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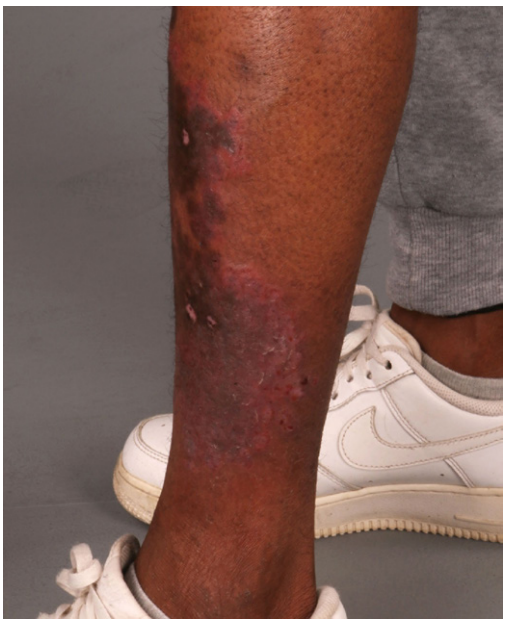

Itching dermatitis on the leg; what is your diagnosis?

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EDITORIAL

Taking care of the multimorbid patient, a primary task of the internist

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In the article by Verhoeff *et al.* published in this issue, a qualitative study is described. Patients with multiple chronic conditions were interviewed on their experiences with the secondary care facilities in a hospital in the Netherlands. It was concluded that a good overview of patient care is an essential element for an individualised approach to care. The patient with multiple chronic conditions does not seem to fit very well into the current care design.

Multimorbidity, or the co-occurrence of two or more chronic conditions in a person, has seen a rising prevalence, especially in high-income countries.[1] Many of the patients who visit a specialist in internal medicine meet with this definition. It is therefore important that our care system is equipped to deal with the specific needs of this growing group of patients. At the moment, the healthcare system is more prepared to handle a single disease than multimorbidity.

Multimorbidity is associated with a higher consumption of healthcare, and as a consequence higher costs.[2] More important, the multimorbid patient experiences a lower quality of life and reports more mental problems. Finally, there is an increase in mortality, especially with specific combinations of diseases. In a study in octogenarians, the combination of atrial fibrillation, chronic kidney disease and visual impairment was found to be the most predictive pattern for mortality.[3]

While we are not able to prevent chronic conditions from developing, we can and must try to organise the needed care in a manner that is as efficient and patient-friendly as possible. As Verhoeff *et al.* have found, apart from the logistics of care, communication is also a key factor. Not just communication between patient and physician, but also between professionals themselves. Patients report they struggle to keep an overview of their care. As the interviewed patients in the study by Verhoeff were relatively independent, it is to be expected that more vulnerable patients, with more interfering chronic conditions, will find it more difficult to take charge of their own care.

The Dutch Association of Internists (Nederlandse Internisten Vereniging, NIV) has issued its vision document, stating: 'the internist is the primary contact point for acute and consultative care on behalf of the patient with a non-surgical medical problem, multimorbidity or polypharmacy'. The article by Verhoeff is a first step in exploring what actions are needed to achieve that goal.

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ORIGINAL ARTICLE

Relevance of healthcare-associated pneumonia for empirical antibiotic therapy in the Netherlands

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ABSTRACT

Background: There is no consensus whether patients with healthcare-associated pneumonia (HCAP) should be considered as a patient with hospital-acquired pneumonia (HAP) and treated with broad-spectrum antibiotics, or as a patient with community-acquired pneumonia (CAP), and treated with narrow-spectrum antibiotics. HCAP research has focused mostly on the predictive value for non-susceptibility to broad-spectrum antibiotics and multi-drug resistant pathogens, in settings with moderate to high levels of antibiotic resistance. We investigated whether HCAP criteria predicts non-susceptibility to different empirical strategies, including narrow-spectrum antibiotics in the Dutch setting.

Methods: In a post hoc analysis of patients with moderate-severe CAP in seven Dutch hospitals, we compared *in vitro* antibiotic susceptibilities of definite and possible causative pathogens of CAP and HCAP to amoxicillin and broader antibiotic regimens. In a sensitivity analysis, pathogens with missing susceptibilities were assumed susceptible (best-case scenario) or non-susceptible (worst-case scenario).

Results: Among 2,283 patients with moderate-severe CAP, 23.1% (n = 527) were classified as HCAP. Non-susceptibility to amoxicillin ranged from 11.3% (95% CI 9.9-12.8%; best-case) to 14.4% (95% CI 12.8-16.1%; worst-case) in CAP patients and from 16.7% (95% CI 13.8-20.1%; best-case) to 19.7% (95% CI 16.6-23.3%; worst-case) in HCAP patients. The largest reduction in non-susceptibility was achieved by adding ciprofloxacin to amoxicillin treatment in both CAP patients (10% absolute risk reduction) and HCAP patients (11-16% reduction).

Conclusions: In the Netherlands, HCAP criteria predict higher amoxicillin non-susceptibility in patients hospitalized with moderate-severe CAP. Although broadening the antibiotic spectrum of empiric treatment reduced the likelihood of non-susceptibility, absolute reductions of non-susceptibility in HCAP patients were too low to justify the universal use of broad-spectrum empirical therapy.

KEYWORDS

Antibiotic resistance, community-acquired pneumonia, empirical antibiotic treatment, healthcare-associated pneumonia

INTRODUCTION

Traditionally, pneumonia is categorized as community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP), as the aetiology and empirical antibiotic treatment differs depending on where and how the infection was acquired. In 2005, healthcare-associated pneumonia (HCAP) was introduced as a novel category by the American Thoracic Society (ATS) and the Infectious Diseases Society of America HAP and VAP guidelines.[1] Patients with HCAP often present at the emergency department, but are distinguished from CAP patients by their recent contact with healthcare institutions. As a consequence, HCAP patients may have a different bacterial aetiology of infection and an increased risk for colonization and

infection with antibiotic-resistant or healthcare-associated pathogens, such as *Staphylococcus aureus*, Gram-negative Enterobacteriaceae, and *Pseudomonas aeruginosa*.[1] Therefore, the guidelines recommend empirically treating HCAP with broad-spectrum antibiotics, similar to HAP and VAP.[1] This has led to a large increase of broad-spectrum antibiotic use without apparent clinical benefit for these patients.[2-5] Recent evidence suggests that the predictive value of HCAP criteria for the need of broad-spectrum antibiotic treatment might be lower than anticipated.[2,6-11] In response to these findings, HCAP was removed from the 2016 ATS HAP/VAP guidelines and it was suggested to consider incorporating HCAP recommendations into CAP guidelines, as both CAP and HCAP patients are initially cared for in the emergency department.[8] Several studies have already evaluated the predictive value of HCAP criteria for bacterial aetiology in CAP patients.[6,7] However, the appropriateness of incorporating HCAP into CAP guidelines depends on the prevalence of pathogens requiring broader antibiotic treatment and the preferred empirical treatment for CAP patients, which differs per geographical region. In the Netherlands, the first choice of empirical treatment for moderate-severe CAP is narrow-spectrum beta-lactam monotherapy.[12] Current HCAP research focuses on predicting the presence of multidrug-resistant pathogens (including Methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum beta-lactamase-producing Enterobacteriaceae) and non-susceptibility to broad-spectrum beta-lactams (ceftriaxone or ampicillin-sulbactam), macrolides and fluoroquinolones.[13-17] In the Netherlands, infections caused by these resistant pathogens are rare and pneumonia acquired in nursing homes is usually considered as HAP. This is why the relevance and predictive value of HCAP criteria for the Northern European or Dutch setting, i.e. for the non-susceptibility to narrow-spectrum beta-lactams, remains unknown. Our main study objective was to evaluate the predictive value of HCAP criteria for narrow-spectrum beta-lactam (i.e. amoxicillin) non-susceptibility (thus needing broad-spectrum treatment) in patients hospitalized for moderate-severe CAP. In addition, we assessed the predictive value of HCAP criteria for non-susceptibility to broader antibiotic regimens, including amoxicillin-clavulanic acid, ceftriaxone, moxifloxacin, amoxicillin plus azithromycin and amoxicillin plus ciprofloxacin.

MATERIALS AND METHODS

Study subjects and design

We performed a post-hoc analysis of an observational cohort study, nested within the Community-Acquired Pneumonia — Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections (CAP-START trial) — which was a cluster randomised trial performed between February 2011 and August 2013 in seven hospitals in the Netherlands.[18] Patients above 18 years of age who were admitted to a non-ICU ward for suspicion of pneumonia were eligible for study participation. The study was approved by the ethics review board of the University Medical Center Utrecht (reference number 10/148). Written informed consent for data collection was obtained within 72 hours after hospital admission.

