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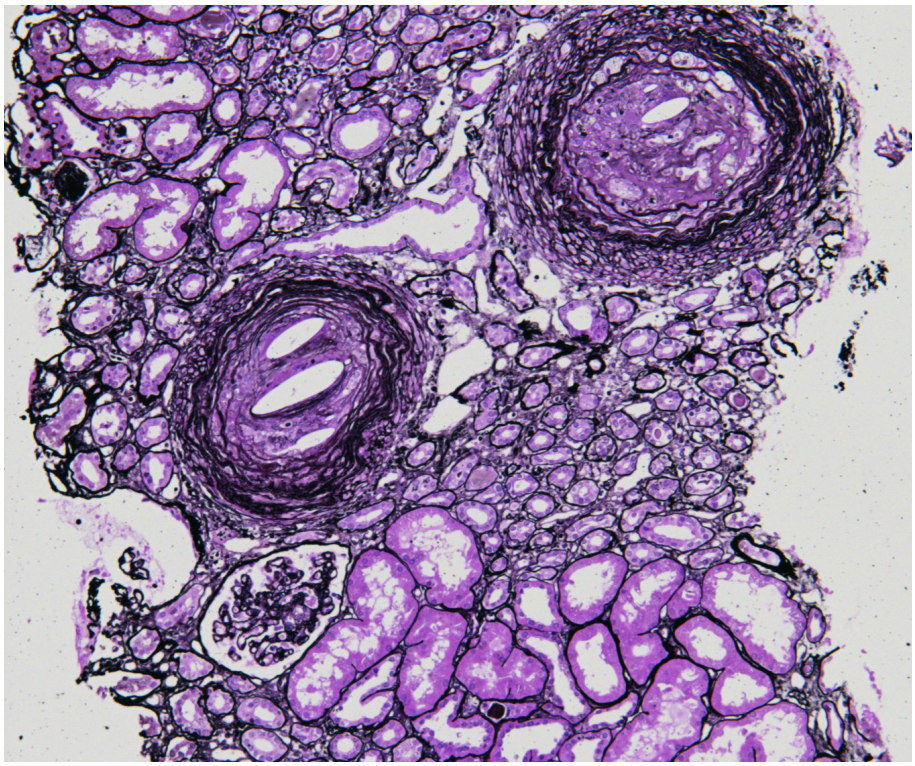

A fatty cause of renal failure; what is your diagnosis?

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Contents

EDITORIAL

Pragmatic barriers to assessing post-emergency department vulnerability for poor outcomes in an ageing society

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As emergency departments (ED) around the world evolve their protocols in adapting to an ageing society with potentially complex biomedical and psychosocial stressors overlying acute illness or injury, feasible and adequately accurate risk stratification for 'vulnerability' will become a cornerstone of older patient's care in the ED. Although multiple ED instruments exist for this purpose, none accurately identifies either high-risk or low-risk older adults.[1] Ideally, an instrument suitable for the ED risk stratification of complex older adults would accurately and reliably identify both high- and low-risk individuals across a variety of illness and injury presentations for heterogeneous populations, without requiring any extra equipment, personnel, or time to which every hospital has access.[2]

De Gelder et al. report the derivation and validation of a prediction model for the composite outcome of functional decline and mortality at 90 days following an ED visit for 1632 non-critically ill patients over the age of 70, excluding acute myocardial infarction or stroke patients who were eligible for thrombolysis.[3] Approximately one in three suffered functional decline or death and the authors report a six-item predictive model that includes age, ambulance arrival, number of medications, assistance required for bathing or showering, prior hospital admission in the preceding six months, and history of dementia. The prognostic accuracy of this new model to identify patients at increased risk for these post-ED adverse outcomes compared favourably with the Identification of Seniors at Risk (ISAR), particularly for the highest-risk patients. The Acutely Presenting Older Patient (APOP) study is another important piece of the puzzle as clinicians and epidemiologists merge efforts to understand, measure, and interpret the components of vulnerability identified during an ED visit, but the work must continue.

Deriving, validating, and implementing clinical prediction instruments represents a long-term endeavour fraught with frequent dead-ends. Multiple examples exist of promising tools for ED scenarios such as transient ischaemic attack, myocardial infarction, and geriatric vulnerability that subsequently failed to be sufficiently accurate when applied in different settings.[4] The unique challenges for building these instruments to assess 'vulnerability' in the fast-paced ED environment and for complex older adults have been well described and are summarised in *table 1*.[1,2] Key decisions surrounding the *process* of using these instruments include a focus on screening (widespread assessment of high- and non-high-risk individuals) or case-finding (targeting at risk individuals), as well as designing for implementation by ensuring that the instrument can be interpreted and administered by diverse individuals in the ED (volunteers, technicians, nurses, physicians). Assessing the *quality* of these instruments includes contemplation about the primary objective to identify increased risk (high likelihood ratio) or decreased risk (low likelihood ratio) subsets, since decision instruments generally cannot do both. Closely related to this objective-defining decision is understanding how accurate 'good enough' is to support widespread adoption of the instrument into guidelines and routine clinical practice? The rule of thumb for a positive or negative likelihood ratio is greater than 10 or less than 0.1, respectively, but none of the existing instruments attain this level of accuracy (yet).[5] While clinicians await more accurate instruments, how will key stakeholders' perspectives and interpretation of risk stratification be

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Table 1. *Challenges for assessment of older adult vulnerability in ED settings*

Process	• Focus on screening or case-finding? • Who will assess at what time during episode of ED care? • What are personnel and monetary costs of routine assessment?
Quality	• Thresholds of instrument accuracy and reliability sufficient to justify widespread use? • Should instruments be designed to identify high-risk or low-risk patients? • Can multiple stakeholders appropriately acquire, interpret, and incorporate instrument's risk stratification? • Which patient-centric intended and unintended outcomes of instrument use should be evaluated? • Can a single instrument predict all adverse outcomes or is one instrument needed for trauma victims, another for medical patients, and another for psychiatric patients?
Definitions	• Standardised or comparable qualifiers for prevalent geriatric syndromes including dementia, delirium, and frailty across specialties and nations? • Equivalent, well-accepted qualifiers for key outcomes such as *preventable* ED returns?
Interventions	• Linkage of available actions to high-risk strata? • One-size fits all interventions or preventive actions guided by individual's unique vulnerabilities?

evaluated? For example, if geriatricians, primary care providers, trauma surgeons, or orthopaedic specialists fail to accept the validity of these instruments then it is unlikely that ED provider's disposition and management recommendations that incorporate the risk assessment will be valued. These stakeholders also include patients and families, as well as governmental insurers who set policy that sometimes links higher quality care to healthcare reimbursements.[6]

The individual components from which these instruments are derived and further validated also require standardisation across nations, languages, and healthcare landscapes. For example, De Gelder et al. use the Six Item Cognitive Impairment test to define dementia, but reference a non-ED study as proof-of-concept for the face validity of this instrument. In fact, one ED-based study of this instrument indicated that it accurately identifies patients at low risk for non-delirium cognitive impairment, but does not identify high-risk individuals so one could argue whether patients were correctly analysed as to the presence or absence of dementia in the current study.[7] Reviewing studies from Australia, Asia, Europe, and North America, clinicians will find a large variety of instruments employed to measure geriatric syndromes such as dementia, delirium, comorbid illness burden, and illness acuity which represents a veritable Tower of Babel for those trying to compare one population, instrument, or intervention against another. Additionally, under-utilised qualifiers for global dysfunction such as frailty exist,[8,9] as well as descriptors of outcomes as 'preventable ED returns'.[1] As more researchers derive and evaluate new instruments against previous models, investigators and funders must agree upon a package of measures that are mutually acceptable in order for others to compare one study's results to another.

Even if key process, quality, and definitional issues are addressed, a largely unanswered question is what to do with the added information from ED vulnerability assessments? At a threshold of ≥ 2 the ISAR identifies 61% of individuals as high risk, while the APOP composite outcome instrument identified over 25% of individuals as amongst the 30% highest risk. Should all of these individuals be admitted to the hospital? If not, which subset can be safely managed as outpatients? Does a one-size-fits-all intervention exist to reduce short-term adverse outcomes or is an individualised approach required? If individualised interventions are needed, which is most likely, then how (and by whom) would this additional assessment occur?

Assessing older adult's vulnerability for short-term adverse outcomes following an episode of ED care is recommended by educators[10] and professional guidelines,[11,12] but clinician's ability to accurately do so remains elusive. In addition to the APOP investigators, ED researchers worldwide are exploring different approaches to distinguish older adults at increased risk for preventable suboptimal outcomes.[13-15] Opportunity exists concurrently with abundant challenges, but assessing ED elder's vulnerability provides the prospect for multidisciplinary, international investigators to collaboratively align emergency care with patient-centric priorities that improves the efficiency and quality of healthcare delivery. Progress awaits these ongoing efforts and will require persistent and substantial energy, funding, and innovation.

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REVIEW

The diagnostic work-up in patients with ascites: current guidelines and future prospects

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ABSTRACT

Accumulation of fluid in the peritoneal cavity – ascites – is commonly encountered in clinical practice. Ascites can originate from hepatic, malignant, cardiac, renal, and infectious diseases. This review discusses the current recommended diagnostic approach towards the patient with ascites and summarises future diagnostic targets.

KEYWORDS

Aetiology, ascites, ascitic fluid analysis, diagnosis, liver cirrhosis

INTRODUCTION

Ascites is a pathological accumulation of fluid in the peritoneal cavity. It is a symptom of numerous medical conditions and has a broad differential diagnosis (*table 1*). Ascites can be classified by the underlying pathophysiological mechanism: portal hypertension, peritoneal disease, hypoalbuminaemia and miscellaneous disorders. Liver cirrhosis (75%) is the most common cause in adults in the Western world, followed by malignancy (10%), heart failure (3%), tuberculosis (2%), and pancreatitis (1%).[1] An adequate diagnosis is necessary for successful treatment.

Ascites can be classified as: mild ascites only detectable by ultrasound (grade 1), moderate ascites evident by moderate symmetrical distension of the abdomen (grade 2), and large or gross ascites with marked abdominal distension (grade 3).

Ascites is a common problem and patients present to a broad range of medical specialties. This review aims to provide a comprehensive overview of the current diagnostic approach to ascites and also discusses recent developments in ascites research.

Table 1. *Differential diagnosis of ascites*

Portal hypertension
Cirrhosis
Alcoholic hepatitis
Hepatic congestion - Congestive cardiac failure - Constrictive pericarditis - Hepatic venous outflow obstruction (hepatic vein thrombosis, sinusoidal obstruction syndrome)
Portal vein thrombosis
Non-cirrhotic portal hypertension
Malignancy
Peritoneal carcinomatosis
Hepatocellular carcinoma
Mesothelioma
Metastatic liver disease
Other intra-abdominal malignancies
Infectious
Spontaneous bacterial peritonitis
Secondary bacterial peritonitis
Tuberculous peritonitis
Chlamydia
Miscellaneous
Pancreatitis
Hypoalbuminaemia
Nephrotic syndrome
Lymphatic leakage
Myxoedema
Urinary leakage

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DIAGNOSIS

History

Patients with ascites should be questioned about the pattern of body weight gain, change in abdominal girth, and ankle oedema. Information about the medical history, medication use, lifestyle, risk factors for liver disease, and infectious disease risk (e.g. migration) are relevant to discover the underlying aetiology.

Physical examination

A screening physical exam should be carried out in every patient, with awareness of signs of liver disease (erythema palmare, spider naevi, splenomegaly), heart failure (peripheral oedema, jugular venous distension, third heart sound, pulmonary rales) and malignancy (lymphadenopathy).[2]

The abdomen should be inspected for the presence of bulging flanks and percussion can reveal flank dullness. Flank dullness is found when approximately 1500 ml of ascites is present. These combined findings have a sensitivity of 75% and a specificity of 57%.[3] Shifting dullness, determined by a 3 cm flank dullness shift when the patient changes from a supine to a lateral decubitus position has a sensitivity of 69% and a specificity of 69%. Detection of a fluid wave or puddle sign is less reliable.[3,4] Complications accompanying ascites such as umbilical, inguinal and other hernias and pleural fluid (hepatic hydrothorax) are particularly common in cirrhotic patients.

Blood tests

It is recommended to assess serum levels of creatinine, urea, electrolytes, prothrombin time and liver function tests and to order a complete blood cell count.[5]

Abdominal ultrasound

Abdominal ultrasound is the first-line imaging method to confirm the presence and quantity of ascites.[5-7] Additionally, ultrasound can provide crucial information about the cause of ascites, detect signs of portal hypertension (splenomegaly and portosystemic collaterals), and offer guidance during paracentesis.

Abdominal paracentesis

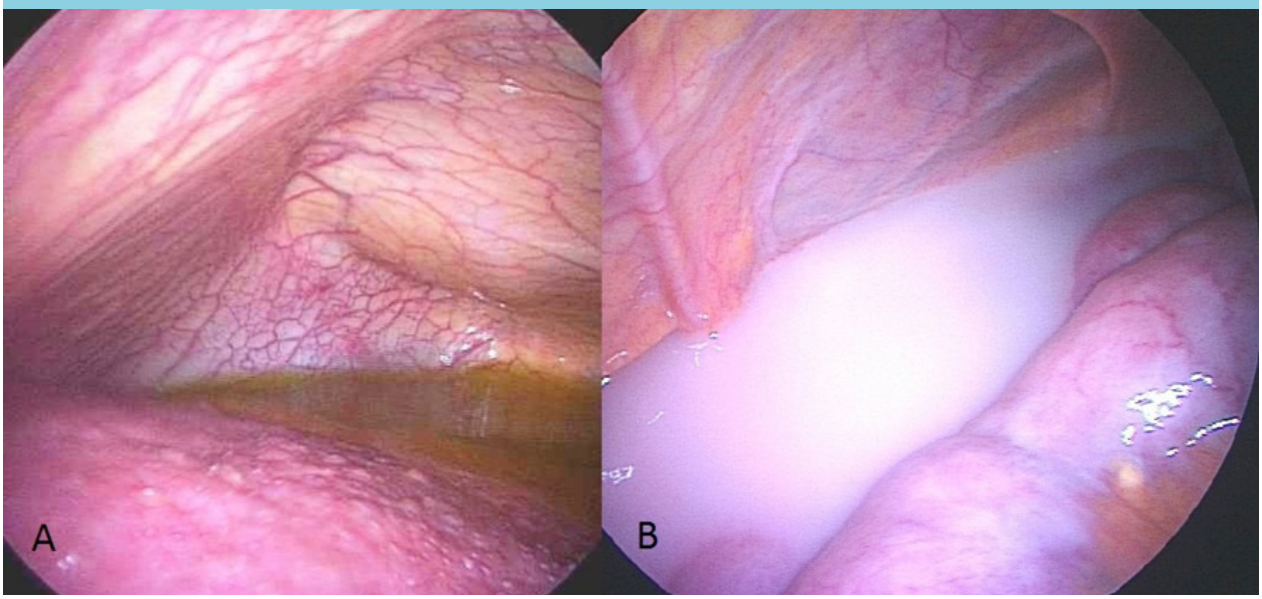
Abdominal paracentesis is the most important step in the diagnostic work-up. It is indicated in every patient with new-onset ascites, patients with known ascites and clinical deterioration or a new presentation to an emergency department. Paracentesis is usually performed in the left lower quadrant, 3 cm cranially and 3 cm medially from the anterior superior iliac spine. Other sites include the right lower quadrant and the midline linea alba between the umbilicus and the pubic bone.[7] Paracentesis should be performed under sterile conditions. Complications occur infrequently and include abdominal wall haematoma (1%), haemoperitoneum (< 0.1%), bowel perforation (< 0.1%), and infection (< 0.1%).[7,8]

Ascitic fluid analysis

Visual inspection

Visual inspection of the ascitic fluid can show a milky, cloudy, bloody, straw coloured or clear appearance (*figure 1*). Milky ascites suggests the presence of chylomicrons, containing predominantly triglycerides, and is therefore called chylous ascites. Chylous ascites can result from malignancy, trauma, liver cirrhosis, infection, pancreatitis, congenital disease and more uncommon causes.[9] Cloudy ascites, also known as pseudochylous ascites, may indicate

Figure 1. *Appearance of ascitic fluid. A: straw coloured ascites in a patient with micronodular liver cirrhosis. B: chylous ascites in a patient with lymph vessel obstruction caused by a small bowel neuroendocrine tumour*



peritonitis, pancreatitis or a perforated bowel. Bloody ascites is often associated with malignancies or results from traumatic paracentesis, whereas straw coloured or clear ascites is common in liver cirrhosis.[10] The first impression of the appearance of ascites is non-specific, but can steer the direction of diagnosis.

