobin level in a patient who is treated with tocilizumab

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To the editor,

Mrs. D is a 65-year-old lady who was diagnosed with giant cell arteritis in 2016. Since then, she has been treated with corticosteroids. As it was not possible to taper corticosteroids without inducing a relapse, methotrexate and leflunomide were consecutively added without much effect. Eventually, tocilizumab was started, leading to a rapid normalization of C-reactive protein (CRP) and erythrocyte sedimentation rate. However, a mild anaemia (Hb 6,9 mmol/l) was noted with a slightly increased lactate dehydrogenase (LDH) level (304 U/l, normal value < 247). An analysis to reveal the cause of the anaemia was initiated. Bilirubin as well as vitamin B12, folic acid, and ferritin levels were within normal limits. However, the haptoglobin level was repeatedly undetectable, leading to a suspicion of haemolytic anaemia. However, when her haemoglobin level spontaneously increased to the pre-existent value, the presence of haemolysis was questioned. We then focused on the cause of the decreased haptoglobin level.

This patient was treated with tocilizumab at the time of measurement of haptoglobin. Tocilizumab is a monoclonal antibody directed against the membrane-bound and soluble interleukin-6 (IL-6) receptor.[1] It is used to treat a variety of auto-immune and auto-inflammatory diseases including giant cell arteritis.[1] IL-6 is produced by many different cells of the immune system and has numerous effector functions. An important function of IL-6 is to induce the production of acute-phase proteins such as CRP, serum amyloid A, and fibrinogen by hepatocytes.[2] Therefore, it is not surprising that CRP levels are low in patients who are treated with tocilizumab.[3] Haptoglobin is also an acute-phase reactant which is produced by hepatocytes in response to IL-6.[4] Indeed, in a cohort of 132 patients with rheumatoid arthritis, haptoglobin levels decreased in parallel to CRP after the start of tocilizumab.[5] Consequently, the serum haptoglobin level is not a reliable marker for haemolysis in patients who are treated with tocilizumab. Of course, other causes of decreased haptoglobin levels always need to be considered when evaluating a patient, such as hepatic dysfunction, elevated oestrogen levels, haemodilution, multiple transfusions, or technical flaws.[6]

For Mrs. D, the initial diagnosis of haemolytic anaemia was abandoned based on a spontaneous increase in haemoglobin level and low bilirubin levels. The undetectable levels of CRP and procalcitonin confirmed our hypothesis that the haptoglobin level was decreased secondary to tocilizumab. Moreover, we found decreased haptoglobin levels in three other patients treated with tocilizumab, ranging from undetectably low levels to 0.11 g/l.

In conclusion, the serum haptoglobin level is not a reliable marker in patients who are treated with tocilizumab.

CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to report.

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