Data collection

Data on HCAP criteria, co-morbidities, clinical presentation, antibiotic use, complications and clinical outcome were retrieved prospectively from medical records by trained research nurses after patient inclusion. As pneumonia acquired in nursing homes are considered as HAP in the Netherlands, these patients were not included in the original trial. Therefore, the following HCAP definition was used: hospitalization within the last 90 days, residence in long-term care facilities other than nursing homes, receiving wound care or intravenous therapy in the previous 30 days or attending haemodialysis clinics.[1]

Microbiology

Sputum and blood cultures, urinary antigen tests and antibiotic susceptibility testing were performed as part of routine care. Susceptibility was determined by routinely performed microbiological tests. To account for the possibility of false-positives due to colonization, the causative pathogen per patient was determined, accounting for the specificity of the different microbiological tests, where positive urine antigen tests and blood cultures were assumed to have a higher specificity for causative pathogens than sputum cultures. For example, in a patient with a positive pneumococcal urinary antigen test and *S. aureus* cultured from sputum, *Streptococcus pneumoniae* was considered the causative pathogen due to the higher specificity of the urinary antigen test, and *S. aureus* was considered as colonization. Susceptibility testing was reported as sensitive, intermediate or resistant by participating microbiology laboratories. Intermediate and resistant results were considered as non-susceptible for all the analyses. In patients with multiple possible causative pathogens (i.e. multiple pathogens in sputum culture and no pathogens from blood culture or urinary antigen tests), susceptibility to antibiotics was determined by the most resistant pathogen. In cases of missing susceptibility data, susceptibility per antibiotic was imputed and assumed to be susceptible (S) if the prevalence of resistance to the antibiotic was ≤ 10% in national surveillance data; non-susceptible (R), if the prevalence was ≥ 90%; or

unknown (U), if the prevalence was between 10 and 90% (*supplementary table S1*). Pathogens were considered susceptible (S) to combination antibiotic therapy if susceptible to any of the two antibiotics; unknown (U) if susceptible to one antibiotic and unknown to the other antibiotic or if unknown to both antibiotics; and non-susceptible (R) if non-susceptible to both antibiotics.

Statistical analysis

Descriptive statistics were used to compare baseline characteristics between CAP and HCAP patients. Sensitivity analyses were performed for cases with unknown (U) antibiotic susceptibility which were either assumed to be all susceptible (best-case scenario) or all non-susceptible (worst-case scenario). Predictive values, sensitivity and specificity for non-susceptibility per empirical antibiotic strategy were calculated using 2 x 2 contingency tables. We calculated 95% confidence intervals using the Wilson score interval method.[19] Analyses were performed using the Statistical Package for the Social Sciences for Windows (Version SPSS 21.0.0.0). Graphs were created using GraphPad PRISM (Version 7.02).

RESULTS

A total of 2,283 patients with moderate-severe CAP were included in the CAP-START study of which, 527 (23.1%) were classified as HCAP. Among these HCAP patients, 318 (60%) were hospitalized within the last 90 days; 111 (21%) resided in an elderly home; 166 (32%) received intravenous therapy in the previous 30 days; 94 (18%) received wound care in the previous 30 days; and 17 (3%) were on chronic haemodialysis. In comparison to patients with CAP, patients with HCAP were older, had more co-morbidities, had higher disease severity scores (PSI on admission), had higher influenza vaccination rates, were more often dependent on daily living activities (ADL) and more often had treatment restrictions (*table 1*). Clinical outcomes of patients with HCAP were worse, with higher in-hospital, 30-day and 90-day mortality rates. There were no differences between patients with CAP and HCAP regarding the frequency with which microbiological testing was performed, except for a slightly higher rate of Legionella urinary antigen testing in patients with CAP (*table 1*).

Microbiology

A bacterial pathogen was identified in 566 (32%) CAP patients and 178 (34%) HCAP patients, most frequently based on sputum culture (n = 368, 50%), urinary antigen testing (n = 224, 30%), blood culture (n = 98, 13%), bronchoalveolar lavage (n = 22, 3%) or serology (n = 13, 2%). The most frequent causative pathogen was *S. pneumoniae*

Table 1. *Descriptive statistics of CAP and HCAP patients*

	CAP (n = 1,756)	HCAP (n = 527)
Male (n, %)	994 (56.6)	139 (61.1)
Age in years (median, IQR)	70 (58-79)	72 (62-81)
PSI-score (mean, SD)	132 (20.5)	137 (27.1)
Received antibiotics before admission (%)	32.2	34.9
Received pneumococcal vaccination (%)	1.9	2.5
Received influenza vaccination (%)	63.2	72.3
ADL dependent (%)	22.8	27.5
Any treatment restriction (%)	23.8	46.1
Co-morbidities		
Immunocompromised* (%)	18.4	39.8
Cardiovascular disease (%)	20.0	24.3
COPD or asthma (%)	38.7	45.4
Cerebrovascular disease (%)	9.2	14.2
Diabetes mellitus (%)	16.0	18.8
Malignancy (%)	10.6	22.6
Chronic renal failure (%)	0.5	4.2
Microbiologic testing performed		
Sputum culture (%)	46.1	44.4
Blood culture (%)	76.1	76.1
Pneumococcal urinary antigen test (%)	79.2	77.0
Legionella urinary antigen test (%)	77.1	72.3
Clinical outcome		
ICU admission during hospital stay (%)	1.9	2.1
All-cause mortality		
In-hospital (%)	2.8	4.7
Day 30 (%)	4.3	8.3
Day 90 (%)	7.1	17.8
Length of hospital stay in days (median, IQR)	6 (4-9)	6 (4-10)

ADL = activities of daily living; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; PSI = pneumonia severity index; SD = standard deviation
*Immunocompromised is defined by a history of HIV, AIDS, leukaemia, lymphoma, Hodgkin lymphoma, multiple myeloma, generalised malignancy, chronic renal failure, nephrotic syndrome, immunosuppressive therapy or transplantation

in both CAP and HCAP patients (14.0% and 11.2%, respectively, *table 2*). In comparison to CAP, HCAP was less frequently caused by *S. pneumoniae* and *H. influenzae* and more frequently caused by *S. aureus, P. aeruginosa* and *E. coli*, and multiple pathogens were more frequently identified. Of all the 4,464 bacterial pathogen / antibiotic strategy combinations, 20% (n = 909) were confirmed by susceptibility testing; 65% (n = 2,921) were assumed to be sensitive or resistant, based on intrinsic resistance or national surveillance; and 15% (n = 634) were unknown.

Predictive value for amoxicillin non-susceptibility

The prevalence of non-susceptibility to amoxicillin for the best-case and worst-case scenarios were 11.3% (95% confidence interval (CI) 9.9%-12.8%) and 14.4% (95% CI 12.9%-16.1%) in CAP patients, respectively, and 16.7% (95% CI 13.6%-20.1%) and 19.7% (95% CI 16.6%-23.3%) in HCAP patients, respectively (*figures 1A and B*). The corresponding negative predictive values, which are the prevalence of amoxicillin susceptibility in CAP patients without HCAP criteria, were 88.7% (95% CI 87.2%-90.1%) and 85.6% (95% CI 83.9%-87.2%) (1 minus non-susceptibility rate in CAP patients) for the best- and worst-case scenarios respectively, with respective sensitivities of 30.8% (95% CI 25.7%-36.3%) and 29.2% (95% CI 24.7%-34.1%) and specificities of 78.0% (95% CI 76.1%-79.8%) and 78.0% (95% CI 76.1%-79.8%)(*table 3*).

Predictive value for broad-spectrum non-susceptibility

When comparing antibiotic non-susceptibility rates, we used the non-susceptibility rate for amoxicillin as a reference, which was 11.3/14.4% (best-case and worst-case) in CAP patients and 16.7/19.7% (best-case and worst-case) in HCAP patients. In comparison to this reference, other antibiotic combinations reduced the proportion of patients with non-susceptibility by 5-10% (CAP) and 7-16% (HCAP). The largest reduction in non-susceptibility compared to amoxicillin was achieved by adding ciprofloxacin to amoxicillin in both CAP and HCAP patients. In CAP patients, the 11.3/14.4% (best-case and worst-case) non-susceptibility to amoxicillin was reduced by 10% to a non-susceptibility of 0.8% (95% CI 0.4%-1.3%; best-case) and 4.1% (95% CI 3.3%-5.1%; worst-case). In HCAP patients, the 16.7/19.7% (best-case and worst-case) was reduced by 11-16% to a non-susceptibility of 1.3% (95% CI 0.6%-2.7%; best-case) and 8.3% (95% CI 6.3%-11.0%; worst-case) with amoxicillin plus ciprofloxacin (*figures 1C and D*).