Biochemical testing

Serum-ascites albumin gradient

The serum-ascites albumin gradient (SAAG) is the most sensitive marker to distinguish between ascites due to portal hypertension/hepatic congestion and other causes, with an accuracy of 97%.[11] The SAAG is obtained by subtracting the level of albumin in the ascitic fluid from that in the serum, both measured at the same time. A value ≥ 1.1 g/dl (or 11 g/l) indicates underlying portal hypertension or hepatic congestion; a value < 1.1 g/dl indicates aetiologies not due to portal hypertension, such as malignancy, pancreatitis or infection.[6,11]

Total protein

Current international guidelines still recommend measuring the total protein concentration in ascites.[5-7] Traditionally, this was thought to indicate the aetiology of ascites according to the transudate-exudate concept, but this approach is now generally considered inferior. The total protein concentration does have prognostic value as concentrations lower than 15 g/l are associated with an increased risk for spontaneous bacterial peritonitis (SBP) in cirrhotic patients.

Amylase

The amylase concentration in ascitic fluid should be measured in particular when pancreatic disease is considered. Pancreatic ascites can be caused by leakage from pancreatic pseudocysts or due to pancreatic duct rupture. An amylase ascitic fluid/blood serum concentration ratio of 6.0 is indicative for pancreatic disease, considering that a ratio of 0.4 is normal in non-pancreatic ascites.[12] However, high levels of amylase have also been detected in patients with malignancy and other conditions making it a rather non-specific finding. Still it can be of significant value in patients with comorbidities such as alcoholic cirrhosis and pancreatitis.[13]

Triglycerides

A concentration of triglycerides in the ascitic fluid that exceeds the blood serum level (2.2 mmol/l) indicates chylous ascites. Previous abdominal surgery, pancreatitis, trauma and retro-peritoneal lymphoma are among the main causes.[9] Malignancy is diagnosed in 80% of patients with chylous ascites; however, it must be noted that ascites in up to 6% of cirrhotic patients has a chylous character.[14]

Adenosine deaminase activity

The activity of adenosine deaminase (ADA), an enzyme of purine metabolism, is a reliable marker to differentiate tuberculous ascites from other aetiologies. An ADA cut-off value between 36 to 40 IU/l has a high sensitivity (100%) and specificity (97%) for diagnosing abdominal tuberculosis.[15] In the Netherlands, the ADA activity assay is available in a limited number of centres.

Glucose and lactate dehydrogenase

Traditionally, determining glucose and lactate dehydrogenase concentrations in ascites constituted part of the diagnostic work-up. A lower glucose concentration in ascitic fluid than in blood serum can indicate the presence of bacteria, white blood cells or cancer cells.[16,17] A low level of lactate dehydrogenase is associated with non-malignant ascites, high levels suggest a malignant aetiology.[18] Unfortunately both measurements are influenced by the SAAG, are non-specific and are no longer recommended.[19]

Urea and creatinine

A very uncommon cause of ascites is urinary leakage into the peritoneal cavity. Urinary ascites is associated with pathological bladder changes and outlet obstruction.[20,21] Normally the ascites/plasma creatinine ratio is approximately one, whereas a ratio of five is reported in case of urinary ascites. Importantly, urinary ascites can be accompanied by pseudo-renal failure due to peritoneal absorption of urea.[20]

Non-biochemical testing

Polymorphonuclear leukocyte count

A polymorphonuclear neutrophil (PMN) count should be performed in the ascitic fluid of all patients with ascites admitted to the hospital or showing clinical signs suggestive of SBP. A PMN count ≥ 250 cells/mm^3 (0.25 x 10^9 cells/l) confirms the diagnosis of SBP in the absence of an evident intra-abdominal source of infection.[22] A PMN count repeated after 48 hours of antibiotic administration can distinguish between SBP and secondary bacterial peritonitis, a decrease suggests SBP and a sustained increase secondary bacterial peritonitis. A repeated PMN count 48 hours after starting antibiotic therapy is recommended to document the efficacy of antibiotic therapy for SBP.[7,16] Although SBP is mainly a complication of ascites due to portal hypertension, it may also develop in patients with ascites of other aetiologies.

Bacterial cultures

Ascitic fluid should be cultured if SBP is clinically suspected. Bedside inoculation of 10 ml under sterile conditions using blood culture bottles, containing aerobic and anaerobic media, leads to identification of an organism

in ~80% of patients with SBP.[7,23,24] Ascitic fluid cultures should be carried out before antibiotic treatment is initiated.

PCR bacterial DNA Mycobacterium tuberculosis

Bacterial DNA of *Mycobacterium tuberculosis* in ascitic fluid can be detected using polymerase chain reaction (PCR) and can be performed when tuberculous ascites is suspected. This method has a high sensitivity (94%) compared with microscopic acid-fast bacilli smears (~0%) and *mycobacterial* culture (~50%).[25,26] Alongside a higher diagnostic accuracy, PCR offers a timesaving method in contrast to current *Mycobacterium* culture techniques. PCR is a widely available biomolecular technique, however, PCR specific for the genus of *Mycobacterium* may not be available in all centres. Furthermore, culturing *Mycobacterium* from ascitic fluid or peritoneal biopsy remains the gold standard test according to national and international guidelines, also allowing antibiotic susceptibility testing.[7]

Cytology

Ascitic fluid cytology should be performed in case of suspicion of malignant ascites or when the underlying aetiology is in doubt (e.g. no decrease in PMN count after 48 hours of antibiotic treatment). Clearly, positive cytology is highly indicative for peritoneal carcinomatosis. The sensitivity of cytology is 83%, but can be as high as 97% if three samples from separate paracenteses are analysed.[27] Crucial factors are avoiding any time delay between obtaining the ascitic fluid and cytology processing as well as obtaining at least 50 ml ascitic fluid, or even 1000 ml if the first test was negative.[27] The sensitivity of cytology in patients with hepatocellular carcinoma and ascites is low (~27%).[28]

Diagnostic laparoscopy

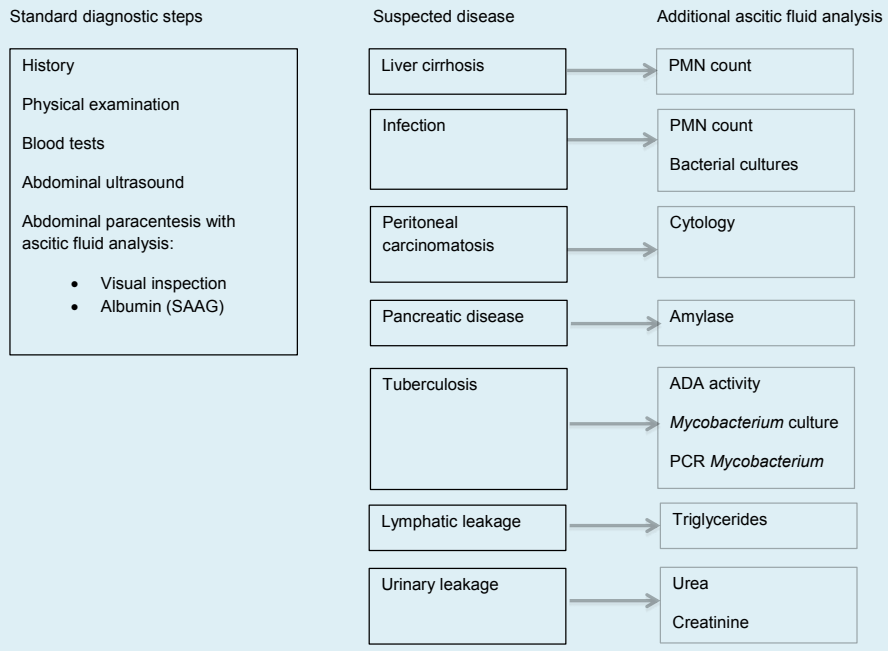
If the conventional work-up fails to disclose the cause of ascites, laparoscopy should be considered. Laparoscopy offers the advantages of visual inspection of the peritoneal cavity in combination with the ability to obtain targeted biopsies for histological and microbiological studies. The procedure may be particularly helpful to diagnose peritoneal carcinomatosis, tuberculous peritonitis and other peritoneal or omental diseases such as mesothelioma and sclerosing peritonitis.[29,30]

Figure 2 shows schematically the diagnostic approach to the patient with ascites.

DIAGNOSTIC DEVELOPMENTS

Novel markers in ascitic fluid analysis have been proposed for the initial differential diagnosis as well as for predicting prognosis in specific diseases. Most discoveries either

Figure 2. *Diagnostic approach to the patient with ascites*



ADA = adenosine deaminase; PMN = polymorphonuclear neutrophil; SAAG = serum-ascites albumin gradient.

target on simplifying, accelerating or reducing the costs of the diagnostic process or they result from advancing biochemical laboratory techniques.

Leucocyte esterase reagent strips

Leukocyte esterase reagent strips are widely used for urinary analysis with the advantages of a simple, inexpensive and rapid bedside test. Several studies have examined the usefulness of this method for diagnosing SBP and found this test had a sensitivity and specificity ranging from 80-93% and 93-98%, respectively.[31] The negative predictive value is remarkably high ranging from 97-99%, which makes it an ideal tool to rule out SBP.[31] Together with the other advantages, the reagent strip could gain a place in routine practice. Recently, an ascitic-specific reagent strip with a cut-off value of 250 cells/mm^3 was introduced, which could further improve diagnostic accuracy.[32]

Viscosity

A few studies have reported the potential usefulness of viscosity measurement of ascitic fluid. Measuring viscosity was found to be able to discriminate between portal hypertension and non-portal hypertension related aetiology and showed a high correlation with the SAAG.[33] These preliminary results await confirmation by additional studies.

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a protein which is fundamental in the process of vasculogenesis and angiogenesis. High concentrations of vascular endothelial growth have been associated with malignant ascites.[34] Additional research is necessary to define the diagnostic value of this test.

Bacterial DNA, cytokines and other proteins

Bacterial DNA was studied in two series of 30 patients with ascites due to liver cirrhosis. The presence of bacterial DNA in ascites was regularly found documenting bacterial translocation, which could indicate a worse clinical prognosis in this patient group, without implicating a diagnosis of SBP. Markers, such as endotoxin and peptidoglycan/β-glucan, could predict a poor clinical outcome.[35,36] Another study, including 52 patients with SBP and 27 control patients with cirrhotic ascites, found that blood serum concentrations of procalcitonin and an ascitic fluid concentration of calprotectin were significantly higher in SBP patients. Both serum and ascitic levels of TNF-α and IL-6 were significantly higher in SBP patients than in non-SBP patients.[37] These findings need to be confirmed in larger series of patients.

Platelet indices

Increased platelet indices, e.g. mean platelet volume and platelet distribution width, have been reported in the blood of cirrhotic patients with SBP. The diagnostic accuracy was not sufficient in this study, however, these indices can be considered as a potential diagnostic tool.[38]

Tumour markers

Several studies have addressed the diagnostic value of tumour markers in ascitic fluid including α-fetoprotein, des-gamma-carboxy prothrombin, carcinoembryonic antigen, cancer antigen 19-9 and cancer antigen 125. Increased concentrations have been associated with underlying malignancies but are also found in medical conditions such as gastritis, diverticulitis, cirrhosis and pancreatitis.[33]

CONCLUSION

The differential diagnosis of ascites is broad and includes a large number of benign and malignant causes. A structured diagnostic approach will likely reveal the aetiology in the large majority of cases and is based on the following elements: history, physical examination, blood tests, abdominal ultrasound and diagnostic paracentesis. Standard ascitic fluid analysis includes visual inspection and determination of the SAAG. In patients with suspected infection or underlying liver disease a PMN count and bacterial cultures are standard. According to clinical circumstances other established diagnostic studies are ascites cytology and determination of levels of amylase and triglycerides. In exceptional cases measuring urea and creatinine levels may be crucial. ADA activity measurements, *Mycobacterium* cultures and PCR for *Mycobacterium* DNA are indicated when tuberculosis is considered. Leucocyte esterase reagent strips are useful, in particular to rule out SBP in patients with a low a priori risk. New diagnostic markers such as viscosity, VEGF, bacterial DNA, cytokines and platelet indices have been proposed, but further research is needed to validate the value of these markers.

DISCLOSURES

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REVIEW

Human metapneumovirus in haematopoietic stem cell transplantation recipients: a case series and review of the diagnostic and therapeutic approach

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ABSTRACT

Human metapneumovirus (hMPV) is a paramyxovirus that causes respiratory tract infections ranging from mild upper airway infection to severe pneumonia. Patients with haematological disease, especially haematopoietic stem cell transplantation (HSCT) recipients, are more likely to develop more severe infections. We describe three cases of hMPV infection in HSCT patients. The most reliable diagnostic procedure for hMPV is multiplex ligation-dependent probe amplification (MLPA) on a nasopharyngeal swab. Sensitivity and specificity of MLPA to detect hMPV is high and time to diagnosis is short. A number of other respiratory pathogens can be tested in one test run. Treatment is mainly supportive and only a few antiviral agents are available for treating paramyxovirus infections. Ribavirin and immunoglobulins were reported to be effective in cases of HSCT patients with hMPV pneumonia but their efficacy has not been studied in randomised trials.

KEYWORDS

Infectious diseases, haematopoietic stem cell recipients, viral infection

INTRODUCTION

Human metapneumovirus (hMPV) is an enveloped, single-stranded RNA virus that was first detected in 2001.[1] However, according to serological studies the virus has already been circulating in humans for more than 50 years. It is a member of the *Paramyxoviridae* family, including respiratory syncytial virus (RSV) and parainfluenza virus. The virus contains eight genes, encoding nine proteins. Two of these proteins are the attachment protein G and the fusion protein F. There are four subtypes of hMPV: A1, A2, B1, B2, classified by the genotypes of the F and G proteins.[2] Human MPV is distributed worldwide and thought to be transmitted by direct or close contact with contaminated secretions, such as saliva, droplets or large particle aerosols,[3] with an incubation period estimated to be 4-6 days.[4] Seroprevalence studies indicate that by the age of 5, most children have been infected with hMPV. In a retrospective study over a 25-year period, 20% of nasal-wash specimens from children with acute respiratory illness contained hMPV RNA.[5] The mean age of infected children was 11.6 months. Human MPV appears second to RSV as a cause of lower respiratory tract infections in children.[6] What seems less common is the attribution of hMPV to childhood upper airway infection (1 to 5%) which is lower than that observed for influenza, parainfluenza, adenovirus and RSV. In adults hMPV associated respiratory disease is also found. Human MPV was detected in 3.4% of adult patients with respiratory tract illness and can occur in adults of all ages.[7] Several outbreaks of hMPV infections related to healthcare facilities have been described.[8,9] Possible vectors of infection in these outbreaks were residents, as well as asymptomatic shedding of the virus in non-residents. Outbreaks were followed up by molecular subtyping of

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Table 1. *Haematopoietic stem cell recipients infected with human metapneumovirus in VU Medical Center and Spaarne Hospital*

Age	Haematologic disease	Treatment	Date of hMPV diagnosis	ANC count at diagnosis	Diagnosis with MLPA/ BAL	Pulmonary characteristics	ICU Admission	ICU Indication	Treatment	Status	Cause of death
57	MM	Autologous SCT	24-2-2014	3.18x10(9)	MLPA	Bilateral consolidations	Yes	Decreased consciousness	No	Died (3-3-2014)	Death of disease
62	AML	Induction therapy 1st cycle	7-3-2014	8.86x10(9)	BAL	Bilateral consolidations	Yes	Respiratory insufficiency	Ribavirin/ IVIG	Died (7-4-2014)	Relapse of CVA
67	PCL	Allogeneic SCT	4-2-2014	0.42x10(9)	BAL	Bilateral consolidations	Yes	Respiratory insufficiency	ribavirin/ IVIG	Alive	No
60	AML	Induction therapy 2nd cycle	26-2-2014	0.00x10(9)	MLPA	Bilateral consolidations	No	No ICU admission	No	Alive	No
65	MM	Autologous SCT	11-3-2014	0.92x10(9)	MLPA	Interstitial pneumonia	No	No ICU admission	No	Alive	No
66	AML	Induction therapy 1st cycle	20-2-2014	0.01x10(9)	BAL	Pneumonia right lower lobe	No	No ICU admission	No	Died (17-4-2014)	Relapse of leukaemia
62	AML	Autologous SCT	27-2-2014	0.00x10(9)	MLPA	Pneumonia right lower lobe	No	No ICU admission	No	Alive	No
70	AML	induction therapy 2nd cycle	17-3-2014	0.00x10(9)	BAL	Bilateral c onsolidations	Yes	Respiratory insufficiency	Ribavirin/ IVIG	Died (02-04-2014)	Lung bleeding
62	ALL	Consolidation therapy	3-3-2014	3.77x10(9)	MLPA	Pneumonia middle lobe	No	No ICU admission	No	Alive	No
66	AML	Induction therapy 1st cycle	17-4-2014	0.01x10(9)	BAL	Bilateral consolidations	Yes	Respiratory insufficiency	Ribavirin/ IVIG	Died (17-05-2014)	Herpes encephalitis
61	MM	Pomalidomide/ dexamethasone	2-5-2014	2.84x10(9)	MLPA	Pneumonia right lower lobe	No	No ICU admission	No	Alive	No
76	AML	Polokinase phase II study	8-5-2014	0.04x10(9)	MLPA	Upper respiratory symptoms	No	No ICU admission	No	Alive	No
69	MM	Autologous SCT	19-2-2014	0.00x 10(9)	MLPA	Pneumonia right lower lobe	Yes	Respiratory insufficiency	No	Died (13-03-2014)	Multiorgan failure, sepsis

MM = multiple myeloma; AML = acute myeloid leukaemia; PCL = plasma cell leukaemia; ALL = acute lymphocytic leukaemia; SCT = stem cell transplantation; MLPA = multiplex ligation-dependent probe amplification; BAL = Bronchoalveolar lavage; IVIG = intravenous immunoglobulin.

the virus in the respiratory specimen. Multiple subtypes can circulate at the same time and in the same location. Repeated infections are common.