Table 2. *Pathogens in CAP and HCAP patients; data are given as n (%)*

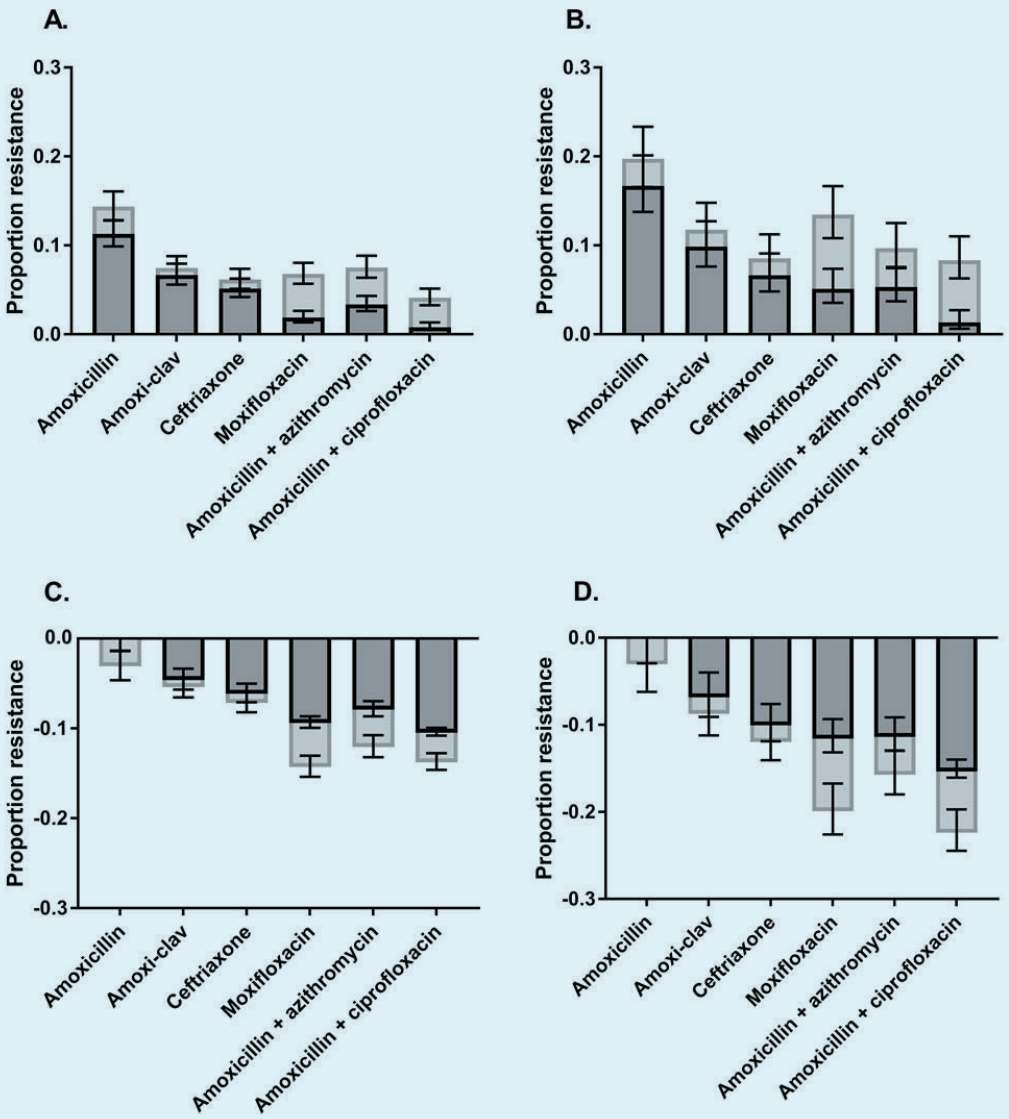
	CAP n = 1,756	HCAP n = 527
Streptococcus pneumoniae	246 (14.0)	59 (11.2)
Haemophilus influenzae	92 (5.2)	17 (3.2)
Multiple pathogens*	52 (3.0)	27 (5.1)
Staphylococcus aureus	30 (1.7)	15 (2.8)
Pseudomonas aeruginosa	27 (1.5)	15 (2.8)
Escherichia coli	23 (1.3)	18 (3.4)
Mycoplasma pneumoniae	23 (1.3)	1 (0.2)
Legionella pneumophila	17 (1.0)	1 (0.2)
Moraxella catarrhalis	12 (0.7)	4 (0.8)
Klebsiella pneumoniae	7 (0.4)	2 (0.4)
Other Gram-negative bacteria	31 (1.8)	13 (2.5)
Other Gram-positive bacteria	6 (0.3)	6 (1.1)
Total	566 (32.2)	178 (33.8)

* Most frequent multiple pathogen combinations were *S. pneumoniae* with *H. influenzae* (20%) and *H. influenzae* with *S. aureus* (15%) in CAP patients; and *H. influenzae* with *M. catarrhalis* (16%) and *H. influenzae* with *E. coli* (12%) in HCAP patients

DISCUSSION

Our study focused on patients with a clinical diagnosis of CAP admitted to non-ICU wards. We determined that non-susceptibility of CAP pathogens to amoxicillin was 5-6% higher in patients who met the HCAP criteria compared to patients without HCAP criteria. The most commonly identified pathogens were *S. pneumoniae* and *H. influenzae* in CAP patients and *S. pneumoniae*, multiple pathogens, *S. aureus, P. aeruginosa* and *E. coli* in HCAP patients. Our findings are comparable to previous reports.[14-16,20] Naturally, this difference in non-susceptibility could be reduced by broadening the empiric antibiotic spectrum for HCAP patients. To our knowledge, this is the first study to assess the predictive value of HCAP criteria for non-susceptibility to narrow-spectrum beta-lactams. As such, the presented data may be useful in the discussion of whether HCAP should be implemented into CAP guidelines in settings where narrow-spectrum beta–lactam monotherapy is the first choice of treatment. Despite the differences in aetiology between CAP and HCAP patients, several observational studies from the United States have failed to demonstrate benefit of broad-spectrum empirical antibiotics on the clinical outcome of HCAP patients, with some even resulting in worse clinical outcomes.[3-5] However, these observational studies most likely suffered from confounding by indication, where underlying conditions such as frailty, severity of disease and treatment restrictions may have influenced the association between treatment and outcome of HCAP patients. In addition, being able to predict non-susceptibility to empirical antibiotics does not

Figure 1. *Non-susceptibility for antibiotics in CAP (A) and HCAP patients (B) and the difference in non-susceptibility compared to amoxicillin (CAP: C and HCAP: D). Dark grey indicates the best-case scenario, white grey indicates the worst-case scenario. Confidence intervals are given for both scenarios*



necessarily mean that such patients would benefit from broader empirical therapy. It may also be safe to start with narrow-spectrum antibiotics and escalate treatment based on culture or urine antigen testing results. Therefore, proper randomised trials are required to assess treatment effects on clinical outcome in HCAP patients in a valid way. As the criteria for HCAP have often been questioned, multiple studies have evaluated other risk factors or scores to predict antibiotic resistance in CAP patients. The risk factors evaluated to date include family members with resistant bacteria, severe pneumonia, prior antibiotic use, functional status, ICU admission, immunosuppression, co-morbidities (cerebrovascular disease, diabetes, COPD), gastric acid suppression medication, tube feeding, prior infection with a drug-resistant pathogen and MRSA colonization.[13,14,16,17,20,21,22] However, many of these risk factors were evaluated in settings with a high prevalence of antibiotic resistance. Whether their predictive value can be generalised to settings with a low prevalence of antibiotic resistance remains to be elucidated. Moreover, many of the aforementioned risk factors, such as previous colonization with MRSA, are not appropriate for settings with low prevalence of antibiotic resistance. In an additional analysis, we explored the predictive value of severe pneumonia (CURB-65 score > 2), prior antibiotic use, functional status (ADL dependence), immunosuppression and co-morbidities (cardiovascular disease, diabetes mellitus, COPD) in a multivariable model. From these variables, only HCAP, immunosuppression, cerebrovascular disease and diabetes

Table 3. *Diagnostic values of HCAP to predict for antibiotic resistance*

	Scenario	Resistance rate		Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
		CAP (n = 1,756) (n (%, 95% CI))	HCAP (n = 527) (n (%, 95% CI))		
Amoxicillin	Best-case	198 (11.3 (9.8-12.8))	88 (16.7 (13.8-20.1))	30.8 (25.7-36.3)	78.0 (76.1-79.8)
	Worst-case	252 (14.4 (12.8-6.1))	104 (19.7 (16.6-23.3))	29.2 (24.7-34.1)	78.0 (76.1-79.8)
Amoxicillin-clavulanic acid	Best-case	117 (6.7 (5.6-7.9))	52 (9.9 (7.6-12.7))	30.8 (24.3-38.1)	77.5 (75.7-79.3)
	Worst-case	131 (7.5 (6.3-8.8))	62 (11.8 (9.3-14.8))	32.1 (25.9-39.0)	77.8 (75.9-79.5)
Ceftriaxone	Best-case	90 (5.1 (4.2-6.3))	35 (6.6 (4.8-9.1))	28.0 (20.9-36.4)	77.2 (75.4-78.9)
	Worst-case	108 (6.2 (5.2-7.4))	45 (8.5 (6.4-11.2))	29.4 (22.8-37.1)	77.4 (75.5-79.1)
Moxifloxacin	Best-case	33 (1.9 (1.3-2.6))	27 (5.1 (3.5-7.4))	45.0 (33.1-57.5)	77.5 (75.7-79.2)
	Worst-case	119 (6.8 (5.7-8.0))	71 (13.5 (10.8-16.7))	37.4 (30.8-44.4)	78.2 (76.4-79.9)
Amoxicillin + azithromycin	Best-case	59 (3.4 (2.6-4.3))	28 (5.3 (3.7-7.6))	32.2 (23.3-42.6)	77.3 (75.5-79.0)
	Worst-case	132 (7.5 (6.4-8.8))	51 (9.7 (7.4-12.5))	27.9 (21.9-34.8)	77.3 (75.5-79.1)
Amoxicillin + ciprofloxacin	Best-case	14 (0.8 (0.5-1.3))	7 (1.3 (0.6-2.7))	33.3 (17.2-54.6)	77.0 (75.2-78.7)
	Worst-case	72 (4.1 (3.3-5.1))	44 (8.3 (6.3-11.0))	37.9 (29.6-47.0)	77.7 (75.9-79.4)

mellitus were predictive for amoxicillin non-susceptibility (*supplementary table S2*). However, the discriminative capacity of the multivariable model remained limited. The predictive value of these variables, in combination with other promising predictors (such as previous colonisation with resistant bacteria) should be evaluated in a prospective cohort study.

This study has several strengths. We used high quality data from a prospective multicentre trial, including consecutive patients with moderate-severe community-acquired pneumonia, irrespective of whether a bacterial pathogen was isolated. In contrast to including patients with positive cultures only, the predictive values presented here are directly relevant for clinical practice.[13,17,20] In addition, we used extensive antibiotic susceptibility data and assessed non-susceptibility over a range of different empirical antibiotic treatment regimens. There were also several limitations. First, patients residing in nursing homes were excluded because their disease was not considered to be CAP. Therefore, one could argue that we did not include the entire spectrum/domain of HCAP and the presented results might not be generalisable to the international HCAP definition. However, these patients would generally be considered as hospital- or nursing-home acquired pneumonia and treated as such. Second, diagnostic testing was performed as part of routine care, which is why blood cultures, sputum cultures and urinary antigen testing were not uniformly performed. Yet, although we cannot exclude the possibility of bias in outcome assessment, there were no major differences between rates of microbiological testing in CAP and HCAP patients. Third, although there were missing susceptibility data for individual antibiotics in certain pathogens, imputed susceptibility data were based on local surveillance data and therefore, generalisable to settings with low antibiotic resistance. In addition, we performed sensitivity analyses on susceptibility patterns that remained unknown with a best-case and worst-case scenario where the unknown susceptibilities were either all susceptible or non-susceptible. These sensitivity analyses yielded only small variations in non-susceptibility for the different antibiotic regimens. Fourth, the probable

causative pathogen was, in many cases, based on sputum cultures, which might represent colonisation rather than infection. We therefore only considered plausible pneumonia pathogens in our analyses. Lastly, we assumed cases of pneumonia without a causative pathogen to be susceptible to all antibiotics, which might not be true in case of false-negative culture results for resistant pathogens in a subset of patients.