The clinical symptoms of hMPV are similar to those of RSV and range from mild upper respiratory tract infection to severe pneumonia requiring mechanical ventilation,

depending on age and health status of the host. Patients with haematological diseases, especially haematopoietic stem cell transplantation (HSCT) recipients are likely to be at increased risk of infection with a prolonged clinical course and risk of respiratory failure.[10,11] We describe our experience with three HSCT patients diagnosed with respiratory infection with hMPV. These three patients were part of a much larger group of patients diagnosed with hMPV infection in that same time frame in our hospital (*table 1*).

CASE 1

A 61-year-old male was diagnosed with acute myeloid leukaemia (monocytic, M5), with a good prognosis because of his NPM1 mutation status. He had no prior medical history, especially no respiratory conditions, and was a non-smoker. He was treated with two courses of induction chemotherapy and after the first cycle a complete remission was achieved. According to our national guidelines a third course of treatment was given, consisting of busulphan/cyclophosphamide followed by autologous transplantation. Nine days after stem cell reinfusion, with an absolute neutrophil count of < 0.1 x 10^9/l, the patient developed fever and a dry cough. Lung auscultation revealed inspiratory crackles in the right lung and a chest X-ray showed signs of pneumonia in the right upper and lower lobe (*figure 1*). After performing sputum culture, blood cultures and a nasal swab for respiratory viral infections, treatment with the broad-spectrum antibiotic imipenem-cilastatin was started. The fever subsided but a non-productive cough persisted for over a week. After two days, multiplex ligation-dependent probe amplification (MLPA) of the throat showed a positive result for hMPV, while bacterial cultures of blood and sputum stayed negative. We decided not to start antiviral treatment because of the mild symptoms and signs of recovery. The clinical course was uneventful and the patient was discharged 17 days after stem cell reinfusion.

CASE 2

A 67-year-old female, with a history of asthmatic bronchitis, was diagnosed with plasma cell leukaemia in May 2013. She received four cycles of bortezomib, cyclophosphamide and dexamethasone and consolidation treatment with an autologous stem cell transplantation after high-dose melphalan. In January 2014 she was admitted for an allogenic stem cell transplantation with a sibling donor because of a poor cytogenetic risk profile. The conditioning regimen consisted of fludarabine, cyclophosphamide and total body irradiation (2 Gy), with cyclosporine A during a 30-day period after transplantation. Four days after transplantation, with an absolute neutrophil count of 0.42 x 10^9/l, the patient developed fever and dyspnoea. A computed tomography (CT) scan of the chest showed areas of alveolar consolidations, tree-in-bud and bilateral pleural effusion (*figure 2*). Under suspicion of bacterial pneumonia, imipenem-cilastatin was started. After three days, voriconazole was added because of persistent dyspnoea and fever. On day 8 after transplantation, her clinical condition worsened and the patient was transferred to the intensive care unit for respiratory support. Bronchial alveolar lavage was performed. MLPA showed a positive result for hMPV, other pathogens all tested negative. We started treatment with intravenous ribavirin with a loading dose of 30 mg/kg followed by 16 mg/kg/day for four days and intravenous immunoglobulin 500 mg/kg for five days. One month after

Figure 1. *Chest X ray showing signs of pneumonia in the right upper and lower lobe*

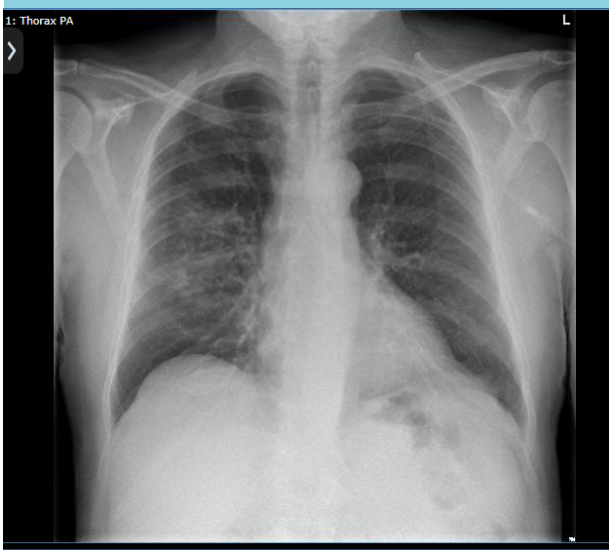
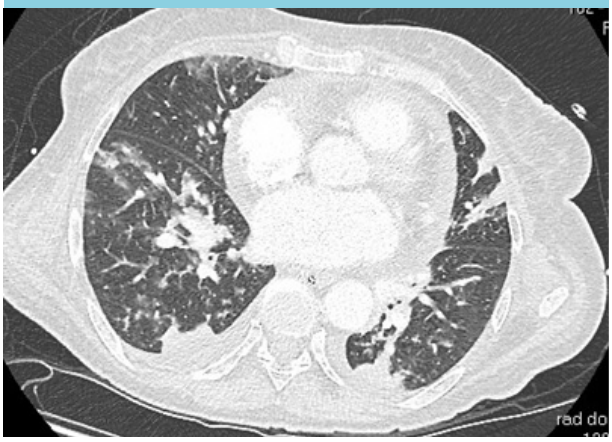


Figure 2. *CT scan of the chest showing areas of alveolar consolidations, tree-in-bud and bilateral pleural effusion*



admission to the ICU she was successfully extubated and transferred to the haematology ward. Six months after the hMPV infection, she is recovering in a nursing facility, with up till now no signs of graft-versus-host disease or plasma cell leukaemia activity.

CASE 3

A 68-year-old man was diagnosed with progressive multiple myeloma. He received autologous stem cell transplantation in 2007 leading to complete remission. Further medical history included coronary artery disease. After six years of remission he developed progressive disease of his multiple myeloma for which he was treated with five cycles of velcade-dexamethasone followed by a second autologous stem cell transplantation after conditioning with high-dose melphalan. He developed fever, cold chills and non-productive cough the day before reinfusion of the stem cells, for which imipenem-cilastatin was started. During stem cell reinfusion he developed an anaphylactic reaction, probably because of the dimethyl sulfoxide given with the cells, which was treated with clemastine and prednisolone. One day after stem cell transplantation he had progressive symptoms of non-productive cough, dyspnoea and fever. Lung auscultation revealed expiratory wheezing. Laboratory examination demonstrated an absolute neutrophil count of 0.1 x 10^9/l and chest X-ray showed a small infiltrate in the right upper lobe. Cultures of blood and sputum stayed negative. Because of persisting fever we added voriconazole empirically after three days. MLPA showed a positive result for hMPV, other respiratory pathogens all tested negative. Because of respiratory insufficiency the patient was admitted to the ICU. Intubation followed eight days after stem cell transplantation because of acute respiratory distress syndrome. A bronchial alveolar lavage was performed and hMPV still tested positive. No other pathogens could be demonstrated. Treatment was stopped on day 26 because of his progressive worsening condition and the patient died shortly afterwards.

IMMUNITY

The first line of defence in the lung is based on innate immune responses, activated upon recognition of a pathogen-associated molecular pattern by cell receptors on neutrophils, macrophages, natural killer cells and dendritic cells. These pathogen recognition receptors activate signalling pathways which leads to cytokine production and regulation of the inflammatory and immune responses in the infected host.[10]

The adaptive immune response (humoral and cellular) is the most important facet of protective immunity. Animal models have shown that passive transfer of antibodies protects from hMPV replication and have also demonstrated the essential role of T-lymphocytes in protection in hMPV infection. Recent observations indicate that CD8+ T cell response is impaired during hMPV infection.[10] What is not clear is whether this defect is responsible for the commonly observed reinfections. Other studies suggest that repeated infections are likely due to waning immunity and limited cross-reactive antibodies.[2]

DIAGNOSIS

Patients with hMPV infection usually present with aspecific symptoms of a respiratory infection. The infection is associated with coughing, nasal congestion, dyspnoea, wheezing and fever. Older people (> 65 years) more frequently suffer from dyspnoea and wheezing than young people.[13,14] More than 70% of virus infections occur in the winter months and over 80% of infections affect young children (< 5 years) or elderly patients. The virus can induce bronchitis, bronchiolitis and even pneumonitis. Pneumonitis is mainly seen in very young patients and patients with an immunosuppressive condition.[14] In patients with haematological disease, stem cell recipients are at high risk to develop an infection. More than 40% of the stem cell recipients who develop hMPV infection also develop lower respiratory infection.[15]

Viral pneumonia is often not detected with conventional chest radiography. In patients with febrile neutropenia, 50% showed a pulmonary lesion on CT which was not detected with conventional radiography.[16] Although different in type, viral infections have the same underlying pathogenic mechanism. Therefore, it is difficult to detect the type of viral agent with CT-based imaging. However, high-resolution CT of the chest is the technique with best discriminatory potential between different viral infections.[16] In hMPV infections the most common findings are patchy areas of ground glass opacity, centrilobular nodules, bronchial wall thickening and multifocal areas of consolidation in a bilateral asymmetric distribution.[16-19]

Human MPV can be diagnosed most reliably by molecular techniques. In our laboratory, we use MLPA technology on nasopharyngeal swabs. MLPA uses a multiplex polymerase chain reaction method which can detect changes in the copy numbers of specific chromosomal regions of the virus.[20] The sensitivity and specificity of MLPA to detect hMPV is high, 100% and 96% respectively.[21,22] Haematological patients can suffer from various respiratory pathogens because of their immunosuppressed

condition. With the technique of MLPA a number of respiratory pathogens including hMPV can be detected in one test run. The time to diagnosis is short for MLPA, as results can be available within six hours.[23]

TREATMENT

Few antiviral agents are available for treating paramyxovirus infections in general and treatment of hMPV infection is still mainly supportive. Although the natural course of this viral infection is associated with full recovery within 1-3 weeks, immunocompromised patients may benefit from early intervention.[24]

To date, experience has been gained from individual case reports and case series,[25-27] with only ribavirin and immunoglobulins used in humans. Ribavirin inhibits RNA polymerase and demonstrated in vitro inhibition of tumour necrosis factor-alfa, interferon-gamma and interleukin-10.[28] This suggests that ribavirin may influence and terminate T-cell immune-mediated damage caused by viral infections. Ribavirin can be administered intravenously, but aerosol therapy is also available. Aerosol ribavirin does have many disadvantages, because of its high cost and because it has direct teratogenic effects on healthcare workers. Especially healthcare providers who are pregnant or are attempting to become pregnant should avoid contact with patients receiving treatment with aerosolised ribavirin.[29] Ribavirin in combination with intravenous immunoglobulin was reported to be effective in treating hMPV pneumonia in immunocompromised patients,[30,31] but no randomised controlled trials in humans have been performed. Immunoglobulins for therapeutic goals can be divided into specific and non-specific immunoglobulin and currently human monoclonal antibodies with biological activity against hMPV are under investigation in vitro and in vivo.[32] These new antibodies could be administered as a preventive measure but are also promising for use after infection. More innovative treatments concern the use of fusion inhibitors and RNA interference treatment modalities. Fusion inhibitors target the first steps of the viral replication cycle and are currently under investigation because of possible prophylactic use, particularly in post-exposure treatment of contacts of infected individuals.[33] RNA interference depends on the action of small non-coding endogenous micro RNAs or exogenous small interfering RNA, which inhibit the translation of the mRNA or induce their cleavage, respectively. Several of these small interference RNAs were tested in vitro, and showed strong inhibitory activity.[34] Another approach in the prevention or treatment of infection with hMPV is vaccine modalities. This is a challenging field because of the difficulty to induce a strong and long-lasting immune response, especially in immunocompromised individuals. Human MPV expresses the major surface glycoproteins F and H and immunisation strategies have been targeted against these surface proteins. Results of studies performed in rodent and non-human primate models look promising, with a variety of live-attenuated, virus vectored, inactivated virus and subunit vaccines.[35] The primary strategy is to develop a live-attenuated virus for intranasal immunisation, generated by reverse genetics or recombinant proteins. The use of inactivated viruses for immunisation showed an enhanced immune response coupled to the absence of neutralising antibody production, which led to an increase in lung diseases in animal models. Research into inactivated vaccines for all paramyxoviruses has therefore been abandoned.[36] Live attenuated vaccines also mimic natural infection, but have a considerably reduced ability to replicate, thus avoiding the development of disease.[37]

CONCLUSION

Human MPV is an important pathogen causing respiratory tract infections. Especially immunocompromised patients are at risk of developing severe respiratory complications, with considerable morbidity and mortality. Here we report three adult patients with hMPV infection after haematopoietic stem cell transplantation with a distinctly different disease course and outcome. While considerable progress has been made at the diagnostic level, proven treatment is still lacking. Ribavirin remains the only drug that has been used in humans to treat hMPV infection, but in the absence of randomised studies it is impossible to conclude with certainty on the efficacy of ribavirin. The development of a vaccine is desirable and ongoing studies are promising.

DISCLOSURES

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ORIGINAL ARTICLE

Predicting adverse health outcomes in older emergency department patients: the APOP study

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ABSTRACT

Background: Older patients experience high rates of adverse outcomes after an emergency department (ED) visit. Early identification of those at high risk could guide preventive interventions and tailored treatment decisions, but available models perform poorly in discriminating those at highest risk. The present study aims to develop and validate a prediction model for functional decline and mortality in older patients presenting to the ED.

Methods: A prospective follow-up study in patients aged ≥ 70, attending the EDs of the LUMC, the Netherlands (derivation) and Alrijne Hospital, the Netherlands (validation) was conducted. A baseline assessment was performed and the main outcome, a composite of functional decline and mortality, was obtained after 90 days of follow-up.

Results: In total 751 patients were enrolled in the Leiden University Medical Center of whom 230 patients (30.6%) experienced the composite outcome and 71 patients (9.5%) died. The final model for the composite outcome resulted in an area under the curve (AUC) of 0.73 (95% CI 0.67-0.77) and was experienced in 69% of the patients at highest risk. For mortality the AUC was 0.79 (95% CI 0.73-0.85) and 36% of the patients at highest risk died. External validation in 881 patients of Alrijne Hospital showed an AUC of 0.71 (95% CI 0.67-0.75) for the composite outcome and 0.67 (95% CI 0.60-0.73) for mortality.

Conclusion: We successfully developed and validated prediction models for 90-day composite outcome and 90-day mortality in older emergency patients. The benefits for patient management by implementing these models with preventive interventions have to be investigated.

KEYWORDS

Prognosis, emergency department, adverse outcomes, mortality, older adults

INTRODUCTION

Older patients presenting to the emergency department (ED) experience high rates of adverse outcomes,[1] but they form a heterogeneous group and it is unknown who is at highest risk. The incidence of adverse outcomes is particularly high after three months, with a mortality rate about 10% and increased functional dependence between 10-45%.[1] Early identification of those at highest risk gives an opportunity to guide preventive interventions and informed treatment decisions.[2]

Current models use either severity of disease or existing geriatric vulnerability for prediction. The Modified Early Warning Score (MEWS) is an indicator of disease severity and showed to be valuable in predicting worse in-hospital outcomes in older patients.[3] However, prognostication of MEWS for long-term outcomes in older adults is unknown. The Identification of Seniors At Risk (ISAR)[4] and Triage Risk Stratification Tool (TRST)[5] focus on existing geriatric vulnerabilities, such as functional and cognitive impairment, to predict adverse health outcomes. Neither of these tools accurately identify high-risk patients,[6,7] while

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that vulnerable group of patients benefits most from an increased level of attention.

We conducted a prospective follow-up study among all older patients who visited the EDs in the region of Leiden. The aim was to develop and validate a prediction model for adverse health outcomes in older emergency patients. To reflect the condition of the patient, both demographics and severity of disease indicators and existing geriatric vulnerability were taken into account.

METHODS

Study design and setting

We performed a prospective follow-up study in the EDs of two hospitals in the region of Leiden, the Netherlands. The Leiden University Medical Center (LUMC, derivation cohort) is an academic hospital with a level 1 trauma centre and Alrijne Hospital (location Leiderdorp, validation cohort) is a peripheral hospital with a level 2 trauma centre. We considered all patients eligible who fulfilled the inclusion and exclusion criteria. The inclusion criterion was patients aged ≥ 70 presenting for the first time to the ED in the study period. The exclusion criteria were patients who were triaged with highest urgency (code red), who we were not able to approach due to an unstable medical condition, lack of permission of the nurse or physician to enter the room for any reason or due to impaired mental status without an authorised relative to provide informed consent. Also a language barrier and patients who left the waiting room were not eligible. Patients were enrolled 7 days a week for 12 weeks with 24-hour coverage in the LUMC and 12-hour coverage (10.00 am to 10.00 pm) in Alrijne Hospital. Written informed consent was obtained before inclusion. The medical ethics committee of the LUMC and Alrijne waived the necessity for formal approval of the present study, as the study closely follows routine care.

Organisation of emergency care in the Netherlands

Basic health insurance is mandatory in the Netherlands and covers the care from general practitioners (GPs), hospital care and specialist care. Emergency care is provided by GPs and in EDs. Patients in need of immediate care can contact the GP, the GP out-of-hours service, call for an ambulance or go to an ED by themselves. Depending on the urgency, patients are expected to contact or visit the GP first. As with the structure of the LUMC and Alrijne, an increasing number of GP out-of-hours centres are integrated close to the ED to avoid unnecessary ED visits.[8] In EDs a triage nurse will prioritise patients first based on the severity of their condition; then the patient can either be directed to the emergency room or the waiting room. In the Leiden region, the LUMC and Alrijne Hospital are the only two EDs, together servicing an unselected catchment area of 400,000 inhabitants of all ages. In both EDs there are no special rooms or trajectories for older patients. Two patient groups bypass the ED and were therefore impossible to include: 1) Older patients with a myocardial infarction in the ambulance who were directly sent to the catheterisation room and 2) older patients with a CVA and eligible for thrombolytic therapy underwent a brief primary assessment in the ED and were then sent to the neurology ward after a CT scan.

Data collection

We included patients in the LUMC from September to November 2014 and in Alrijne Hospital from March to June 2015. In both hospitals teams of medical students were present at the ED from 10.00 am until 10.00 pm to enrol patients, and in the LUMC the ED staff were responsible for inclusion from 10.00 pm until 10.00 am. Before the start of the inclusion period, the medical students and ED staff of the LUMC attended training sessions to guarantee convergence on conducting the questionnaires. The ideal moment for conducting the questionnaires turned out to be 30-45 minutes after arrival of the patient to the ED. At that moment the patient had spoken to the physician and was waiting for lab results or further analysis. The questionnaire took 5-10 minutes to complete. A representative was permitted to answer questions when the patient was unable to provide answers, with the exception of the cognition and self-reported quality of life questions. Questions were collected on a tablet computer and sent directly to a secured database. Additional medical data were extracted automatically from the medical records, verified manually and added to the database.

Baseline

At baseline, data on three domains were assessed: demographics, severity of disease indicators and geriatric measurements. Demographics consisted of age, gender, living arrangements and level of education. A low level of education was defined as elementary school, basic education as community college, middle education as secondary education and high education as higher vocational training or university. Severity of disease indicators consisted of characteristics related to the ED visit: way of arrival, triage category by the Manchester Triage System,[9] fall-related ED visit, indication to measure vital signs and indication to perform a blood test. Whether the visit was fall related was obtained by asking the question: Is the reason for presentation related to a fall? Indication to measure vital signs or laboratory tests was scored positively when, at the moment of presentation, vital signs needed to be measured or a laboratory test was ordered based on the Manchester Triage System and

local protocols. Geriatric measurements consisted of the number of different medications mentioned by the patient, history of diagnosed dementia reported by patient or proxy, current use of a walking device, the Identification of Seniors at Risk (ISAR)[4] screening tool, the Six Item Cognitive Impairment test (6CIT)[10] and the Katz Index of Activities of Daily Living (ADL)[11] questionnaire. The ISAR was developed for patients aged ≥ 65 and aims to predict the risk of adverse health outcomes six months after the ED visit. The ISAR consists of six dichotomous questions and scores range from 0 to 6 with higher scores denoting higher risk. The 6CIT is a short cognition test and was validated in a Dutch population against the Mini Mental State Examination (MMSE)[12] with a score on the 6CIT of ≥ 11 indicating cognitive impairment (MMSE < 24).[13] Six questions lead to a score ranging from 0 to 28 with higher scores indicating more cognitive impairment. The Katz ADL indicates functional status two weeks before presentation to the ED to eliminate possible effects of the acute illness and consists of six dichotomous questions on dependence in bathing, dressing, toileting, transfer, eating and incontinence. Scores range from 0 to 6 with higher scores an indication of more dependency.

Outcomes

The main outcome of the study was composite outcome, a composite of functional decline or mortality at 90-day follow-up. Functional decline was defined as at least one point increase in the Katz ADL score or new institutionalisation, defined as a higher level of assisted living at 90 days after ED visit. We analysed 90-day mortality separately. Mortality can be seen as the ultimate decline and might then be taken together with functional decline. On the other hand, the intervention strategy could differ for patients at high risk for mortality. For that reason we developed a separate prediction model for 90-day mortality. A model solely for functional decline is not feasible. Excluding deceased patients would imply that the model is only applicable in patients who will not die within a certain period, which we do not know at the moment of presentation. Three months after the ED visit the patient was contacted by telephone. In case of no response after three attempts on three consecutive days, the GP was contacted to verify the phone number and living status. Finally a letter with the follow-up questions was sent to patients who had not moved to a higher level of assisted living and who were alive according to the information from the GP. Data concerning mortality were derived from the municipal records.

Statistical analysis

Baseline characteristics are presented as mean with standard deviation (SD) in case of normal distribution, median with interquartile range (IQR) in case of skewed distribution or as numbers with percentages (%). Adequate statistical power for obtaining good predictions requires a minimum of 10 events per candidate predictor.[14] This rule was followed for the composite outcome. To reduce the number of candidate predictors, the most relevant questions from the questionnaires (Katz ADL, ISAR, 6CIT) were pre-selected. Single questions with the highest R-square values on the entire questionnaire score were selected and added to the list of candidate predictors for development of the prediction model. Missing predictors were imputed via single imputation techniques.[15] The prediction model was derived via backward elimination with Akaike's Information Criterion (equivalent to $p < 0.157$ for predictors with 1 df). With this technique the least contributing candidate predictors are deleted until the deterioration in model fit is too large. Discrimination of the models was assessed with the area under the receiver operating characteristic curve (AUC). Internal validation was conducted with a 500 bootstrap sample procedure, where we repeated the backward elimination procedure in each bootstrap sample to estimate the optimism-corrected performance that is expected if the derived prediction model is applied in other datasets. The internal validation procedure also provided a shrinkage factor to adjust the estimated regression coefficients for overfitting.[16] The adjusted regression equation provides predictions for new individuals. It was validated in the Alrijne patients.[17] Calibration of the model, which reflects how well predicted and observed outcomes agree, was examined by using the adjusted regression equation. Calibration was examined graphically with calibration plots, with a goodness of fit test (Hosmer and Lemeshow test[18]). The formula $1/(1+e^{(-\text{linear predictor})})$ was applied with the adjusted regression equation to determine the individual risks of experiencing the outcome. Performance of the model for the patients with the highest 30%, 20% and 10% predicted risk was evaluated according to sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio and negative likelihood ratio, with 95% confidence intervals. To compare our model performance with the existing six-item ISAR questionnaire, predictive performance of the ISAR on different cut-off points was also calculated. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics package (version 20) and R version 3.1.1.

RESULTS

In the three-month inclusion period a total of 995 older patients presented to the ED of the LUMC. Of these, 19 patients were excluded due to a language barrier or leaving the waiting room. Another 92 patients could not

be approached due to their medical condition, resulting in 884 eligible patients. Of these, 65 patients were missed for inclusion and 68 patients refused informed consent, which led to a study population of 751 patients (85% of eligible patients). Similarly, 881 patients were included in Alrijne Hospital (*figure 1*).

The median age of LUMC patients was 78 years (IQR 74-83) and 80 years (IQR 75-84) in Alrijne patients (*table 1*); 405 (53.9%) patients of the LUMC arrived by ambulance and 201 (26.1%) were triaged as 'very urgent'. In Alrijne 432 (49.0%) arrived by ambulance and 58 (6.6%) were triaged as 'very urgent'. In both hospitals the majority of the older patients were independent, with a median Katz ADL score of 0 (IQR 0-1).

In total 230 LUMC patients (30.6%) experienced the composite outcome within 90 days of follow-up and 71 patients (9.5%) died. In Alrijne Hospital 247 patients (28.0%) had the composite outcome and 84 (9.5%) died.

Details on the univariate and multivariable analyses on both outcomes can be found in *supplemental tables 1 and 2*.

The final model for the composite outcome combined age, arrival by ambulance, number of different medications, help needed with bathing or showering, hospital admission in the past six months, help needed at home on a regular base and history of dementia (*table 2*). Ninety-day mortality could be best predicted by combining information of age, gender, living arrangements, a fall prior to ED visit, indication for blood tests and needing help in dressing. Accuracy of the final models was fair to good, with in the derivation cohort an area under the curve (AUC) of 0.73 (95% CI 0.69-0.77) for the composite outcome and of 0.79 (95% CI 0.73-0.85) for mortality. External validation in Alrijne patients showed an AUC of 0.71 (95% CI 0.67-0.75) for the composite outcome and 0.67 (95% CI 0.60-0.73) for mortality. The formula of the original final models to calculate the individual risk can be found in the legend of *table 2*.

Calibration of the predicted probabilities was satisfactory (*figure 2*), with all Hosmer and Lemeshow goodness-of-fit p-values above 0.05. A stricter limit to assign patients at high risk increased specificity, PPV and the positive likelihood ratio (*table 3*). The PPV ranged from 0.55 (95% CI 0.48-0.61) to 0.69 (95% CI 0.57-0.79) for the composite outcome and from 0.21 (95% CI 0.16-0.27) to 0.36 (95% CI 0.26-0.49) for mortality, depending on the threshold chosen. This implies that in the highest risk group 69% of the patients experienced the composite outcome and 36% died.

The conventional cut-off of 2 points or higher for the ISAR resulted in a PPV of 0.40 (95% CI 0.36-0.45) for composite outcome and 0.13 (95% CI 0.10-0.16) for mortality (*supplemental table 3*). Raising the ISAR cut-off to a score of ≥ 4 points to define patients as high risk yielded a PPV of 0.50 (95% CI 0.40-0.60) for the composite outcome and 0.18 (95% CI 0.12-0.26) for mortality.

Figure 1. *Flowchart of LUMC and Alrijne patients*

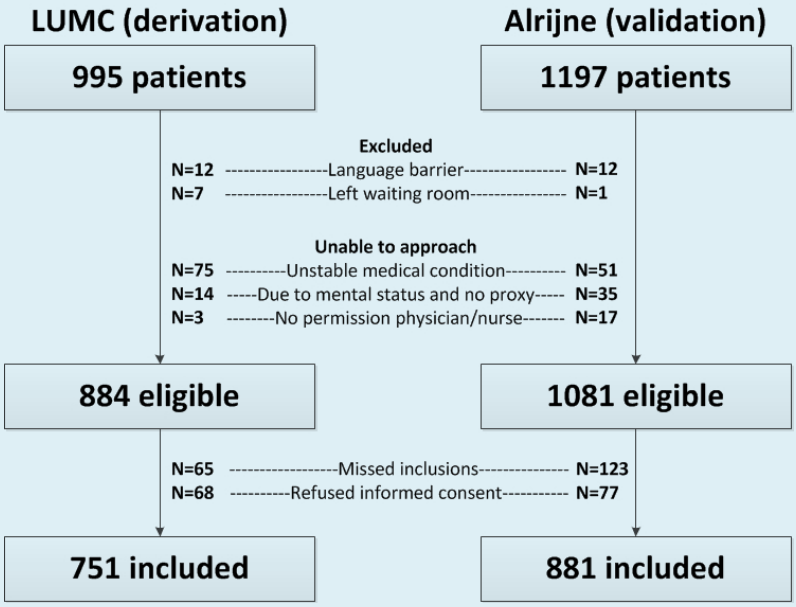

Table 1. *Baseline characteristics of older emergency patients at LUMC and Alrijne*

Characteristics	LUMC (n = 751)*	Alrijne (n = 881)#
Demographics		
Age (years), median (IQR)	78 (74-83)	80 (75-84)
Female	389 (51.8%)	454 (51.5%)
Living in residential care or nursing home, n (%)	63 (8.4%)	69 (7.8%)
High education, n (%)	155 (20.8%)	164 (18.6%)
Severity of disease indicators		
Arrival by ambulance, n(%)	405 (53.9%)	432 (49.0%)
Triage category, n(%)		
- Standard (Green)	159 (21.2%)	353 (40.1%)
- Urgent (Yellow)	391 (52.1%)	470 (53.3%)
- Very urgent (Orange)	201 (26.8%)	58 (6.6%)
Fall-related visit, n(%)	211 (28.1%)	192 (21.8%)
Indication to perform vital sign measurement(s), n(%)	661 (88.0%)	776 (88.1%)
Indication to perform blood test, n(%)	603 (80.3%)	749 (85.0%)
Geriatric measurements		
Number of different medications, median (IQR)	5 (3-8)	5 (3-8)
Use of walking device, n(%)	302 (40.4%)	378 (42.9%)
Katz ADL score, median (IQR)[1]	0 (0-1)	0 (0-1)
ISAR score, median (IQR)[2]	2 (1-3)	2 (1-3)
History of dementia, n(%)	34 (4.5%)	42 (4.8%)
6CIT score, median (IQR)[3]	4 (2-8.5)	4 (0-8)

N = number; IQR= Interquartile range. *LUMC data incomplete for education (n = 746), use of walking device (n = 747), Katz ADL score (n = 745), ISAR score (n = 748) and 6CIT score (n = 697). #Alrijne data incomplete for education (n = 878), use of walking device (= 878), Katz ADL score (n = 859), ISAR score (n = 872), 6CIT (n = 791). [1]Higher scores indicating higher dependency (0-6). [2]Higher scores indicating higher risk of functional decline (0-6). [3]Higher scores indicating worse cognition (0-28).

DISCUSSION

New externally validated prediction models were presented for older emergency patients by using a combination of demographics, severity of disease indicators and geriatric vulnerability. Performance of the models was satisfactory, with good accuracy and high PPVs.

The predictors used in our models have previously been shown to be predictive of negative health outcomes in other models. The Identification Seniors at Risk (ISAR)[4] tool and Triage Risk Screening Tool (TRST)[5] were developed for older patients at the ED. The ISAR is suitable for all older patients, whereas the TRST was developed for those discharged home. Both tools include predominately geriatric vulnerabilities, such as functional and cognitive impairment, and are validated for prediction of negative health outcomes, including functional decline and mortality.[4,19,20] Scoring systems for disease severity are also used to predict negative health outcomes of which the Acute Physiology and Chronic Health Evaluation (APACHE II)[21] and Early Warning Score (MEWS)[3] are well known. APACHE II is available online and predicts mortality in intensive care unit patients by using an algorithm consisting of 12 physiological and two disease-related variables. The MEWS weighs the severity of five physiological parameters to identify patients at risk of clinical deterioration and can be used as a bedside evaluation instrument to predict mortality and admission in ED patients.[22] The MEWS and APACHE II scores were developed for prediction of worse in-hospital outcomes, whereas the prognostic capabilities in the longer term are unknown, especially in the older population. Recently we showed that directly available clinical data describing disease severity and geriatric vulnerability can be used for prediction in hospitalised older patients.[23] The present study also selected predictors reflecting the acute

Table 2. *Final model for 90-day composite outcome and 90-day mortality in older patients*

	Composite adverse outcome		Mortality	
	beta	*OR (95% CI)*	*beta*	*OR (95% CI)*
Demographics				
Age (per 5 years increase)	0.293	1.34 (1.16-1.54)	0.462	1.59 (1.28-1.97)
Female			-1.397	0.25 (0.14-0.45)
Living in residential care or nursing home			0.730	2.08 (0.94-4.58)
High education				
Severity of disease indicators				
Arrival by ambulance	0.477	1.61 (1.14-2.28)		
Triage category				
- Standard (Green)				
- Urgent (Yellow)				
- Very urgent (Orange)				
Fall-related ED visit			-0.627	0.53 (0.26-1.10)
Indication for vital measurement(s)				
Indication for blood test(s)			1.254	3.50 (1.24-9.93)
Geriatric measurements				
Number of different medications	0.044	1.05 (1.00-1.09)		
Use of walking device				
Needs help bathing/showering	0.665	1.94 (1.24-3.05)		
Needs help dressing			1.281	3.60 (1.97-6.58)
Hospital admission in past 6 months	0.404	1.50 (1.03-2.17)		
Needed help prior to ED visit	0.716	2.05 (1.38-3.03)		
History of dementia	-0.794	0.45 (0.20-1.01)		
Disorientated in time				
Intercept	-6.557		-10.538	
AUC (95%CI) of final model	0.73 (0.69-0.77)		0.79 (0.73-0.85)	
AUC (95%CI) in Alrijne patients	0.71 (0.67-0.75)		0.67 (0.60-0.73)	