To conclude, HCAP criteria predict for higher non-susceptibility rates to amoxicillin in patients hospitalized with CAP and admitted to non-ICU wards in the Netherlands. However, we consider the absolute risk difference of non-susceptibility to amoxicillin between CAP and HCAP patients as being too low to justify treating all HCAP patients with broad-spectrum antibiotics. Future research should focus on identifying and validating risk factors to predict for narrow-spectrum beta-lactam antibiotic non-susceptibility that are appropriate for settings with low antibiotic resistance. Furthermore, prediction rules need to be evaluated in randomised clinical trials to show benefit on clinical outcome.

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Supplementary table S1. *Assumed antibiotic susceptibility patterns of pathogens in cases of missing resistance data*

	AMO	ACL	CTR	AZI	MOX	CIP
Streptococcus pneumoniae	S	S	S	U	S	R
Haemophilus influenzae	U	S	S	U	S	S
Escherichia coli	U	U	S	R	U	U
Staphylococcus aureus	R	S	S	U	U	U
Pseudomonas aeruginosa	R	R	R	R	R	U
Mycoplasma pneumoniae	R	R	R	S	S	S
Legionella pneumophila	R	R	R	S	S	S
Moraxella catarrhalis	R	S	S	S	S	S
Klebsiella pneumoniae	R	U	U	R	U	U
Stenotrophomonas species	R	R	R	R	S	R
beta-haemolytic streptococcus	S	S	S	S	S	U
Serratia marcescens	R	R	R	R	U	U
Enterobacter species	R	R	R	R	U	U
Klebsiella oxytoca	R	U	U	R	U	U
Enterobacter cloacae	R	R	U	R	U	U
Morganella morganii	R	R	U	R	U	U
Pneumocystis jirovecii	R	R	R	R	R	R
Acinetobacter species	R	R	U	R	U	U
Citrobacter freundii	R	R	S	U	U	U
Citrobacter species	R	R	S	U	U	U
Coxiella burnetti	R	R	R	U	U	U
Enterobacter aerogenes	R	R	U	R	S	S
Klebsiella ozaenea	R	S	S	R	S	S
Proteus mirabilis	U	S	S	U	S	S
Serratia liquefaciens	R	R	U	R	S	S

AMO = amoxicillin; ACL = amoxicillin-clavulanic acid; CTR = ceftriaxone; AZI = azithromycin; MOX = moxifloxacin; CIP = ciprofloxacin
(S) susceptible; prevalence of resistance to the antibiotic ≤ 10%
(R) non-susceptible; prevalence of resistance to the antibiotic ≥ 90%
(U) unknown; prevalence of resistance to the antibiotic > 10% and < 90%

Supplementary table S2. *Multivariable and univariate prediction model results for amoxicillin non-susceptibility*

		Bootstrapped OR (95% CI)	AUC* of ROC curve (95% CI)
Best-case scenario	HCAP (univariate)	1.6 (1.2-2.1)	0.54 (0.5-0.58)
	HCAP	1.5 (1.1-2.0)	0.58 (0.54-0.61)
	History of cerebrovascular disease	1.8 (1.2-2.6)	
	Diabetes mellitus	0.7 (0.4-0.9)	
Worst-case scenario	HCAP (univariate)	1.5 (1.1-1.9)	0.54 (0.5-0.57)
	HCAP	1.4 (1.1-1.8)	0.56 (0.53-0.6)
	History of cerebrovascular disease	1.5 (1.0-2.1)	
	Diabetes mellitus	1.5 (1.1-2.2)	
	Immunosuppression	0.7 (0.5-1.0)	

*Area under the curve (AUC) of the receiver operating characteristic (ROC) curve

ORIGINAL ARTICLE

Secondary care experiences of patients with multiple chronic conditions

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ABSTRACT

Background: This study aimed to investigate patients' experiences, beliefs and understandings of the current secondary care of patients with multiple chronic conditions (MCC) in the Netherlands.

Methods: A qualitative, interpretative description design was used. We conducted semi-structured, in-depth interviews with patients with MCC, who visited at least two physicians in Gelre Hospitals for at least two appointments in the previous year. After eight interviews data saturation was achieved.

Results: Being a patient with MCC in the hospital can be complex and keeping an overview required effort, according to the participants. Most participants would appreciate more coordination and communication. However, the exact needs seemed to differ. The multiple visits transformed them into experienced patients: based on their experiences and observations they developed strategies to sustain themselves in the hospital. Different types of communication (an important, overarching theme) evoked specific feelings and expectations that were important for the patients' care experiences as well.

Conclusion: An overview of patient care seems an essential element for a more coordinated, individualised approach to care. Future research might focus on ways to engage both healthcare professionals and patients in the improvement of care. It could aim to find ways to create an overview and coordination, and define responsibilities, but also to clarify which groups of patients need assistance. It might also investigate the effect of good and clear communication on reducing obstacles that patients perceive when dealing with healthcare situations. Overall, also in the future, patients' care experiences could play an important role in determining the direction of new interventions.

KEYWORDS

Multiple chronic conditions, multimorbidity, patient experience

INTRODUCTION

As the prevalence of multiple chronic conditions (MCC) increases, the coordination of care for patients with MCC becomes more important. In general, 'multiple chronic conditions' is defined as the presence of two or more chronic medical conditions in an individual.[1] In 2010, the prevalence of patients with MCC in European countries ranged between 32 and 58%.[2] The United Nations predicts that the number of people aged 60 years and older will increase by 56% between 2015 and 2030.[3] Because the occurrence of MCC is strongly related to rising age,[4-6] it is expected that the prevalence of MCC will also increase in the future. Irrevocably, the number of patients with MCC consuming healthcare will supposedly increase over the upcoming years. According to several studies, patients with MCC utilise more healthcare than patients with a single condition; they have more contacts with healthcare providers and have a higher risk of functional impairment or hospitalisation.[7-10] As a consequence, current research is increasingly focusing on reforming chronic care delivery for patients with MCC.[5,11,12]

Research on the optimal management of patients with MCC first started in the primary care setting. Further development of communication and coordination, in order to improve a patient's involvement and self-management, offered a promising perspective. According to Kenning et al., 'hassles' (obstacles that patients perceive when dealing with healthcare situations) might have an influence on a patient's self-management of MCC and self-reported medication adherence.[11] Interestingly, there

was a trend towards improved prescribing and medication adherence in the review about current organisational interventions by Smith et al. They suggest that focusing on specific problems experienced by patients with MCC might be an important element of improving outcome.[5] Moreover, a recent review by Hasardzhiev et al. identified knowledge and involvement in decision-making, proper communication and coordinated care as important factors influencing patients' experiences of care and consequently patient outcome.[12] Overall, in primary care it seemed that improving a patient's care experience and organisation might eventually improve their outcome.

Current secondary care primarily focuses on diseases and today's hospitals are mostly organised around single disciplines.[2] However, the care of patients with MCC usually transcends disciplines. Interdisciplinary consultation is common in hospital, but interdisciplinary treatment plans are usually only used for single diseases. To face the increasing number of patients with MCC and their healthcare needs, improving the coordination of care might be necessary in secondary care. The UK National Institute for Health and Care Excellence (NICE) guideline for MCC (2016) recommends considering a patient-centred approach, for example when patients experience problems in managing their treatments, when multiple care providers are involved or when patients take multiple medicines. However, the evidence available for this individual plan is limited, because patients with comorbidity are frequently excluded from trials and outcomes of interest for those groups are not taken into account.[13] This raises the question which specific factors influence the quality of (secondary) care for patients with MCC and what is the best way to investigate them.

Inquiring about patients' care experiences can be used to obtain insights into their perspectives on current secondary care.[14] The NICE guideline summarises the research on the barriers experienced by patients and healthcare professionals in obtaining optimal care for patients with MCC. They describe themes such as understanding MCC, accessibility and format of services, communication and patient-specific factors.[13] In order to compare and define whether a change in the conventional Dutch secondary care is necessary, we decided to first conduct a qualitative study. The aim was to explore outpatients' experiences, beliefs and understandings of the current secondary care, because it is indicated that this is important to form new hypotheses.[15] What is, in the patient's opinion, currently affecting their experience of care? Do they experience the secondary care to be disease-specific and monodisciplinary oriented? After exploring the patient's experiences, the themes found might be used to offer a new angle for the design or implication of interventions for patients with MCC in the outpatient hospital care.

METHODS

Design

A qualitative, interpretative description design was used[15,16] with semi-structured interviews, qualitative content analysis and collection of baseline participant characteristics.

Study population

The study population was recruited from the internal medicine and geriatric outpatient departments of the Gelre Hospitals in Apeldoorn using posters, flyers and direct recruitment by internal medicine physicians and geriatricians during a consultation. The physicians were instructed to recruit patients who met the inclusion criteria. Inclusion criteria were: aged 18 years or older, with the ability to communicate in Dutch and/or English and with two or more chronic conditions of which at least two necessitated regular outpatient visits (≥ 2 times a year). Moreover, they had to be treated by at least two specialists in outpatient departments of Gelre Hospitals.