ED = emergency department; AUC = area under the receiver operator curve; CI= confidence interval. Final model equations:
1: 90-day composite outcome: 1/(1+exp(-(-6.557 + 0.293 x '(age/5)' + 0.477 x 'arrival by ambulance' + 0.044 x 'number of medications' + 0.665 x 'need help bathing or showering' + 0.404 x 'hospital admission in the past six months' + 0.716 x 'need help prior to ED visit' + -0.794 x 'history of dementia')))
2: 90-day mortality: 1/(1+exp(-(-10.538 + 0.462 x '(age/5)' + -1.397 x 'female gender' + 0.730 x 'living in residential care/nursing home' + -0.627 x 'fall related ED visit' + 1.254 x 'indication of blood test' + 1.281 x 'need help dressing'))).

condition of the older patient visiting the ED and developed prediction models with high specificity and high PPVs.
As shown in *table 2*, demographics and severity of disease indicators are important for predicting mortality and geriatric measurements for predicting the composite outcome. It is arguable that those patients with functional impairment at baseline have a higher risk of further decline, and this stresses the importance of obtaining these measurements of functional capacity in combination with the other parameters for accurate prediction. We showed that history of dementia decreased the risk of the composite outcome. It was an unexpected finding and it may be caused by a larger proportion of patients with dementia living in an institution, and thus better protected from poor outcome, or the group of patients with dementia were less severely ill but referred to the

Figure 2. *A: Calibration plot at internal validation of 90-day composite outcomes with a Hosmer and Lemeshow goodness-of-fit p-value of 0.77. The vertical lines represent the relative frequency distribution of predicted probabilities*
B: Calibration plot at internal validation of 90-day mortality with a Hosmer and Lemeshow goodness-of-fit p-value of 0.19. The vertical lines represent the relative frequency distribution of predicted probabilities

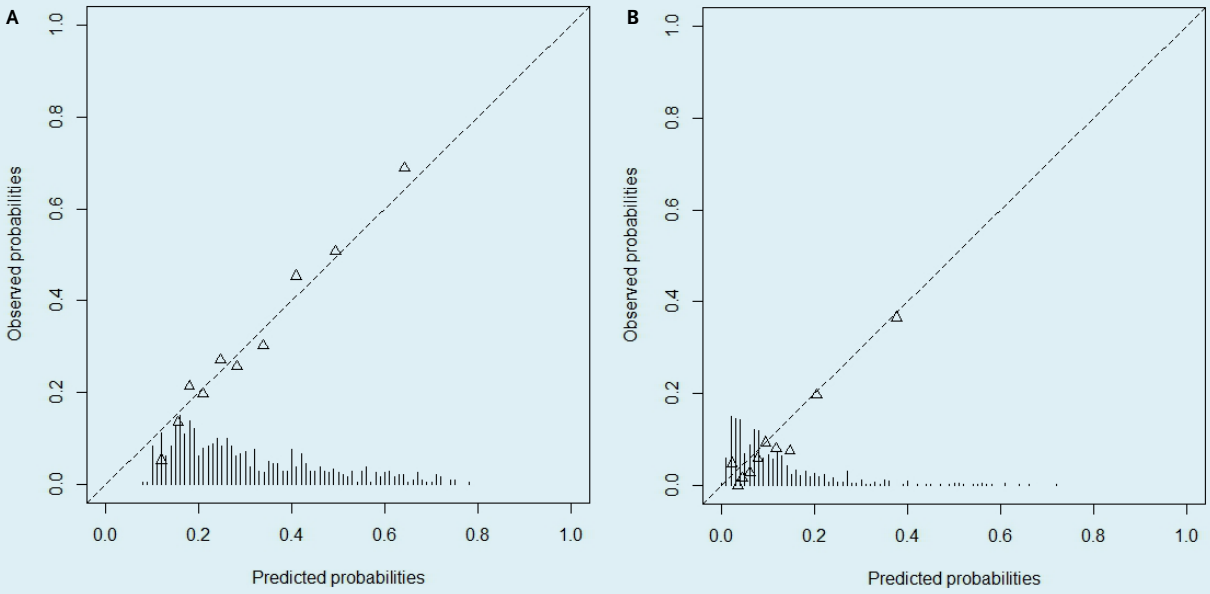

Table 3. *Predictive performance of final prediction model for 90-day composite outcome and 90-day mortality*

	Number of patients	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)
30% at highest risk							
Composite outcome	225	0.53 (0.47-0.60)	0.80 (0.77-0.84)	0.55 (0.48-0.61)	0.80 (0.76-0.83)	2.73 (2.21-3.38)	0.58 (0.50-0.67)
Mortality	225	0.66 (0.54-0.77)	0.74 (0.70-0.77)	0.21 (0.16-0.27)	0.95 (0.93-0.97)	2.53 (2.05-3.12)	0.46 (0.33-0.63)
20% at highest risk							
Composite outcome	150	0.39 (0.32-0.45)	0.88 (0.85-0.91)	0.59 (0.51-0.67)	0.77 (0.73-0.80)	3.30 (2.48-4.40)	0.69 (0.62-0.77)
Mortality	152	0.59 (0.47-0.70)	0.84 (0.81-0.86)	0.28 (0.21-0.36)	0.95 (0.93-0.97)	3.66 (2.82-4.73)	0.49 (0.37-0.65)
10% at highest risk							
Composite outcome	75	0.23 (0.17-0.29)	0.96 (0.93-0.97)	0.69 (0.57-0.79)	0.74 (0.70-0.77)	5.12 (3.21-8.16)	0.81 (0.75-0.87)
Mortality	74	0.38 (0.27-0.50)	0.93 (0.91-0.95)	0.36 (0.26-0.49)	0.94 (0.91-0.95)	5.50 (3.67-8.25)	0.67 (0.55-0.80)

Sens = sensitivity, Spec = specificity, PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio, CI = confidence intervals. Predictive performance was calculated by applying the results of internal validation procedure.

ED sooner. Alternatively, it could be a chance finding in a small group of patients. Another notable finding is that a comparable percentage of patients in both hospitals arrived by ambulance, while the patients in LUMC are triaged more urgently (*table 1*). We do not have an explanation for this finding, since there are many reasons to arrive by ambulance and both hospitals use the Manchester Triage System. However, we showed that patients who arrive by ambulance are at increased risk to experience the composite outcome. Expected or unexpected, the final prediction models have to be tested in a different population or setting to support general applicability. External validation of both models in the Alrijne patients resulted in a comparable discrimination for the composite outcome and a decrease in AUC of 0.12 for mortality. It is difficult to explain the reason for this decrease in mortality. The fact that the inclusion timeframe was different between hospitals (24 hours in the LUMC vs. 10 am to 10 pm in Alrijne Hospital) is unlikely to have influenced the results substantially, as there were only a very limited number of patients included during the night, and endpoints did not differ between those included during the 'daytime' vs. those included at 'night'. More likely, it could be minor differences in the study population, in ED protocols or parameters which we did not or cannot measure.

Predictive performance of a comparable model, the ISAR,[4] was analysed in the same study population (*supplemental table 3*). The performance was characterised with high sensitivities and low specificities, resulting in relatively low PPVs and high NPVs. As a consequence ISAR is more useful to 'rule out' patients at high risk, where our models target patients at highest risk. Prediction of individual risk scores on multiple outcomes, as shown with the composite outcome and mortality enable emergency physicians to guide preventive interventions and tailored treatment decisions. As an example, for patients with a predicted risk for the composite adverse outcome of 50% to 65%, safety procedures could be applied, whereas a predicted risk of 65% or higher can lead to more intensive interventions. On one hand standardised interventions should be administered, such as nursing these patients in a comfortable bed and informing the general practitioner. On the other hand, the predicted risk could support the physician in deciding to start physiotherapy or in making an outpatient appointment to prevent deterioration. If the risk of 90-day mortality is also high, this could be an argument to spend more time on diagnostic and therapeutic shared decision making and advanced care planning.

To date, there is no standard screening program for older adults in the ED. This could be due to the low proportion of evidence-based studies designed for the elderly,[24,25] specifically due to the low number of clinical impact studies.[26] The ultimate goal is to introduce a new generalised prediction tool, suitable for all older emergency patients and to design and test effectiveness of different interventions. Such a model should consist of patient-related parameters rather than organisation-dependent factors, such as the indication to perform measurements. The present model is accurate for older patients in Western Europe. We are planning such external validation studies, which will show whether the model needs to be updated to specific settings. The algorithm can simply be integrated in the electronic patient record to incorporate screening into routine care or be used as an application as developed on the website: http://screener.apop.eu.

One of the limitations in the current study is the lack of baseline data on potentially important determinants such as malnutrition, depression and instrumental ADL functioning. Since time is scarce in the acute setting we had to limit the number of questions, instead of performing a comprehensive geriatric assessment. A second limitation is the low proportion of deceased patients within 90 days of follow-up. As a consequence, power for prediction of 90-day mortality was low. The major strength is the unselected representative study population. We included 85% of the eligible older patients 24/7 during 12 weeks. A second strength is the fact that demographics, severity of disease and geriatric vulnerability of the patient were taken into account as a reflection of the condition of the patient.

In conclusion, we successfully developed and validated prediction models for 90-day composite outcome and 90-day mortality in older emergency patients. The benefits for patients by implementing these models with preventive interventions have to be further investigated.

DISCLOSURES

Conflict of Interest: The authors declare no conflict of interest.

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Supplemental table 1. *Univariate and multivariable associations of candidate predictors for 90-day composite outcome in older emergency patients of the Leiden University Medical Center*

	Univariate		Multivariate	
	OR (95% CI)	*p-value*	*OR (95% CI)*	*p-value*
Demographics				
Age (per 5 years increase)	1.51 (1.33-1.71)	< 0.001	1.29 (1.10-1.50)	0.002
Female	1.16 (0.85-1.58)	0.353	1.00 (0.70-1.44)	0.985
High education	0.81 (0.54-1.20)	0.285	1.06 (0.68-1.66)	0.784
Living in residential care or nursing home	3.93 (2.31-6.68)	< 0.001	1.66 (0.89-3.11)	0.114
Severity of disease indicators				
Arrival by ambulance	2.01 (1.46-2.77)	< 0.001	1.75 (1.17-2.61)	0.006
Triage category				
Standard (Green)				
Urgent (Yellow)	1.09 (0.73-1.62)	0.684	0.93 (0.58-1.50)	0.772
Very urgent (Orange)	0.92 (0.58-1.45)	0.704	0.60 (0.33-1.11)	0.081
Fall related ED visit	0.95 (0.67-1.34)	0.775	0.77 (0.51-1.19)	0.239
Indication of vital measurement(s)	1.63 (0.97-2.75)	0.067	1.22 (0.56-2.65)	0.616
Indication of blood test(s)	1.48 (0.98-2.23)	0.065	1.06 (0.57-1.96)	0.865
Geriatric measurements				
Number of different medications	1.08 (1.04-1.12)	< 0.001	1.04 (0.99-1.09)	0.087
Use of walking device	3.14 (2.28-4.34)	< 0.001	1.33 (0.86-2.05)	0.194
Needs help bathing/showering	3.94 (2.74-5.66)	< 0.001	2.19 (1.17-4.12)	0.015
Needs help dressing	3.07 (2.09-4.50)	< 0.001	0.66 (0.34-1.27)	0.213
Hospital admission in the past 6 months	1.68 (1.20-2.34)	0.002	1.40 (0.96-2.04)	0.085
Needed help prior to ED visit	3.34 (2.63-5.04)	< 0.001	1.97 (1.29-3.00)	0.002
History of dementia	1.25 (0.61-2.57)	0.546	0.45 (0.19-1.08)	0.073
Disorientated in time	1.78 (1.16-2.73)	0.008	0.93 (0.55-1.57)	0.777

Supplemental table 2. *Univariate and multivariable associations of candidate predictors for 90-day mortality in older emergency patients of the Leiden University Medical Center*

	Univariate		Multivariate	
	OR (95% CI)	*p-value*	*OR (95% CI)*	*p-value*
Demographics				
Age (per 5 years increase)	1.62 (1.34-1.95)	< 0.001	1.59 (1.25-2.02)	< 0.001
Female	0.33 (0.19-0.57)	< 0.001	0.21 (0.11-0.40)	< 0.001
High education	0.76 (0.40-1.46)	0.415	0.65 (0.31-1.36)	0.251
Living in residential care or nursing home	4.79 (2.59-8.86)	< 0.001	1.96 (0.86-4.44)	0.109
Severity of disease indicators				
Arrival by ambulance	2.03 (1.20-3.43)	0.008	1.53 (0.79-2.97)	0.210
Triage category				
Standard (Green)				
Urgent (Yellow)	1.06 (0.57-1.99)	0.847	0.65 (0.31-1.35)	0.248
Very urgent (Orange)	0.89 (0.43-1.84)	0.747	0.46 (0.19-1.13)	0.091
Fall related ED visit	0.49 (0.26-0.93)	0.030	0.51 (0.24-1.05)	0.076
Indication of vital measurement(s)	5.13 (1.24-21.29)	0.024	2.47 (0.42-14.70)	0.320
Indication of blood test(s)	3.12 (1.39-8.89)	0.008	2.20 (0.64-7.63)	0.213
Geriatric measurements				
Number of different medications	1.05 (0.99-1.11)	0.123	0.97 (0.91-1.05)	0.470
Use of walking device	2.25 (1.37-3.72)	0.001	0.71 (0.34-1.48)	0.359
Needs help bathing/showering	4.88 (2.95-8.08)	0.001	2.05 (0.80-5.25)	0.133
Needs help dressing	4.92 (2.95-8.21)	< 0.001	2.20 (0.87-5.56)	0.097
Hospital admission in the past 6 months	1.81 (1.09-2.99)	0.021	1.46 (0.81-2.60)	0.206
Needed help prior to ED visit	2.87 (1.74-4.73)	0.001	1.46 (0.71-3.00)	0.310
History of dementia	1.29 (0.44-3.78)	0.638	0.50 (0.13-1.85)	0.296
Disorientated in time	2.22 (1.20-4.10)	0.011	0.79 (0.36-1.71)	0.542

Supplemental table 3. *External validation of the Identification of Seniors At Risk (ISAR) with different cut-off points in LUMC study population*

	Sens (95%CI)	Spec (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR- (95%CI)
ISAR ≥ 2 (61%)						
Composite outcome	0.80 (0.74-0.85)	0.48 (0.43-0.52)	0.40 (0.36-0.45)	0.84 (0.80-0.88)	1.53 (1.38-1.70)	0.42 (0.32-0.54)
Mortality	0.83 (0.72-0.91)	0.42 (0.38-0.45)	0.13 (0.10-0.16)	0.96 (0.93-0.98)	1.42 (1.26-1.61)	0.41 (0.24-0.68)
ISAR ≥ 3 (35%)						
Composite outcome	0.55 (0.48-0.61)	0.74 (0.70-0.77)	0.48 (0.42-0.55)	0.79 (0.75-0.82)	2.13 (1.77-2.57)	0.61 (0.53-0.70)
Mortality	0.61 (0.48-0.72)	0.68 (0.64-0.72)	0.17 (0.12-0.22)	0.94 (0.92-0.96)	1.90 (1.53-2.36)	0.58 (0.43-0.77)
ISAR ≥ 4 (15%)						
Composite outcome	0.24 (0.19-0.31)	0.89 (0.86-0.92)	0.50 (0.40-0.60)	0.73 (0.69-0.76)	2.27 (1.62-3.17)	0.85 (0.79-0.91)
Mortality	0.28 (0.18-0.40)	0.86 (0.84-0.89)	0.18 (0.12-0.26)	0.92 (0.90-0.94)	2.08 (1.37-3.16)	0.83 (0.72-0.96)

Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; CI = confidence interval.

ORIGINAL ARTICLE

The use of ultrasound during and after central venous catheter insertion versus conventional chest X-ray after insertion of a central venous catheter

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ABSTRACT

Background: After insertion of a central venous catheter (CVC) a conventional chest X-ray (CXR) is usually taken to check for complications and correct position. Ultrasound might be equally effective as CXR and is less time consuming. We studied the use of ultrasound versus CXR after insertion of a CVC in general ward patients.
Methods: General ward patients in need of a CVC were included. CVCs were inserted under direct ultrasound guidance. After insertion, ultrasound was performed and compared with CXR to check for complications and position. The waiting time for CXR was noted.
Results: In total, 53 patients were included. In 52/53 patients ultrasound was feasible. The results of ultrasound and CXR only differed in 3 of 53 patients. The sensitivity of ultrasound in detecting the correct CVC position was 98% (89.4-100%). No complications were detected (ultrasound or CXR). The median waiting time for CXR was 24.5 minutes.
Conclusions: Our study shows that an integral use of ultrasound during and after CVC insertion is effective in establishing that the CVC is correctly positioned and for identifying post-procedural complications in patients from the general ward when compared with CXR.