Patients with severe cognitive impairment defined by inability to recall diseases and hospital visits were excluded. Patients who were hospitalised less than four weeks prior to the interview were excluded as well. After recruitment by the physicians or posters/flyers, the executive researcher (MV) performed the final assessment using the inclusion and exclusion criteria and either included or excluded the patients. The research protocol was approved by the regional and local research ethics committee.

Participant characteristics

Five participants were female. The age ranged from 67-92 years, with a median age of 71.5 years. Seven participants were or had been married. Five participants were living alone (including one married couple who were living separately). Moreover, all participants were Dutch and educated at primary school level, four participants received further education (*table 1*).

Data collection procedure

Interviews

Interviews were carried out in May and June 2017 by the executive researcher. The interviews were conducted at the participant's home address or at the geriatric outpatient clinic, depending on the participant's preference. Participants were requested to fill out a written consent form beforehand. The duration of each interview was approximately 1.5 hours. The interviewer used a predesigned interview guide (*Appendix 1*). All interviews were audio recorded and transcribed verbatim.

Table 1. *Participant characteristics*

Recruited	**(n= 8)**
Recruited by hospital-based physicians	
Single participant	4
With partner	2
With son/daughter	1
Responded to poster/flyer	1
Gender	
Male	3
Female	5
Age	
Median (range)	71 (67-92)
Marital status	
Single/never married	1
Married	4
Widowed	2
Divorced	1
Living situation	
Living alone	5
Living with partner	3
Highest education achieved	
Primary school	4
Secondary vocational education	1
Pre-university education/general secondary education	0
Intermediate vocational education	1
University bachelor education	2
Multiple chronic conditions	
Disease count (as done by Barnett et al. 2012, 0-40 points)	3-8 (7)
Charlson's Comorbidity Index (0-30 points)	3-9 (5.5)
Cumulative illness rating score (0-56 points)	25-38(29.5)
Functional characteristics	
KATZ-ADL 6 (0-6 points)	0-2 (1)
Clinical Frailty Scale (1-9 points)	3-6 (5)
Number of visits and medicines	
Hospital outpatient visits in last 365 days	7-33 (18)
Number of medicines in electronic file, range (median)	4-17 (14.5)

Medical records

Baseline participant characteristics were collected through interview and from the Electronic Medical Record (gender, age, illnesses, education and work, medication, number of visits in the last year, number of hospitalisations and re-hospitalisations in the last year, current living situation, use of home care or informal care, functional status with Katz-ADL-6 scores and clinical frailty scale (CFS)). For the description of MCC three different measures were used: disease count (according to Barnett et al, 2012[17]),the Charlson Comorbidity Index (CCI) and the Cumulative Illness Rating Scale (CIRS). We decided to use three measures to enhance comparability and chose these three because they are among the most commonly used in primary care and community settings.[18] Descriptive statistics were used to give an overview of the population.

Data analysis and data saturation

Interviews were held until data saturation was achieved, which meant that no new insights emerged from the data. A coding structure was developed iteratively. During the coding process Atlas.ti, version 7, was used as a supportive computer program. The executive researcher coded the first transcripts using sensitising concepts and an open coding approach. Using close reading and constant comparisons, new themes and categories were identified. Following open coding, the different categories and themes were connected during the axial coding process. After the axial coding process, one senior researcher assessed the codes and corresponding quotes. Consequently, the executive researcher and senior researchers reached consensus through discussion. The final coding structure was then developed, and core categories and themes were integrated using selective coding. The executive researcher then coded all interviews using the final coding structure.

RESULTS

Interviews

Eight interviews were conducted (*table 1*). Three internal medicine physicians and two geriatricians recruited seven participants from their outpatient clinic. One participant responded to the flyer/poster.

Three patients (two recruited by one internal medicine physician, one recruited by poster/flyer) were excluded: One of these patients was hospitalised less than 4 weeks prior to the interview, one was not treated by multiple hospital-based physicians in Gelre Apeldoorn and one interview was cancelled because of a participant's acute illness.

MCC and functional characteristics

Most of the participants were suffering from 7 or 8 conditions. The CCI scores ranged from 3-9; most participants scored 5 or 6 points. The CIRS ranged from 25-38 points, with a median of 29.5 points. The participants were relatively independent in daily life, with KATZ-ADL 6 scores varying from 0 to 2 points and CFS fluctuating between 'managing well' (3 points) and 'moderately frail' (6 points) (*table 1*).

Identification of themes

The eight identified themes were divided into two groups (*table 2*).

Being a patient with MCC in the hospital

The participants described how they had to manage multiple hospital visits and interact with several hospital-based physicians. They sometimes depended on others for support. Eventually, they become experienced patients who know how to plan, what to expect and how to get things done, the participants stated.

a) Living with MCC

Not ill, but more functionally impaired and less independent

Participants reported that they do not realise on a daily basis that they have MCC but try to accept it. Some said that being ill does not or did not keep them from doing what they desire in their lives, such as *'strolling through the woods'* or *'accomplishing a successful career'*. They did, however, notice the gradual decline of functional status and mobility that is entangled with ageing and having MCC. The loss of independence hangs over their heads every time they experience symptoms, develop a new condition or when their conditions interact.

'Well, things changed slowly. Previously, when I had to visit the hospital, I would drive there myself. Now I am not able to do that anymore. Other than that, nothing has changed.' (P2)

Ambivalent coping with MCC

Living with MCC required coping and participants described how they experience feelings of acceptance and self-distancing, but also of insecurity, frustration and guilt. On the one hand, some described that they *'do not (want to) dwell on being ill'* and *'(try to) just put up with it'*. On the other hand, others reported feeling insecure and sometimes frustrated when the diagnosis or the future was uncertain. Some participants portrayed how they experience adapting to a new situation every time: sometimes they are *'hoping it will get better'* and *'trusting'* that they can *'manage on their own'*. At other times, they must *'give in'* and, sometimes reluctantly, acknowledge they need help or care equipment such as a wheeled walker.

The complexity of handling medication

The number of medicines per participant ranged between 13 and 17, with one outlier with only four medicines. Six participants managed their own medications, three of these participants used a compliance device (baxterrol). Two participants (one also had a compliance device) said *'I rely on my partner'*. Three participants reported that they know for every medicine why they take them, others *'roughly know'* or *'had no idea'*.

'Well, the brown one is for <condition> and there are medicines I have been taking for years, that one is for, well, I do not know right now. I trust it is...' (P5)

Two of them trusted that the doctors could see all the medication in the computer; others always brought the medication compliance device or a printout of their medication to the hospital. It might be essential, but difficult, to remember who prescribed the medication when you want a renewal: *'With some you know and with some you do not know' (P4)*. One participant would *'start thinking: is it for my heart? Or is it for something else? And that is the way you find out'*.

Moreover, the participants noted that side effects of medication sometimes interfered with daily life. Two participants mentioned that after they take their morning medication they *'do not feel well'* and have to *'take it easy for a few hours'* or *'take a nap'*. One participant reported how a side effect caused an acute hospitalisation. The participants also described different coping strategies: one participant described that he *'will just stop with that*

Table 2. *Identified themes*

Being a patient with MCC in hospital	Communication, feelings and expectations in hospital
a. Living with MCC	e. Content of appointments
b. Managing multiple appointments	f. Doctor-patient communication
c. Doctor-doctor communication	g. Errors, complications and oddities
d. Being an experienced patient	h. Communication from and to the hospital

medicine', sometimes without discussing this with the doctor, where another described always contacting the doctor for advice when experiencing side effects.

b) Managing multiple appointments

Multiple appointments are indispensable

In general, visiting the hospital was considered a necessary evil when living with MCC. The participants described that they gradually become experienced in planning and logistics and that multiple appointments *'are a part of it'* and *'have to happen'*. Two participants remarked that it takes a lot of time, because each doctor only focuses on his own specialty. On the other hand, some participants mentioned the comfort *'when the <doctors> keep an eye on you'*; they did not think it is a burden. Hospital visits usually offered reassurance and contentment when everything was stable and clear, but when elements remained unclear or uncertain they could cause several negative emotions, according to the participants. Overall, they considered multiple appointments to be indispensable.

Combining appointments: desired by most, but only occasionally possible

Logistically, it required planning and initiative for most of the participants to manage and coordinate the multiple appointments. One participant never asked for a combination, so *'it never happened'*. Two participants described how they inquired about the possibilities, but with little success: *'the other doctor had no available appointments'* (P4) or '*We cannot plan this appointment half a year in advance, you will receive a letter at home. I have tried calling, but by then he is completely booked, and nothing can be moved.'* (P5's family member) However, two other participants had inquired for a combination with more success and three participants noted that they sometimes find a *'smart'* assistant who notices the other appointment and offers to combine them.

Seven out of eight participants reported that they would prefer combining appointments. They said: *'it would be pleasant to handle everything on one day'*. One participant mentioned: *'It is of little importance for me. I am retired and I live close to the hospital.' (P7)*

More dependency or symptoms required more planning

Physically going to several appointments required organisation and time, effort and was costly (especially parking costs), according to the participants. They might have to make an appeal to their friends or family repeatedly or take time-consuming public transportation to get to the hospital. Moreover, sometimes it was necessary to bring a companion such as one of their children, their partner or a, sometimes paid, family friend. Some depended on their companions for transportation; others took companions for support or an extra ear to '*listen in*' in the consultation room, especially when '*there are new things'*.

For some participants, this dependency on others resulted in feelings of guilt for taking up their time: *'I find it much worse for <caregiver who drives to the hospital>.' (P5)* They described how they try to adapt the appointments to their companions' schedules. This was one of the main reasons why two participants who did not mind going to the hospital regularly, still preferred the combination of appointments.

c) Doctor-doctor communication

Participants usually assumed that doctors will consult each other if necessary and that they can read about new developments in their electronic file. All participants thought that interdisciplinary consultation would be beneficial. They reckoned it would help doctors to '*be informed about their patients*' and '*take each other into consideration*'. Two participants thought it would benefit the speed of the (diagnostic) process.

However, the participants said that they do not see or hear doctors communicating about them. Ideas about doctor-doctor communication varied from *'No, I do not think there is any communication'* to *'I suppose there is communication, because somehow they know what to take into account'*. Three participants described situations where they found themselves in-between two doctors who said different things about the proposed treatment, either within the hospital or when consulting doctors in two different hospitals.

The participants reckoned that all information about them and their conditions could be found in their electronic file on the computer, if necessary: '*they can see all information [in the computer], if they want to'*. The participants described that some doctors take the initiative to check if anything new has happened. One of the participants mentioned that the doctor often *'first starts the computer'* and *'gazes towards the screen'*. Some participants described that they take the initiative in pointing out to the doctor that they have *'visited their colleague'*, *'something has changed'* or *'another doctor has blood results'*.

d) Being an experienced patient

Experience provides strategies to survive in the hospital

Participants illustrated the knowledge they had acquired after regularly visiting the hospital. They described how they know for each outpatient clinic and doctor how much time to calculate for waiting and for the appointment. The experiences within one hospital, but also in different or former hospitals, offer grounds for comparison: '*Over there, you could read everything in your own medical file.' (P7)* Although they *'know their way around the hospital'*, the participants still experienced barriers in getting what they want or need. Participants described how they use strategies such as *'send a child/partner'*, *'get emotional'* or *'repetitively request something'*. It was an unintended

result of encountering a barrier or used on purpose. Participants said they *'regret'* that they have to use these strategies, but described that *'this is how it goes'* sometimes. *'Yes, that too is experience. It is not a good thing, it is a pity it is the way it is, you against the struggles of a hospital. But anyway, experience delivers at a certain point. (...) You are not impressed by a white coat anymore.'* (P4's family member) Most of the participants also mentioned they see that many healthcare professionals suffer from a high work-pressure. They described that is why they are usually *'understanding'* when there are waiting times, few available appointments or scarce communication between doctors.

Communication, feelings and expectations in the hospital

Although the following themes are presumably not unique for a patient with MCC, they seemed important enough for the care experience to mention. The participants mentioned that some things that are connected to the treatment by healthcare professionals in the hospital are out of their control. These were recurrent or incidental events they simply *'have to accept'* or *'undergo'*, such as waiting times, the occurrence of complications and hospitalisations. The participants described the importance or lack of communication and the evoked feelings and expectations for these events.

e) Content of appointments

Every appointment comes with its own feelings and expectations

During analysis of the interview sections about the multiple appointments in the hospital, it struck the researchers that different types of appointments gave rise to different feelings and expectations according to the participants. Not all participants specifically mentioned different feelings and expectations, but what they did mention is summarised in *table 3*.

f) Doctor-patient communication

All participants described several experiences with the communication by healthcare professionals. There was always an event or specific type of behaviour that evoked feelings with certain consequences, according to the participants. 'Proper' consultations seemed to be a result of an optimal combination of content and behaviour of a healthcare professional. Participants described a clear-cut and relaxed consultation with a professional who *'listens and takes time'*, *'is interested and understanding'* and who *'treats them like a human'*. The participants also described 'bad' consultations, where healthcare professionals did the opposite of one or more of the above mentioned. They depicted healthcare professionals who did not seem to listen or be interested because *'they were completely focused on the computer screen'* or *'they nearly broke their neck to get to the coffee table'* after a short consultation.

g) Errors, complications and oddities

Insufficient communication might result in dissatisfaction

Six out of eight participants described that they experienced an error or complication in the past. Sometimes without permanent repercussions, but other times with outcomes that influence the quality of their lives. Whether the participants reported on a 'big' event, such as an error or complication, or on an oddity, the discontent always seemed to be caused by an experienced lack of or insufficient communication.

'So maybe I also felt like the doctors were ashamed too. But I thought: you should have thought it through. I do hope someone said something internally, like 'boys, this has to go differently from now on'. But I do not know whether that happened.' (P7)

h) Communication from and to the hospital

Climbing the wall to reach the hospital doctor

When they have a question about a treatment plan or medicine, most participants said they (would) *'try to contact the hospital doctor'*. Some of the participants never tried to contact their hospital doctor and one participant mentioned he did not know whether he would try if he had a question. Two participants described their experiences: *'you will*

Table 3. *Overview of feelings and expectations mentioned by some of the participants*

Type of appointment	Feelings	Expectations
Checkup	Most: *'I know what the appointment is for, so I know what to expect'* If all is good: relief, reassurance *'Consultation on autopilot' (P7)*	Answer to: is it good or is it not good/stable? Difference in desire for explanation
Diagnostic	Most: *'Sometimes I do not know what to expect'* *'Sometimes I know the next step, but not where it is headed'*	Answer to: what is going on? Participant wants to know *'where he/she stands'* *'Please as quickly as possible'*
Treatment	Some: *'You just have to surrender'* Fear, for example because of experience in their personal environment	Answer to: the specific complaint Health professionals know what to do and explain this in an easy and comprehensive way (before/during) Health professionals do their best

Figure 1. *Sliding scale of patients from a health and social perspective*

first get the assistant, you have to ask your question and then the assistant will discuss this for you'. One participant was content about this, but one family member was less satisfied: '*Sometimes because of the answer to the question, you have more questions, but the assistant cannot give you the answer. This can become a time-consuming process*.' (P4's family member) Overall, most participants experienced a wall to reach their own hospital doctor: they thought or experienced that '*assistants are instructed to keep everything away*'. This often resulted in dissatisfaction or in refraining from calling the hospital doctor, the participants reported.

DISCUSSION

Relationship to existing literature

In a qualitative study on the management of MCC in the Canadian community setting, the participants described their struggle with loss of functional ability and the gradual decline, which are similar to the struggles of our study population.[19] This decline seemed to result in ambivalent coping: the participants were sometimes forced to acknowledge their healthcare needs, while on the other hand they did not always want to focus on 'being ill'. According to previous research, physical functioning and quality of life are associated with MCC. Increasing age is also a contributing factor: it is related to more MCC and physical functioning.[10-21] Moreover, a review by Ryan et al. indicated that the number of conditions and disease severity were predictors of functional decline.[22] This study emphasises the significant roles that gradual and functional decline play in a patient's life with MCC.

Our study also indicates that keeping an overview of diseases, appointments and health professionals in the hospital can cost initiative, attention and effort. The ability to keep an overview and the need for information might be influenced by individual characteristics. According to the World Health Organisation (WHO), the need for information depends on a patient's characteristics, including education, skills, coping strategies, preferences and beliefs.[23] From a health and social perspective, patients can be distributed on a sliding scale (*figure 1*).[24]

The patients who were interviewed for this study might be outspoken participants because of the selection procedure. Moreover, as mentioned before, they were relatively independent, cognitively strong and/or supported by family, so they were most likely positioned somewhere in the middle of this scale. For patients positioned on the outer left side it might require even more effort to keep an overview or not even be possible. However, on the outer right side, patients might experience few difficulties. Therefore, our participants' abilities and needs, but also the required effort to keep an overview might differ from individuals with other characteristics or positions on this scale.

Moreover, MCC and its complexity do not seem to fit into the current care design. The Canadian community study concluded that the health and social care systems do not have the ability to meet the needs of older adults and caregivers and the participants experienced fragmentation of care.[19] Our participants reported the same fragmentation in their secondary care experience: multiple appointments that were rarely combined, possibly conceivable communication between their hospital doctors and multiple medicines from different prescribers. Overall, the complexity of MCC seems to be a barrier to optimising care, but also to the patients' and doctors' knowledge about the different diseases, treatments and interactions.[13]

'Experienced difficulties in interacting with the healthcare system' are defined as 'hassles'.[11,25] Our participants described how many of processes and logistics in the hospital's outpatient clinic remain unclear, but they have assumptions about them. They reported that because of the multiple visits and observations they make, they became experienced and developed strategies to manage their own cases within the hospital and cope with these hassles. Two other studies described that patients with MCC reported experiencing more 'hassles' than patients with a single condition. These hassles usually concerned the amount of information about their diseases, taking medication, finding time or the right moment to discuss all of their problems or poor doctor-doctor communication.[25-27] Moreover, Kenning et al. reported that these 'hassles' were predictors for self-management in patients with MCC.[11]

Consequently, hassles appear to play an influential role in patients' secondary care experiences and in patients self-management, in the hospital and at home.

Communication seems to have a crucial influence on expectations and feelings and presumably affects the secondary care experience for patients with MCC as well. Our study provides a modest insight into how experiencing different communication styles and multiple different appointments with several healthcare professionals resulted in various expectations and feelings. Moreover, our study offers a personal insight into the specific feelings that were elicited by either good or poor communication. The Institute for Healthcare Communication emphasises the importance of good communication between healthcare professionals and patients. Their research shows that for all patients, communication seems to play a large role in patient satisfaction and experience, but also in adherence to treatments, self-management and prevention behaviour.[28] According to a recent randomised controlled trial, being empathetic and inducing positive expectations has a significant effect on reducing anxiety and negative mood and increases satisfaction.[29]

Overall, the study findings indicated that the planning, logistics and communication of being a patient with MCC in the hospital demands considerable effort from this specific group of patients. However, the needs and abilities for organisation and overview might differ, based on individual factors. Partly because of experiencing hassles, the participants seemed to have gradually become experienced patients. Concurrently, the quality of communication might be an important influence not only on patients' experience, but also on the patients' management of themselves.