KEYWORDS

Central venous catheter, (lung) ultrasound, chest X-ray, echocardiography, complications, general ward

INTRODUCTION

Patients on the general wards regularly need a central venous catheter (CVC) for the administration of intravenous feeds or medications, especially if a peripherally inserted central catheter is not feasible or for the purpose of haemodialysis.
Most CVCs, however, are introduced in the intensive care unit (ICU) or emergency department and it was estimated that in the UK 200,000 CVCs were inserted annually.[1] For introduction of a CVC for patients on the general ward in our hospital, the patient has to be transported to a specialised unit or room and that will be the case in most other hospitals. If patients from the general ward are in need of a CVC, the use of ultrasound during and after insertion could be of great value. Using ultrasound during insertion will help in getting the CVC into the correct vessel, and because ultrasound can also be done immediately after insertion there will be no need to do a chest X-ray (CXR). This strategy might also be safe and time efficient for the general ward patients in need of a CVC.
It has been shown that the use of ultrasound during the insertion of a CVC in the internal jugular vein results in fewer complications and fewer attempts are necessary for correct placement compared with the landmark technique.[2] Many guidelines and expert opinions prescribe the use of ultrasound guidance during insertion of a CVC into the internal jugular and subclavian vein.[1,3-5]
By using the Seldinger technique, a guide wire is introduced after puncture of the vessel under direct ultrasound guidance. Afterwards, the position of the wire is checked by ultrasound, further reducing the problem of misplacement.[6] After introduction of a CVC, the position

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is checked by CXR, acknowledging that a pneumothorax or malposition may be missed through this investigation. Furthermore, there is little consensus on what the best position is on a chest radiograph;[7] there are conflicting reports on the use of ultrasound for this question.[8,9]

Ultrasound has advantages compared with CXR.[10,11] It has been shown to be superior to CXR in the identification of an anterior pneumothorax and can be performed immediately after the procedure, while waiting for a CXR takes time and is associated with discomfort and the need of radiation exposure for the patient. Furthermore, the immediate appearance of microbubbles in the right atrium after injection of agitated saline through the CVC proves unequivocally the intravascular position of the CVC.

We performed a proof of concept prospective study in which we compared ultrasound versus CXR in general ward patients receiving a CVC in the internal jugular or subclavian vein for the detection of post-insertion complications and to confirm the correct position of the CVC. Ultrasound was used as guidance during insertion. We also studied the time interval between the procedure itself and the results of the CXR.

MATERIAL AND METHODS

We conducted this study in a large teaching hospital in the Netherlands. General ward patients in need of a CVC were included. We excluded patients < 18 years and pregnant women. The study protocol was approved by the Local Ethics Committee and consent was obtained directly. Sex, age, body mass index, approach used for CVC placement, reason for CVC placement (antibiotics, total parental nutrition, lack of other venous access, combination of reasons) and the time (minutes) needed to obtain the result of a bedside CXR were noted.

Complications during insertion were noted separately (e.g. bleeding or rhythm disturbance).

All CVCs were placed under direct ultrasound guidance by experienced doctors (staff and residents). Due to logistic reasons general ward patients were transported to the ICU for insertion of the CVC during this study.

All CVCs were inserted using the Seldinger technique. After puncture of the vessel the position of the guide wire was checked by ultrasound in the long axis. In our departments triple lumen CVCs (Edwards Lifesciences) are used. For the left-sided CVCs a catheter of 20 cm is used, on the right side 15 cm. For dialysis purposes Medcomp catheters are used, also in two different lengths (20 and 15 cm).

After insertion, while waiting for the CXR, the following ultrasound examinations were performed by MB and FB, both experienced in the use of ultrasound:

- With the use of a linear-array ultrasound probe (CX50 Philips) the ipsilateral internal jugular vein was examined (in case of insertion in the subclavian vein) or the ipsilateral subclavian vein was examined (in case of insertion in the internal jugular vein).
- With the use of a linear-array ultrasound probe (CX50 Philips) the ipsilateral thorax was screened for pneumothorax. The linear transducer was used to examine several ipsilateral anterior intercostal spaces for the presence of lung sliding with its presence ruling out pneumothorax.
- B-mode cardiac ultrasound (CX50 Philips): subcostal view or apical view if subcostal view was impossible: direct visualisation of the right atrium, right ventricle and inferior vena cava. Contrast-enriched ultrasound was performed using the standard technique (10 ml syringe containing 9 ml of saline solution and 1 ml of air, mixed with a stop clock to obtain a homogenous solution). Under view of the right atrium 5 ml was injected through the distal lumen of the central line. The pattern of microbubbles entering the right atrium was observed. Interpretation of the images was done according to the study by Cortellaro et al.[8] (*table 1*). If needed, a further 5 ml was administered (maximum 10 ml). The saline/air mix was injected after checking the correct functioning of the CVC by sucking blood in each lumen and flushing the lumens with saline.

Incorrect CVC position was defined as:

- Tip in right atrium or right ventricle (cardiac misplacement);
- In homolateral or contralateral veins, or in the brachiocephalic vein (intravascular misplacement).

Position was defined as incorrect if there were no or few air bubbles, or a late appearance (> 2 seconds) of bubbles, seen from the superior vena cava entering the right atrium, or if there was turbulent flow in the right atrium or right ventricle.

The ultrasound examinations were done blinded from the CXR results. All CXRs were viewed by the attending radiologist who was not informed about the ultrasound results.

A true positive result was defined as the correct ultrasound placement confirmed by CXR and true negative placement as incorrect ultrasound confirmed by CXR. False positive was defined as correct placement by ultrasound not confirmed by CXR, and false negative placement as incorrect ultrasound placement not confirmed by CXR.

Calculation

Continuous data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical data are presented as frequencies and percentages. Using CXR as a reference standard, the sensitivity of ultrasound with a 95% confidence interval

Table 1. *Interpretation of microbubbling injection pattern*

Characteristics	Interpretation
No bubbles	Negative test: possible extravascular, extracardiac placement
Few bubbles or appearance > 2 seconds	Negative test: intravascular misplacement in neck veins or tip position too far from RA
Numerous bubbles with turbulent flow in the RA or direct visualisation of catheter tip in right atrium	Negative test: intracardiac (RA) misplacement
Numerous bubbles with linear flow coming from SVC within 2 seconds	Positive test: correct tip positioning

RA = right atrium; SVC = superior vena cava.

was calculated. Statistical analysis was performed using IBM SPSS Statistics (version 21).

RESULTS

Between January 2015 and September 2015, 53 patients were included (*table 2*). In this study 25 (47%) patients were male, aged 64 (± 12.8), with a body mass index (BMI) of 26.7 (± 5.2).

Other characteristics such as the reason for CVC insertion, the approach used (jugular or subclavian), whether the CVC was inserted by staff or a resident and the time needed for CVC insertion are also described in *table 2*.

In all but one patient ultrasound was feasible. In one patient no cardiac view could be obtained. In one patient ultrasound revealed a correct position but the CXR showed an aberrant location of the catheter. In this patient the attending radiologist advised an iodine contrast cavogram which showed an anatomical anomaly of the superior vena cava. Therefore this CVC was correctly positioned in the superior vena cava. In one patient a catheter introduced in the internal jugular vein ended in the ipsilateral subclavian vein (also a large vessel). In this patient ultrasound showed a correct position, including normal pattern of microbubbles in the right atrium.

In one patient ultrasound showed a correct position but the radiologist concluded that the CVC was in the right atrium (*table 3*).

The sensitivity of the use of ultrasound in detecting that the CVC is correctly positioned (with CXR as a reference standard) was 98% (89.4-100%). The time needed for

Table 2. *Patient characteristics*

Patient characteristic	Number, % or SD
Sex (male/female (%))	25/28 (47/53)
Age (years ± SD)	64 (12.8)
Body mass index (kg/cm² ± SD)	26.7 (5.2)
Reason for CVC (N / %) Antibiotics Inotropes TPN Other	 12 (23%) 2 (4%) 25 (47%) 14 (26%)
Approach (N / %) Left IJV Right IJV Left SCV Right SCV	 5 (9%) 45 (85%) 2 (4%) 1 (2%)
Staff/resident (n/%) Staff Resident	 7 (13%) 46 (87%)
Time needed for CVC insertion (minutes mean ±SD)	17 (8,6)

SD = standard deviation; ICU = intensive care unit; CVC = central venous catheter; TPN = total parenteral nutrition; IJV = internal jugular vein; SCV = subclavian vein.

Table 3. *Concordance between ultrasound and CXR for correct position*

	CXR correct position	CXR incorrect position	total
US correct position	49	3	52
US incorrect position	1	0	1
Total			53

US = ultrasound; CXR = chest X-ray

CVC placement was 17 ± 8.6 minutes (mean ± SD). The median time needed to wait for the result of the CXR was 24.5 minutes (IQR 18.1- 45.3). We omitted one patient who was included in the study when the digital radiology system was down for 44 hours due to severe technical failure.

In this study no post-procedural complications after CVC insertion were detected by either ultrasound and CXR.

DISCUSSION

In this prospective observational study, we have shown that ultrasound is sufficient to exclude the existence of a

pneumothorax and the absolute proof that the catheter is placed in a large vessel. For intensive care patients the use of ultrasound before and after CVC insertion has already been endorsed[12] but ICU patients are not the only group of patients in need of a CVC. In this study we included general ward patients in need of a CVC. According to the current hospital protocol they were transported to the ICU for CVC insertion but this study opens the alternative of safely inserting a CVC in another designated area using mobile ultrasound. After insertion using ultrasound a check for correct positioning and complications can be done on the spot. In this way the patient is spared the burden of uncomfortable transport, extra waiting and additional radiation.

Furthermore, we have shown that a possible complication of the insertion can be examined immediately with ultrasound, while this is not the case with CXR. No post-insertion complications were found with either of these techniques. After insertion, ultrasound was directly used to check for position and complications. Extra time was needed to wait for the result of the CXR (median 24.5 minutes); in one case the result of the CXR was delayed for almost two days due to a serious technical failure.

In our study of 53 patients there were only three patients in whom discordance was found between ultrasound and CXR in determining the correct position of the CVC. In one patient the CXR proved to be wrong and in two patients ultrasound proved wrong (in one patient the radiologist found the CVC to be positioned in the right atrium which is a difficult call to make using bedside CXR). The position in the subclavian vein was of no clinical significance, since this is a large vessel, regularly used for access or for location of a peripherally inserted central catheter. The location in the right atrium was doubtful and probably also not significant. Comparing the two techniques, the sensitivity of the use of ultrasound in detecting whether the CVC was correctly positioned (with CXR as a reference standard) was 98% (90.1-100%).

There are more reports on the use of ultrasound after CVC insertion but these studies focus on ICU patients. There are more differences, for instance in our study we combined different factors to optimise correct positioning. All CVCs were inserted under direct ultrasound guidance including the identification of the guide wire before the skin; subcutaneous tissue and vessel wall were dilated. With the use of two different lengths (20 cm for left-sided lines and 15 cm for right-sided lines) the chance of a position being too deep in the average Dutch adult patient is limited.[13,14]

The use of different lengths is a different strategy compared with the study by Cortellaro et al.[8] In the Cortellaro study CVCs of 20 cm length were used on both sides. They reported a very low incidence of incorrect positioning in the right atrium. Due to the fact that ultrasound identified only half of the incorrectly positioned CVCs, the authors state that ultrasound cannot substitute CXR in detecting incorrect positioning after insertion. In our study all but one of the CVCs were positioned above the right atrium and in almost all cases this was correctly detected by both CXR and ultrasound investigation.

In another study[9] a good concordance between ultrasound and CXR was shown in detecting complications and correct position after CVC insertion. However, in this study ultrasound was not used as guidance during insertion. In this study also CVCs of 20 cm length were used on both sides and, compared with our study, substantially more subclavian veins were used (77% versus 5.7% in our study). In this study, due to the relatively high incidence of complications and incorrect positions of CVCs, good concordance between ultrasound and CXR in detecting complications and incorrect positioning was shown. In our study the a priori chance of complications and an incorrect position was limited by using ultrasound guidance during insertion and by using different catheter lengths for a left- and right-sided approach.

There is discussion about the correct position of CVCs anyway. In a recent review by Frykholm et al. the topic of catheter position was also discussed. After a search of the literature they concluded that there are no conclusive studies on optimal catheter tip position. Since less rigid catheter materials are used, the risk of cardiac tamponade associated with catheter tips in the right atrium is very low. In the case of a central line for the purpose of dialysis the position of the catheter tip in the right atrium might even be better.[15]

So perhaps the exact depth is less important than, for instance, whether the line follows the contour of the vessel (and is not perpendicular to the vessel wall).[7] It is true that the angle of the CVC cannot be seen on ultrasound but in our study there were no cases of a CVC position perpendicular to the vessel wall and there is no scientific evidence that such a position might be dangerous. Furthermore, the rapid appearance of the contrast material in the right atrium proves a good flow of fluids through the catheter.

In a prospective clinical study by Pikwer et al.[16] it was shown that when using CXR in 1619 patients there was a low incidence of detecting an incorrect CVC position. In only 0.37% the CVC position needed adjustment after insertion. They state that CXR should not be routinely used but only when the CVC insertion procedure was difficult. Another problem using CXR is that the CVC position may vary about 1 cm craniocaudally during breathing.[17]

In our study no complications were detected (0%). When introduced under direct ultrasound guidance, the incidence of complications after inserting a CVC in, for instance, the internal jugular vein is also reported to be

very low.[2,18] The sensitivity of lung ultrasound for the detection of pneumothorax is excellent when compared with CXR, which is known to be notorious for missing anterior pneumothorax.[10,19]

Another argument in favour of the use of ultrasound is the fact that ultrasound is more time efficient. In our study, due to technical failure the hospital radiology system (PACS) was out of order for 44 hours. Disregarding this incident, a substantial amount of time was needed before a CXR result was obtained. The time saving aspect can be of clinical significance.

Our study has a number of limitations. First, a small number of patients were included. The problem is that due to the a priori very low incidence of complications and incorrect positioning of CVCs the required number of inclusions is infeasibly high.

Another criticism might be that in our study only doctors experienced in ultrasound were involved in performing the ultrasound examination after CVC insertion. Although with ample training point of care ultrasound can be taught[20] it is possible that in less experienced hands the results would be different. The recognition of laminar versus turbulent flow in the right atrium requires experience but can also be taught when the right ultrasound view can be obtained.

Our patients had an average BMI of 26.7 (± 5). We did not select patients by BMI but included all possible patients so this set of patients represents the average Dutch patient in need of a CVC. The one patient in which no cardiac view could be obtained was a patient with a BMI of 28.7, who had undergone recent abdominal surgery. The low number of patients in which no cardiac view could be obtained in our study is not different from reports in recent literature.[21] With modern ultrasound equipment adequate cardiac views can be obtained in the vast majority of patients.

CONCLUSION

Our proof of concept study shows that an integral use of ultrasound during and after CVC insertion is effective in establishing correct CVC positioning and post-procedural complications in patients from the general ward when compared with CXR. Our study demonstrates that CXR is only necessary if lung sliding cannot be demonstrated or if there is not a rapid (< 2 sec) appearance of microbubbles in the right atrium. To further investigate the occurrence of infrequently occurring complications, we suggest that a larger study should be performed.

DISCLOSURES

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CASE REPORT

Coloenteric fistula in a young patient with recurrent diverticulitis: A case report and review of the literature

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ABSTRACT

The development of colonic diverticula is common in developed countries and complications of colonic diverticulosis are responsible for a remarkable burden of the disease. The natural history and management of complicated and recurrent diverticulitis in young patients are still a matter of debate. Coloenteric fistula is a rare complication of diverticulitis in young adults. In this report, and utilising a case study, we will review the natural history, outcome and management of acute diverticulitis in the young.

KEYWORDS

Diverticulitis, coloenteric, fistula

What was known on this topic?
Spontaneous coloenteric fistula formation is a rare complication of acute diverticulitis in young adults. The natural history and management of complicated and recurrent diverticulitis in young patients are still a matter of debate.

What does this add?
Based on the current literature, younger patients with diverticulitis, though historically considered to have a higher risk of recurrence and virulence, should be managed in a similar manner to other age groups.

INTRODUCTION

Internal intestinal fistulae between the colon and small bowel can occur in postoperative, chronic infection or inflammatory states.[1] Spontaneous fistulae are commonly found in Crohn's disease and less commonly in complicated diverticulitis. Colovesical fistulas constitute the most common type of spontaneously occurring fistulas associated with diverticular disease[2] while coloenteric fistulas are relatively uncommon.[3]

The natural history and the management of complicated and recurrent diverticulitis in young patients are still a matter of debate. Here we describe a case of a young patient with history of recurrent diverticulitis complicated by coloenteric fistula formation. We also review the natural history, outcome and management of acute diverticulitis in young adults.