STRENGTHS AND LIMITATIONS

Strengths

The participants suffered from many comorbidities, had experiences with multiple hospital doctors and most of them had visited the outpatient clinics very often in the last year, which made them ideal patients to share their experiences for this study. The interviews were mostly done at the participant's home, in a trusted environment and were conducted by an independent interviewer who had no apparent relation with any of the healthcare professionals in the hospital. If the interviewer sensed a certain level of reservation in patients to openly express their feelings, the interviewer actively assured them that the interviews would be processed anonymously and that the information they provided would by no means be transferred to the healthcare provider in a way that could unravel their identity. The semi-structured design offered an insight into the expectations, feelings and coping strategies these patients have and developed.

Limitations

Data saturation was achieved after including only eight patients. There was variation in age and education, with a small overrepresentation of patients aged 65-74 years and 50% low education level against 19% in the general population aged 65 years and above in the Netherlands in 2014.[30] Moreover, all participants were Dutch and relatively independent. So this seemed to be a relatively outspoken and fit population without much cultural diversity. However, as patients with multiple chronic conditions are often older with a lower education level, the variation in age and education was expected for this sample.

Nevertheless, younger patients, patients with a different ethnicity or more dependent patients might not endorse the results. Changing the selection procedure to include more diverse patients might lead to different results.

Implications for the future

The complexity of MCC might require a more coordinated, individualised approach of care, as the World Health Organisation (WHO), the American Geriatric Society(AGS) and the NICE guideline described.[13,31,32] However, an overview of the patient's conditions, care providers and treatments seems an essential element for this approach. In our research, the relatively independent and cognitively strong participants and their family members described that the organisation of the conditions and appointments could require a great effort. Despite their efforts, the course of events could remain obscure and the logistics within the hospital non-transparent. At the same time, healthcare professionals seemed to operate only on their separate islands. If policymakers think a coordinated and individualised approach is beneficial for patients with MCC, we might first have to answer the question: whose responsibility is it to create and maintain an overview of the care for a patient with MCC?

However, not every patient might require and desire more coordination and communication regarding their care. Organising multiple appointments and doctor-doctor communication are themes that seem specifically related to MCC and improving these aspects might improve the care experience for patients with MCC. However, it might be necessary to narrow the target group for these interventions first, as not all participants in this study felt the same desire for change as others. On the other hand, information or feeling sufficiently informed about diseases, treatments or logistics seems to be one of the pillars for a good patient experience, according to our participants, but also to other studies on care experience of patients with MCC.[25-27] The participants seemed to

fill their gaps of information with assumptions and eventually with experience. They all report the need for information, but to what extent differs. More coordination and communication might particularly be required by patients who are dependent, who do not have support from their environment or suffer from (mild) cognitive disorders.[33]

In conclusion, future research could focus on finding ways to create overview and defining responsibilities of the care for patients with multiple chronic conditions. Moreover, it could attempt to clarify which group of patients needs assistance and how to improve communication and care coordination for them. Overall, patients' care experience could play an important role in implementing a coordinated, individualised approach of care for patients with multiple chronic conditions.

DISCLOSURES

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Appendix 1. *Interview Guide 'Secondary care experience of patients with multiple chronic conditions'*

Before we start, what do you definitely hope to share during this interview?

Living with MCC

1. Tell me about your experiences in living with more than one chronic condition at a time.
2. What do you notice about having multiple chronic conditions at once?
3. When you think about the hospital, what do you think about?
4. What do you think about when you think about the healthcare professionals in the hospital?

Multiple visits

5. Can you tell me what appointments you had the last year?
6. Can you describe the feelings you got from these appointments?
7. Can you tell me about the schedule of your day, the day of your last visit?
8. At what time did you leave for the hospital and at what time were you home again?
9. How do you feel about the time it takes you to go to the hospital?
10. How do you go to and from the hospital?
11. Does someone always join you for the appointments or do you go by yourself?
12. Do you spend any money in the hospital? If yes, on what?
13. What do you think about the number of times per year that you have to visit the hospital for an appointment with one of your specialists?
14. Who determines when the appointments are scheduled? Can you give your opinion about that?
15. Do you think your hospital doctors communicate with each other? Do you notice this communication?
16. What do you think about communication between your multiple hospital doctors?
17. Are all hospital doctors always up-to-date on your treatments? Or do you have to bring them up-to-date?
18. Did you ever find yourself in between the communication of two doctors?

Communication with physician

19. What would your ideal hospital day look like?
20. What would your ideal hospital guidance look like?
21. Can you remember your last visit to the specialist?
    With which specialist was this appointment?
    How would you describe the contact with this doctor?
22. Do you always know who your doctor is?
23. What do you consider important at a consultation with your hospital doctors?
24. Do you, next to the contact with your specialist, also have contact with other employees of the hospital?
    If yes, can you tell me what you think about these encounters?
25. Is part of your regular check-ups for one of your diseases done by a physician assistant?
    If yes, how do you feel about that?
    If no, skip question 26.
26. Are there differences between the consultation with the specialist and the physician assistant?
27. What do you think about the organisation of the multiple visits to several different specialists?
28. What do you think about the coordination of the different care providers in relation to the different diagnostic tests (i.e. blood tests, X-rays and scans etc.)?
29. What do you think about the specialist's communication from the hospital to the care providers concerned outside of the hospital, such as the general practitioner?
30. Do you think all visits are useful?
    If yes, what do the visits include that you find useful?
    If no, what are the things you find useful and that things do you find useless?
31. Do you always know the purpose of the appointment?
32. Would you rather change some of your appointments to a telephone consultation?
33. Do you always understand everything that is discussed during a consultation?
34. Do you think you have enough time to ask all the questions you have?
35. Is it always clear to you what the treatment plan is?
36. Do you have the feeling that you have the power to decide about the treatments?
37. Who do you ask when you have questions about a proposed treatment or medication?
38. How do you reach your specialist when you have questions about something or when you have something you would like to discuss?
39. What do you think about the accessibility of your specialist when you have questions?
40. Did something ever go wrong with your treatment?
    If yes, what?

Geriatrics

41. Have you ever visited a geriatric doctor?
    If yes, what did you think about that?
    If no, skip question 42.
42. Are there certain things that were striking about your visit to the geriatric doctor?

Medication

43. Can you tell me how you organise the different medicines you take?
44. Do you know which medication you use and what for?
45. Do you know who prescribed the medication?
46. What are your experiences with obtaining prescriptions from the hospital?
47. Have you ever experienced bad side effects?
    If yes, what did you do?
    And could you easily consult your specialist?

CASE REPORT

Progressive kidney failure in chronic myelomonocytic leukaemia: don't forget lysozyme damage

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ABSTRACT

Kidney failure is common in haematologic malignancies. However, the nephrotoxic effect of lysozyme is seldom recognized. We present a 78-year-old male with chronic myelomonocytic leukaemia who developed progressive kidney failure due to increased production of lysozyme.

KEYWORDS

Chronic myelomonocytic leukaemia, kidney failure, lysozyme

What was known on this topic?
Kidney failure in haematologic malignancies occurs because of various causes. Lysozyme-induced kidney injury is a rare and unknown complication of chronic myelomonocytic leukaemia.

What does this add?
This case report emphasizes that due to its infrequency, lysozyme-induced kidney injury may be overlooked. Recognition of specific signs is essential for limiting consequences of the disease, so that treatment of the malignancy may improve kidney function.

INTRODUCTION

In patients with haematologic malignancies, acute and chronic kidney failure may be caused by tumour lysis syndrome, leukaemic invasion of the kidney, urethral obstruction, chemotherapy-induced toxicity or paraprotein-induced disease (*table 1*). Fewer, and therefore infrequently recognised, causes of malignancy-associated kidney disease have also been described.[1,2] We present a patient with chronic myelomonocytic leukaemia (CMML) who developed progressive kidney failure. A kidney biopsy raised the suspicion of a rare complication of CMML, which was confirmed by additional investigation.

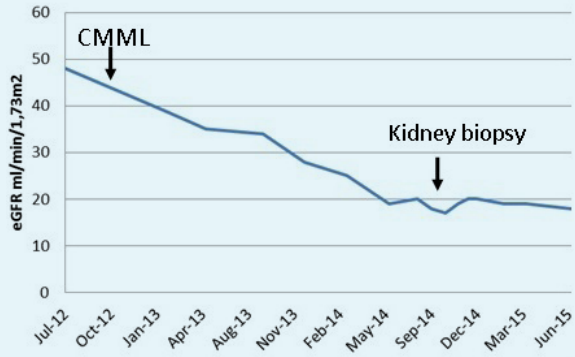
Table 1. *Causes of kidney disease in haematologic malignancies*

Intravascular volume depletion
Tumour lysis syndrome
Leukaemic invasion of the kidney
Urethral obstruction
Chemotherapy-induced toxicity
Intravascular leukostasis
Paraprotein-induced disease
Lysozyme-induced nephropathy