CASE REPORT

A 38-year-old male patient presented with left lower quadrant abdominal pain, nausea, vomiting and chills for three days. He also reported a weight loss of 35 pounds over a six-month period. The patient's past medical history was notable for schizophrenia, migraine headaches and two prior episodes of acute diverticulitis. His physical exam revealed an ill looking middle-aged male with abdominal tenderness and a palpable mass in the left lower quadrant. The rest of the physical examination was otherwise unremarkable.

His initial lab results showed a white blood cell count of 12.5 x 10^9/l, haemoglobin 10.24 mmol/l, and platelets 316 x 10^9/l. The rest of his lab work was negative (or normal) including liver function tests, kidney function tests, albumin, C-reactive protein, urine analysis and carcinoembryonic antigen. Computed tomography (CT) scan of the abdomen and pelvis with contrast showed diverticulosis of the colon, prominent inflammatory

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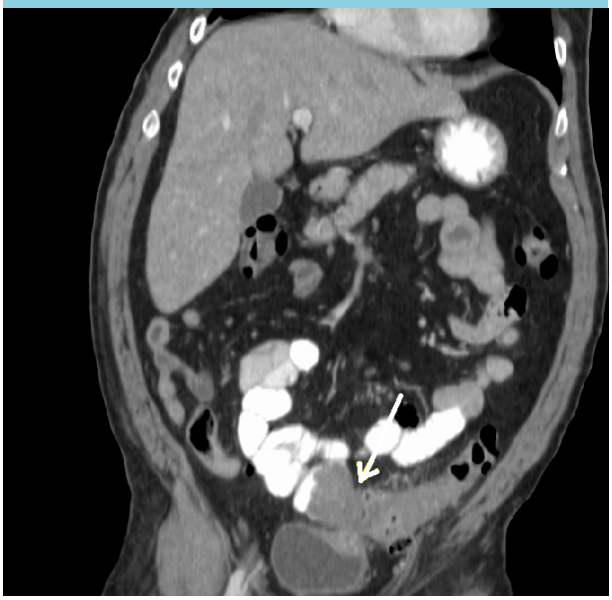
Figure 1. *CT scan of the abdomen and pelvis revealing an ill-defined pelvic mass involving sigmoid colon and ileum with a question of possible invasion into the bladder (arrow)*



changes surrounding the lower descending colon and proximal sigmoid colon, and an ill-defined pelvic mass involving the sigmoid colon and ileum with a question of possible invasion into the bladder (*figure 1*). The patient was evaluated by a surgery team who recommended supportive treatment with a nothing by mouth status, intravenous fluids, intravenous antibiotics and a colonoscopy once the acute inflammation resolved to rule out malignancy.

The C-reactive protein value was not repeated to evaluate resolution of the inflammation because it was normal on admission. Colonoscopy was performed on day 5 of admission after the patient's white blood cell count normalised and his symptoms improved. Colonoscopy examination revealed extensive diverticulosis, an abrupt transition from colonic vascular mucosa to granular and glistening mucosa of what appeared to be small bowel at approximately 30 cm from the anal verge, consistent with a coloenteric fistula. A biopsy was taken which confirmed small bowel mucosa. No masses were identified in the colon. Cystoscopy did not reveal any evidence of fistula involving the urinary bladder and the patient was taken to the operating room where he underwent adhesiolysis, segmental left colectomy, small bowel resection, jejunojejunostomy and colo-rectal anastomosis. Surgical pathology confirmed multiple diverticulae with acute diverticulitis, abscess formation and acute serositis consistent with a ruptured diverticulum in the colonic segment (*figure 2*) with the small bowel segment showing evidence of a coloenteric fistula tract (*figure 3*). The patient did well postoperatively and made a full recovery.

Figure 2. *Histology from colonic segment showing a diverticulum with associated acute inflammation and fibrin indicative of a ruptured diverticulum (H&E x10)*

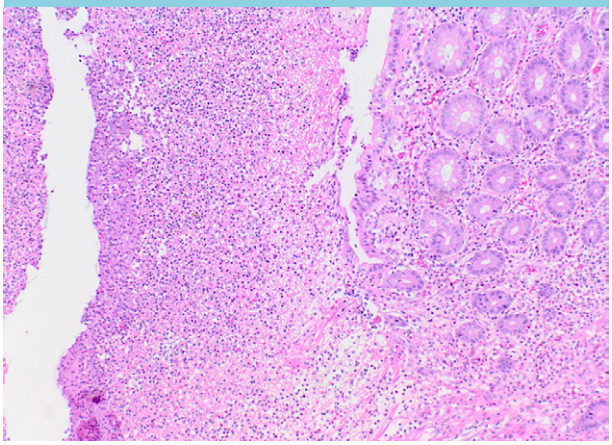
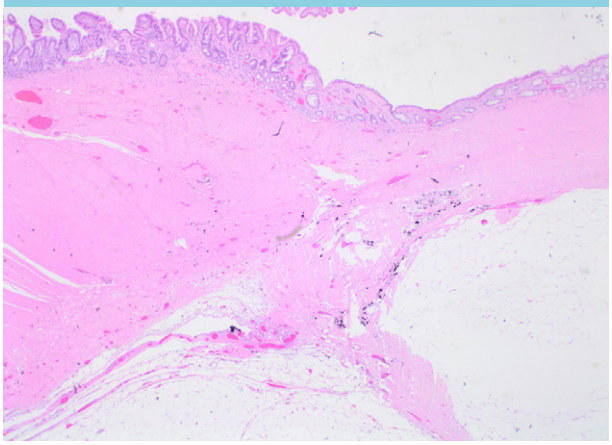


Figure 3. *Histology from surgically resected specimen demonstrating a coloenteric fistula with small bowel appearing on the left of the image transitioning into colon on the right (H&E x2)*



DISCUSSION

Almost 25% of patients with acute diverticulitis develop complicated diverticulitis, defined as development of a perforation, phlegmon, abscess, stricture or fistula.[4] Fistulas comprise approximately 2-4% of complicated diverticulitis. About 60% of these fistulas are colovesical, 30% are colovaginal and only 3% of these fistulae are reported as coloenteric.[2] About 50% of patients with colovesical fistulas are diagnosed with diverticulosis after the fistula becomes clinically evident. Endoscopic evaluation of colovesical fistulae traditionally has a low yield, with a reported detection rate of less than 10%.[5,6] However, evaluation of the remainder of the colon by colonoscopy is important to rule out concurrent disease processes including malignancy.[7]

In the United States, complicated disease at presentation is more common in African-American patients and in individuals who lack medical insurance (based on an analysis from the Nationwide Inpatient Sample).[8] Diverticulitis in the young has been treated as a special subset due to previous reports of high virulence, higher recurrence and the need for more frequent surgery.[9-12] However, several studies indicate that young age in itself is not a predictive factor of poor outcome in the management of first or recurrent episodes of acute diverticulitis.[13-22]

Guzzo and Hyman examined 762 patients admitted to their institution with sigmoid diverticulitis between 1990 and 2001, including 259 individuals younger than 50. The risk of requiring surgery during the first admission was comparable between older and younger patients. In addition, out of 196 younger patients who were treated medically at the time of their initial admission, only one (0.5%) presented with perforation during a median follow-up of 5.2 years.[13] West et al. reported that diverticulitis in young patients at their institution did not appear to take a more aggressive course than the same disease in older patients.[14] Similar conclusions were made by Ritz and colleagues when they assessed the clinical outcome of 1019 patients with acute diverticulitis presenting between 1998 and 2010.[15] A recent study by Ünlü et al. also highlighted that younger age is neither associated with a more severe presentation of diverticulitis nor with a higher incidence in recurrence,[16] which is in accordance with two other studies.[17,18]

In terms of management of acute and recurrent diverticulitis in young adults, a study performed by Nelson and colleagues proposed that young patients with uncomplicated disease findings as defined by CT criteria should be managed according to the same guidelines as those used for older populations.[19] In a retrospective study performed by Faria et al. comparing the course of acute diverticulitis in younger and older patients after stratification of diverticulitis according to the Hinchey classification, the authors recommend that diverticulitis management should be based on the severity of the disease and not on the age of the patient.[20] Furthermore, a study by Kotzampassakis et al. concluded that there was no difference in the rate of successful conservative treatment between patients with a first episode and those with recurrence in either age group.[21] Finally, a recent meta-analysis performed by Katz and colleagues proposed that factors other than age should also be considered while choosing a therapeutic regimen for acute diverticulitis.[22]

Based on the available contemporary data, it appears that young age in itself is not a predictive factor of poor outcome in the management of first or recurrent episodes of acute diverticulitis. There does not seem to be sufficient justification to recommend elective surgery after one attack of sigmoid diverticulitis in younger patients and rather the disease should be treated similarly in both younger and older patients depending on its severity and inclination to recurrence.

CONCLUSION

Spontaneous fistulae from acute diverticulitis remain an uncommon complication. Prompt diagnosis and adequate antibiotic treatment remain the mainstays of the management of patients diagnosed with acute diverticulitis with surgery reserved for exceptional cases. However, recurrent episodes of diverticulitis, especially in non-compliant patients with suboptimal care, can lead to complications such as fistulae. Younger patients should be managed in a similar manner as other age groups based on the current literature.

DISCLOSURES

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CASE REPORT

Coxiella burnetii chronic pericarditis: a case report

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ABSTRACT

Coxiella burnetii is capable of causing a variety of acute and chronic infections. We present a case of pericarditis with serologically confirmed chronic *C. burnetii* infection. This case report emphasises the justification of serological testing for chronic *C. burnetii* infection in patients with prolonged or recurrent pericarditis, particularly in countries endemic for *C. burnetii* infection.

KEYWORDS

Chronic pericarditis, *Coxiella burnetii*, recurrent pericarditis

What was known on this topic?
Recurrent pericarditis is usually considered to be idiopathic. *C. burnetii* is capable of causing chronic pericarditis.

What does this add?
Prolonged and/or recurrent pericarditis should be tested for chronic *C. burnetii* infection. This would add to the knowledge about aetiology and treatment of these types of pericarditis.

INTRODUCTION

In over 80% of cases, acute and recurrent pericarditis remains aetiologically unexplained. Even with a very extensive diagnostic examination, infectious pathogens are detected in about 20% of patient with acute pericarditis.[1] Among the infectious agents enteroviruses are the most common, while bacterial pathogens such as *Mycoplasma pneumoniae, Coxiela burnetii, Borrelia burgdorferi, Brucella species*, or tuberculosis, are found much more rarely.[2,3] However, many practitioners give up an extensive microbiological work-up, especially for viruses, generally because there is no specific antiviral therapy. Although relapsing pericarditis is usually considered idiopathic, probably most of them are autoimmune diseases.[4] Infectious recurrent pericarditis may only seem of such a nature as relapse occurs due to interruption of anti-infectious therapy.[1,4] *C. burnetii* is capable of causing a wide spectrum of acute and chronic infections. A chronic infection is considered to be confirmed by phase I IgG antibody titre, generally determined by the indirect fluorescence antibody (IFA) test. A chronic infection requires antibiotic administration for 18-24 months and in some cases for an indefinite period, and doxycycline combined with rifampicin, or ciprofloxacin, or hydroxychloroquine is a recommended treatment.[5] We present a rare case of chronic *C. burnetii* infection with a clinical feature of recurrent pericarditis.

CASE REPORT

A 76-year-old male patient was hospitalised following three weeks of progressive fatigue, with a fever up to 37.8 °C, chest tightness and dyspnoea on physical effort. The patient had chronic atrial fibrillation, but he felt well and was not taking any medication. There were no data about other chronic diseases, and the patient had not undergone any surgical procedures such as prosthetic heart valve or vascular graft placement. Physical findings on admission were unremarkable. Electrocardiography showed atrial fibrillation with a ventricular response of 80 beats/min. Thoracic multi-slice computed tomography and transthoracic echocardiography (TTE) showed a circumscribed 3-mm pericardial effusion ahead of the right ventricle, a partially organised 8-mm effusion behind

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the posterior wall of the left ventricle and thickening of parietal pericardium; the valvular apparatus was found to be normal. The erythrocyte sedimentation rate (ESR) was 72 mm/1 hour, C-reactive protein (CRP) 85 mg/l, leukocytes 4.6 x 10^9/l (neutrophils 72%); red blood cells, platelets, serum biochemistry findings, tumour markers (CEA, CA15.3, CA19.9) and thyroid hormones were within the normal limits. When selecting empiric treatment, idiopathic pericarditis, as well as infectious pericarditis such as that caused by *Mycoplasma pneumoniae*, were taken into consideration. Therapy with colchicine 275 mg three times a day for three weeks plus doxycycline 100 mg twice daily for two weeks was introduced. The patient became afebrile with subsequent reduction of symptoms, normalisation of laboratory findings, and minimal pericardial effusion at discharge. Two weeks after treatment discontinuation, the symptoms of pericarditis reappeared, and he turned febrile with a temperature up to 39 °C. Physical findings were unremarkable again, there was no heart murmur, and peripheral arterial pulsations were normal. TTE showed 4 mm of pericardial effusion in diastole, located behind the posterior wall of the left ventricle; the valvular apparatus was normal, without haemodynamic impairment, and no masses or floating formations were found. Chest X-ray findings were normal. ESR was 76 mm/1 hour, CRP 158 mg/l, and leukocytes 7.3 x 10^9/l (neutrophils 81%), and Mantoux test with two purified protein derivative (units produced induration of 6 mm in diameter. Antinuclear antibodies, blood cultures, as well as serology for brucellosis, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* were negative. Serological testing for *C. burnetii* was done at the Department of Clinical Microbiology, University Hospital Split, using the Q Fever Dual-Spot IFA (Focus Diagnostics, Cypress, California, USA), and its result indicated chronic infection (*table 1*). Subsequently, the patient recalled that he occasionally visited his relatives engaged in sheep wool processing, but he could not recall any febrile illness in the recent past that could be associated with *C. burnetii* infection. Doxycycline alone, without anti-inflammatory therapy, was re-introduced. The patient became afebrile within seven days, his subjective discomfort gradually subsided, and the laboratory findings normalised. Due to prolonged doxycycline-induced diarrhoea he refused addition of hydroxychloroquine, and finally discontinued doxycycline having completed nine months of therapy. After three months of treatment, TTE showed normal findings and he was completely free of symptoms. Two years later, he was still free from pericarditis relapse, and phase I IgG titre showed an 8-fold drop.

Table 1. *Results of indirect fluorescent antibody (IFA) test for Coxiella burnetii in patient with recurrent pericarditis*

IFA		Antibody titre			
		2 mo*	3 mo*	8 mo*	20 mo*
Phase I	IgM	1:50	1:50	1:50	1:50
	IgG	1:1600	1:1600	1:400	1:200
Phase II	IgM	1:50	1:50	1:50	1:50
	IgG	1:400	1:400	1:100	1:100

*months after first symptoms of pericarditis

DISCUSSION

Pericarditis is a rare manifestation of *C. burnetii* infection. Among 1383 patients with *C. burnetii* infection, Raoult et al. found that 1% had acute pericarditis.[6] However, up to 3.5% of the cases of acute pericarditis diagnosed as idiopathic have been shown to be caused by acute *C. burnetii* infection.[3,7] Recurrent pericarditis is most frequently idiopathic.[2] However, some of these recurrent cases refer to the incessant type of pericarditis in which disease relapse occurs within six weeks of discontinuation of anti-inflammatory therapy.[4] Reviewing the literature we only found three cases of chronic pericarditis briefly described by Raoult and al.[6] Just as our patient, all three showed a feature of relapsing pericarditis with phase I IgG titres ≥ 1:800. Phase I IgG titre of 1:1600, as found in our patient, confirms chronic infection with a predictive value of > 95%.[5,6] *C. burnetii* infection is common in southern Europe, in particular among people living in rural areas.[6,8] Therefore, serology for *C. burnetii* infection, preferably IFA, is advisable in the aetiological work-up of all pericarditis cases in countries with a high incidence of *C. burnetii* infection. Finally, in a case of prolonged and/or recurrent pericarditis, phase I IFA testing should be done in search of chronic *C. burnetii* infection. Such an approach could widen our knowledge about aetiology and optimise the therapeutic management of these types of pericarditis.

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PHOTO QUIZ

A fatty cause of acute renal failure

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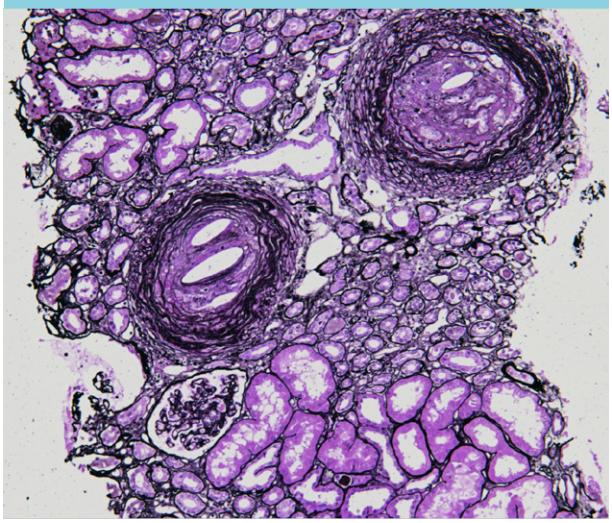
CASE REPORT

A 72-year old man had a collapse, severe hypertension (RR 200/100 mmHg), and malaise. He had a history of nicotine abuse and had been started on acenocoumarol because of pulmonary embolism four months earlier. At the outpatient clinic, his blood pressure was 180/95 mmHg and no oedema or skin lesions were observed. Screening blood tests showed acute renal insufficiency, with an estimated glomerular filtration rate (eGFR) that had decreased from 74 to 41 ml/min/1.73 m^2 over the past five months. Urinary sediment microscopy showed 3-10 non-dysmorphic erythrocytes per view. The albumin/creatinine ratio was 44 mg/mmol. Abdominal ultrasonography did not show any postrenal obstruction or renal parenchymal abnormalities; the kidneys were normal in size. It did, however, show aneurysmatic dilatation of the abdominal aorta, maximum diameter 3.6 cm. Doppler ultrasonography did not show renal artery stenosis. Analyses of secondary causes of hypertension were negative. Because of progressive renal failure and microscopic haematuria, renal biopsy was performed. The result of the biopsy is shown in *figure 1*.

Figure 1. *Light microscopy image of the renal biopsy (silver staining, original magnification 100x), showing an area of zonal interstitial fibrosis/tubular atrophy and cross sections through two small arteries. Arteries show intimal fibrosis and occluded lumina as a result of recent atheroembolism. Note the conspicuous almond-shaped cholesterol clefts*



WHAT IS YOUR DIAGNOSIS?

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ANSWER TO PHOTO QUIZ (PAGE 365)

A FATTY CAUSE OF ACUTE RENAL FAILURE

DIAGNOSIS

Renal biopsy showed a chronically injured kidney with severe arteriosclerosis but also evidence of extensive and recent atheroembolism, with cholesterol emboli surrounded by a cellular infiltrate but no fibrosis. It was assumed that atheroemboli had dislodged from atherosclerotic lesions in the aorta and/or renal arteries and had caused acute renal failure. Renal atheroembolism is iatrogenic in the majority of cases. Angiographic procedures and cardiovascular surgery are well-known triggering events. Long-term anticoagulation and/or fibrinolytics as triggers for atheroma rupture are less known, but were also present in 76% of patients in one case series.[1,2] Oral anticoagulants, heparin, low-molecular-weight heparin, and fibrinolytics such as streptokinase may dissolve clots that stabilise atherosclerotic plaques.

Renal complications of atheroemboli may be acute, subacute, or chronic,[3] but may also be a coincidental finding in renal biopsies or autopsies.[4] Most of the time, renal involvement is accompanied by other signs and symptoms of systemic embolisation. These may vary, but may include fever, wasting, laboratory evidence of inflammation, decreased C4 levels, and high eosinophil counts. Cutaneous signs are virtually always present. Fundoscopy demonstrates retinal cholesterol crystals in 22% of cases.[1] In the vast majority of cases, non-renal biopsies (e.g. skin biopsies) are diagnostic of atheroembolism and renal biopsy can be avoided. In the current case, the C-reactive protein was minimally elevated at 18 mg/l, the eosinophil count was normal, as were the C4 levels. Fundoscopy was not performed due to a low clinical suspicion for atheroemboli.

After establishing the diagnosis, acenocoumarol was substituted for acetylsalicylic acid, six months after the pulmonary embolism. Intensive hypertension control, including an ACE inhibitor and statin therapy, were initiated. Six months after kidney biopsy, the eGFR had stabilised at 39 ml/min/1.73 m^2. Therefore, additional glucocorticoid therapy was not initiated.

CONCLUSION

Anticoagulation and/or fibrinolytics can be triggers for atheroma rupture and renal atheroemboli. In patients with atherosclerotic plaques or aortic abdominal aneurysms the risks and benefits of anticoagulation should be weighed.

DISCLOSURES

The authors declare no conflicts of interest.

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PHOTO QUIZ

What does the skin tell us in this haemodialysis patient?

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CASE REPORT

A 66-year-old male haemodialysis patient with chronic kidney failure caused by hypertension presented at the emergency department after being found on the floor at home. He had multiple comorbidities and was known to be noncompliant to his prescribed medication. He suffered from pain in both upper legs and was not able to get up by himself. At admission his international normalised ratio was 1.2, potassium 5.5 mmol/l, phosphate 4.1 mmol/l, calcium 2.59 mmol/l and parathyroid hormone 137.0 pmol/l. He was taking acenocoumarol for atrial flutter. We noticed a colour change at multiple sites on his upper legs, which later progressed into blue discolorations with necrosis and palpable, very painful skin lesions several centimetres wide in arbitrary areas (*figure 1*). Duplex ultrasonography and computer tomography of the abdominal and large arteries of the limbs revealed vascular wall calcification in all the major vessels but no vascular occlusions (*figure 2*).

WHAT IS YOUR DIAGNOSIS?

See page 368 for the answer to this photo quiz.

Figure 1. *Right upper leg*

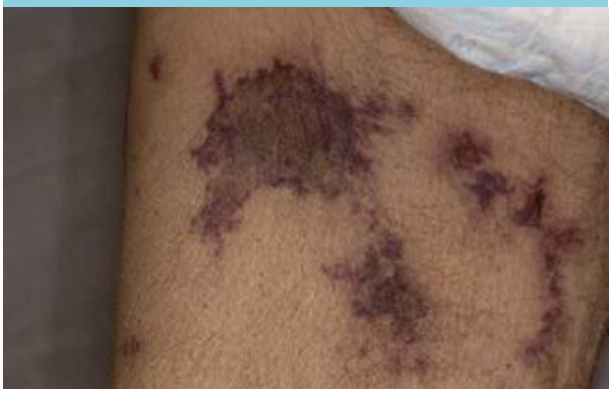
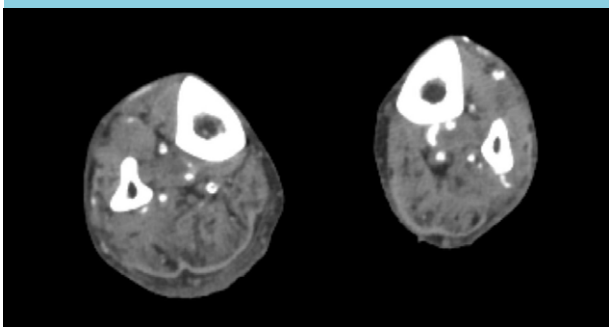


Figure 2. *CT scan showing both legs with intradermal, intramuscular and vascular calcifications*



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ANSWER TO PHOTO QUIZ (PAGE 367)

WHAT DOES THE SKIN TELL US IN THIS HAEMODIALYSIS PATIENT?

DIAGNOSIS

Computer tomography additionally showed intramuscular and intradermal calcifications. We diagnosed calciphylaxis as a complication of chronic kidney failure and non-adherence to medication because of the combination of the pain, the clinical presentation and the long-term bone and mineral imbalance. No skin biopsy was taken to avoid superimposed infection. The treatment was multifactorial, starting with adequate pain control. We intensified the haemodialysis to six times weekly with low calcium in the dialysis fluid. Vitamin D suppletion was ceased. With the intention to dissolve the calcium depositions intravenous sodium thiosulphate was given at the end of the dialysis session. Acenocoumarol was stopped because this may maintain calciphylaxis since the vitamin K-dependent matrix Gla protein is a potent inhibitor of arterial calcification. In addition, coumarin-induced skin necrosis was a second potential cause of the painful legs. During treatment the phosphate and parathyroid hormone levels normalised. Unfortunately, the skin lesions did not disappear and the patient died after two months of treatment.

CONCLUSION

Painful skin lesions in chronic kidney failure can be caused by soft-tissue calcification. Calciphylaxis is a potential lethal disease and requires intensive treatment.

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PHOTO QUIZ

Pathological fracture and osteolysis of the rib with pleural effusion – is this malignant?

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CASE REPORT

A 35-year-old man was referred to our hospital for further diagnostic procedures. At admission, the patient presented with right-sided chest pain and dry cough of six weeks duration. He had no history of chest trauma or rib fractures, and the medical histories of the patient and his family were unremarkable.

On physical examination, the patient was afebrile, in general good condition and there was dullness over the right hemithorax extending up to the angle of the scapula, along with a corresponding reduction in the breath sounds. His chest X-ray showed massive right-sided pleural effusion (*figure 1*) and a diagnostic and therapeutic thoracentesis was performed. Pleural fluid analysis revealed a haemorrhagic exudate with protein 49 g/l, glucose 7.1 mmol/l, lactate dehydrogenase 129 U/l and adenosine deaminase 23.6 U/l. Pleural fluid examination was negative for malignant cells. Chest computed tomography demonstrated a large right-sided pleural effusion with osteolysis of the seventh right rib, a pathological fracture of the eighth right rib without changes in the lung parenchyma (*figure 2*). The patient underwent right-sided thoracotomy with decortication of lung and partial resection seventh and eighth ribs.

Figure 1. *A chest X-ray shows a large right sided pleural effusion*

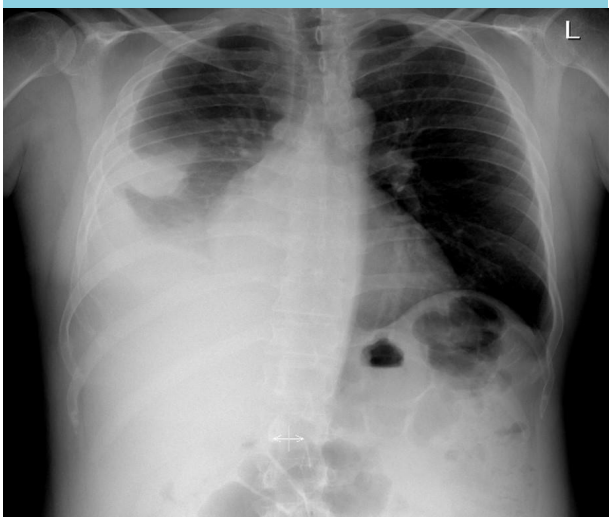
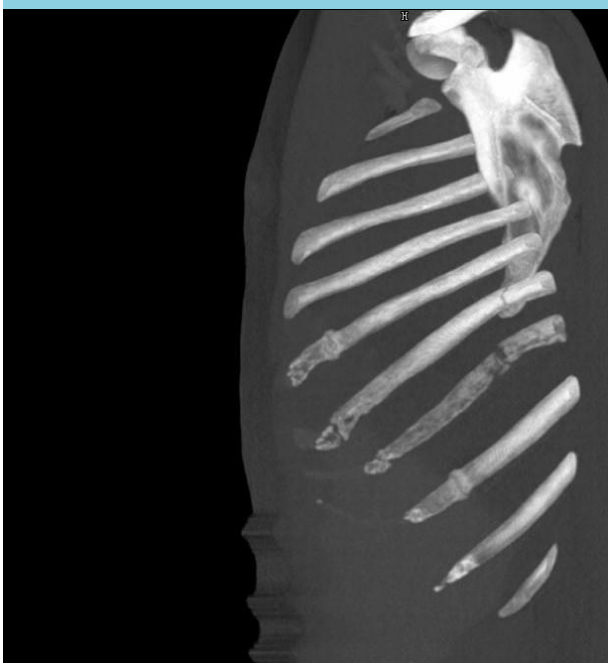


Figure 2. *Chest CT shows osteolysis of the seventh and pathological fracture of the eighth right rib*



WHAT IS YOUR DIAGNOSIS?

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ANSWER TO PHOTO QUIZ (PAGE 369)

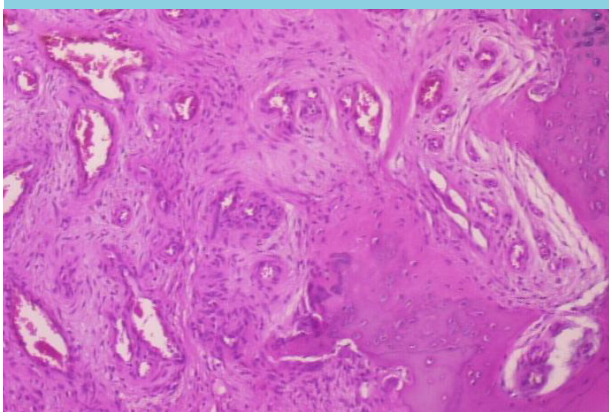
PATHOLOGICAL FRACTURE AND OSTEOLYSIS OF THE RIB WITH PLEURAL EFFUSION – IS THIS MALIGNANT?

DIAGNOSIS

Macroscopic examination revealed a polycystic tumour containing haemorrhagic tissue. Microscopically, the tumour was composed of dilated vessels (partial venous partial arterial) in the bone and adjacent soft tissues. The postoperative histological diagnosis was arteriovenous haemangiomas of the rib (*figure 3*).

The postoperative course was uneventful, and the patient was discharged on the 15th postoperative day. There has been no evidence of recurrence of rib tumour or pleural effusion after one year of follow-up.

Figure 3. *Histology of rib haemangioma. Microscopically, the tumour was composed of dilated vessels (partial venous partial arterial) in the bone and adjacent soft tissues*



DISCUSSION

Haemangioma of the rib is a rare benign vascular tumour so it is often misdiagnosed.[1,2] About half of costal tumours are malignant (metastatic or primary malignant tumours), and it is difficult to distinguish an osteolytic haemangioma of the rib from a malignant tumour[2,3] especially if it presents with a pathological fracture of the rib.

So far, in the literature only a few cases of rib haemangiomas have been described.[2-5] Rib haemangiomas are usually asymptomatic and tumours are generally incidental findings on radiological study[5] but occasionally they may present with pain and swelling.[2-4] Pleural effusions are rarely associated with rib haemangioma, and only one report of haemangioma of the rib with accumulation of pleural fluid has been published to date.[4] The tumour in our case showed several malignant features in terms of symptomatology and diagnostics with pain, swelling and radiological findings of extensive pleural effusion and pathological fractures of the ribs, despite its benign nature.

CONCLUSION

Haemangioma of the rib is an uncommon condition that should be considered a rare cause of pleural effusion and osteolytic lesions or pathological fracture of the rib.

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LETTER TO THE EDITOR

Levetiracetam (Keppra), urinary retention and literature search

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To the Editor

Levetiracetam (Keppra) is being used to treat epilepsy and has been available as a generic drug in the UK since 2011. Its adverse effects primarily include effects on the central nervous system (somnolence, headache, dizziness, coordination difficulties, etc.) and mild neuropsychiatric symptoms (apathy or agitation, anxiety, depression, etc.).[1,2] Urinary retention has not been previously reported.

A 40-year-old man with epilepsy and mental retardation was admitted following recurrent seizures. His drug history included levetiracetam (Keppra) 1000 mg twice daily and topiramate (Topamax) 100 mg twice daily over the last eight months. He was also taking tamsulosin 0.4 mg once daily started more recently for lower urinary tract symptoms ascribed to benign prostatic hypertrophy. On admission seizures were controlled with intravenous diazepam and valproate but he had urinary retention of 1200 ml which required catheterisation. His physical examination, blood tests and urinalysis were normal. When the catheter was removed, painful urinary retention of 1000 ml soon recurred and the patient had to be catheterised again for several days. However, the prostate appeared normal to palpation and ultrasound imaging (2.8 x 2.8 x 3.6 cm, ~15 g). Suspecting that the urinary retention was drug-induced we researched this adverse event in PubMed for each of his anticonvulsive drugs. Zero hits were found and the association was considered non-existent. To our surprise, our intern who attempted a plain language Google search ('Could Keppra cause urinary retention?') immediately found a site of personalised health information (eHealthMe) that reported 19,957 people who had adverse effects when taking Keppra. Among them, 74 (0.37%) had urinary retention, at various ages and times on the drug. We decided to stop Keppra (half-life 6-8 hours) and remove the urinary catheter one day later. The patient was overjoyed and grateful and reported freely flowing urine. Post-voiding ultrasound confirmed minimal residual urine (40 ml). A re-challenge was judged to be unethical. He was discharged on Topamax and phenytoin and remained asymptomatic at subsequent follow-up visits.

Our observation suggests that urinary retention is a rare, seldom-reported adverse event of levetiracetam (Keppra). The calculated Naranjo's causality rule[3] yields a score of 5-8, consistent with a probable adverse drug reaction. No less intriguing is the finding that an informed application of the 'Wisdom of Crowds' accessed through a Google search may be used to advantage in clinical decision-making, albeit with caution. Another reliable source of information is the European Database of Suspected Adverse Drug Reactions Reports (EMA). It currently includes 5004 reports associated with the use of Keppra in patients over the age of 18; none mention urinary retention. In fact, our experience reiterates the need for a more comprehensive reporting of adverse drug events to official drug surveillance systems such as a national pharmacovigilance centre or EMA.

DISCLOSURES

The author declares no conflict of interest. No funding or financial support was received.

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