CASE REPORT

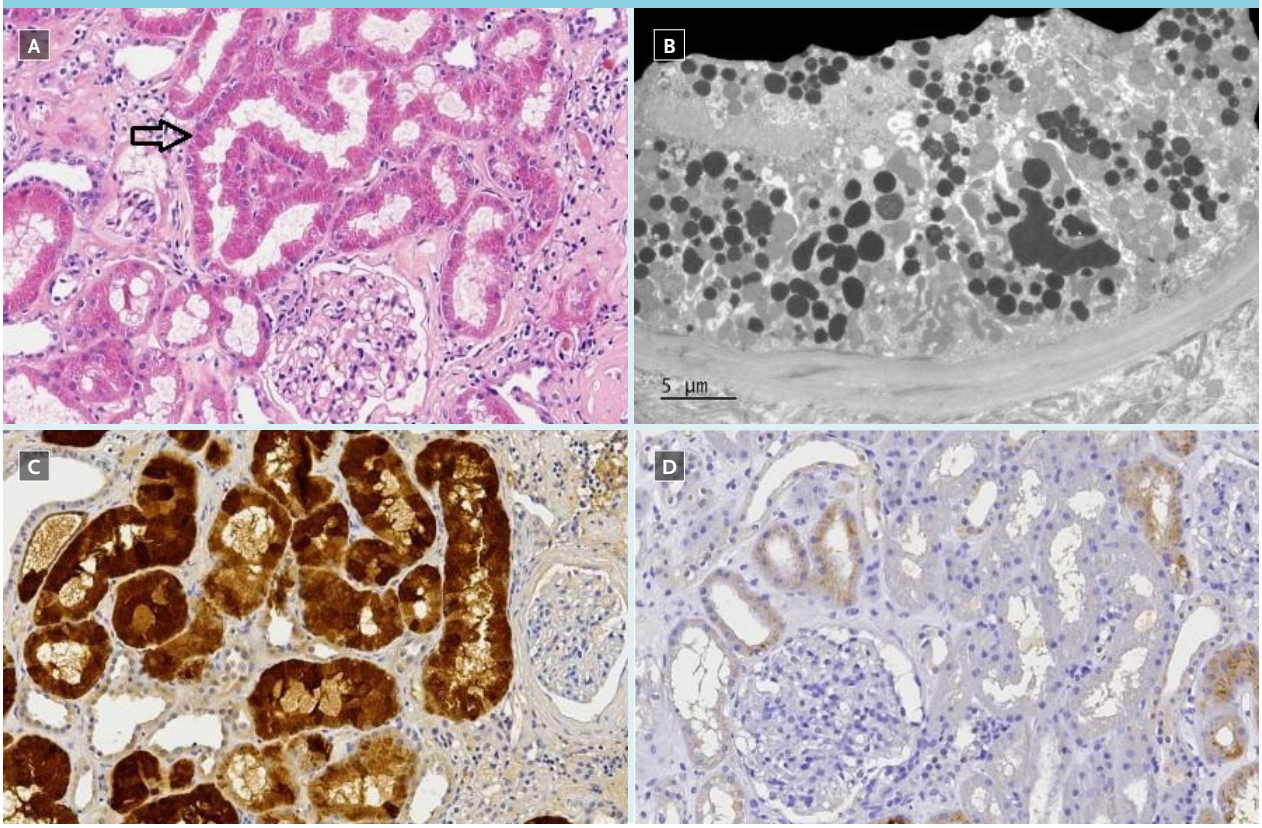
A 78-year-old man, with diabetes type 2 and narcolepsy, presented in 2014 at our outpatient department with progressive kidney failure. In 2012, he was diagnosed with CMML, which required no treatment. However, since that time, his kidney function deteriorated (*figure 1*). The patient was prescribed dexamphetamine to treat

Figure 1. *The slope of renal function (eGFR calculated by MDRD) over time*



narcolepsy, and his other medications included metformin, glimepiride and lisinopril. Family members had no kidney diseases. His blood pressure was 143/78 mmHg and physical examination was unremarkable. Laboratory investigation showed the following results: haemoglobin 6.8 mmol/l; leukocytes 31.7 x 10^9/l; cell differentiation: monocytes 9.39 x 10^9/l ; metamyelocytes 0.48 x 10^9/l; neutrophils 17.85 x 10^9/l; lymphocytes 3.68 x 10^9/l; no myeloblasts (blasts); no promonocytes; platelets 153 x 10^9/l; potassium 4.7 mmol/l; urea 14.1 mmol/l; uric acid 0.59 mmol/l; creatinine 265 µmol/l; phosphate 1.2 mmol/l; calcium 2.35 mmol/l; albumin 37 g/l; and HbA1c 57 mmol/mol (NGSP HbA1c 7.4%). Serum protein electrophoresis showed no M protein and the gamma-globulin fraction was not increased. Serum-free light chains had a kappa/lambda ratio of 1.7. Bone marrow findings included dysplastic features in all cell lines without increase of blasts, but increase of monocytes up to 10-15%. The urinary sediment contained no dysmorphic erythrocytes and no erythrocyte or leukocyte casts. The urine albumin/creatinine ratio was 3.6 mg/mmol Cr, or an albuminuria of approximately 40 mg/24 hours. Total proteinuria was 700 mg/24 hours, thus indicating the loss of protein other than just albumin, however Bence Jones protein could not be identified. Kidney ultrasound showed normal-sized kidneys.

Figure 2.
A. *HE staining, original magnification 200X. Proximal tubular epithelium shows prominent eosinophilic granules (arrow)*
B. *Transmission electron microscopy. Proximal tubular epithelium shows unusually abundant electron dense lysosomal structures*
C. *Immunoperoxidase staining for muramidase. Note the strong staining for muramidase in proximal tubular epithelium*
D. *Immunoperoxidase staining for muramidase in a patient with minimal change nephropathy and tubulopathy due to protein overload*



Diagnostic focus and assessment

A kidney biopsy was performed because there was no explanation for the progressive renal failure (eGFR slope -10ml/min/1.73 m²/year). Microscopy showed subcapsular cortex with approximately six glomeruli, half of which were globally sclerotic. Remaining glomeruli showed no abnormalities. There were areas of interstitial fibrosis/tubular atrophy. Non-atrophic proximal tubules showed a massive accumulation of eosinophilic droplets (*figure 2A*) which, when observed with electron microscopy, resembled lysozymes (*figure 2B*). Immunoperoxidase staining for muramidase confirmed accumulation of lysozyme in the proximal tubules (*figure 2C*). This muramidase staining is not usually evident on renal biopsy: note the difference with a biopsy of another patient with only weak staining of muramidase (*figure 2D*). Routine immunofluorescence was negative, ruling out paraprotein-related kidney disease. The biopsy findings with tubular lysosomal structures were suggestive for renal failure caused by lysozyme. To support this hypothesis, serum lysozyme concentration was determined and shown to be elevated to 47.5 mg/l (normal range 10-17 mg/l). Based on the above, we made a diagnosis of lysozyme-associated renal failure due to CMML.

Follow up and outcomes

The advanced renal failure and elderly age of our patient discouraged us from starting systemic CMML treatment, in addition to low success rate of CMML treatment and its considerable side effects. Although we didn't start systemic CMML treatment, we did focus on conservative management of his chronic kidney failure to prevent further damage. Two years later, the patient died of an unknown cause; the last measured eGFR was 16 ml/min/1.73m².

DISCUSSION

Lysozyme, also called muramidase, is a basic, cationic protein, primarily produced by monocytes and macrophages.[2] It is part of the innate immune system and contributes to hydrolysis of the Gram-positive bacterial cell wall, causing lysis of bacteria. It is known that human tears, saliva, sputum and nasal secretions contain high concentrations of lysozyme.[3] Normally, lysozyme is reabsorbed in the proximal tubules, where its concentration in the cortex may be 10-25 times greater than in the medulla. It is generally agreed that high concentrations of lysozyme can damage the proximal tubular cells, ultimately leading to tubular necrosis, tubular atrophy and interstitial fibrosis. Rat studies have shown that accumulation of lysozyme droplets in the proximal tubulus was associated with tubular damage.[4] Histological changes (hyaline droplets in the proximal tubulus cells) have also been correlated with renal impairment in clinical cases.[5] Examples of indications of lysozyme-induced tubular damage include an increased urinary alfa-1-microglobulin/creatinine ratio or signs of Fanconi syndrome (glucosuria, low serum phosphate, metabolic acidosis).

Table 2. *Causes of increased lysozyme levels in serum and/or urine*

Sarcoidosis
Generalized carcinomatosis
Multiple myeloma, plasma cell leukaemia
Hodgkin's disease
Reticulum cell sarcoma and other lymphomas
Myelomonocytic and monocytic leukaemia
Kidney transplantation
Fanconi syndrome
Lowe's syndrome
Regional ileitis (increased faecal lysozyme levels)
Typhoid fever
Cadmium poisoning

An increased serum lysozyme level can be found in various diseases including hematologic malignancies, generalized carcinomatosis and typhoid fever (*table 2*). Sarcoidosis is another disease known for its elevated lysozyme levels, however this is currently not used as a diagnostic parameter.[1,6] In addition to tubular damage caused by increased lysozyme levels, renal failure can also be caused by lysozyme amyloidosis. This is a rare form of systemic amyloidosis, causing a heterogenous range of symptoms (GI-haemorrhage, hepatic rupture, sicca syndrome, haemorrhagic skin lesions, lymphadenopathy and renal failure). It is important to distinguish between both forms of amyloidosis because there are no indications for chemotherapy treatment in lysozyme amyloidosis.[7]

Previous investigations performed by Osserman and Lawlor showed that serum lysozyme concentrations ranged from 40-150 mg/l in patients with monocytic leukaemias, whereas in control patients, serum contained approximately 7 mg/l of lysozyme. The increased filtration of lysozyme exceeds the reabsorptive capacity of the tubules, thus resulting in increased excretion of lysozyme in the urine, as demonstrated in patients with leukaemia.[3] These observations were confirmed by Pruzanksi and Platts, who found elevated serum lysozyme concentrations in all patients during the active phase of the monoblastic and myelomonocytic leukaemia.[5] Both studies suggest a strong relation between the elevated concentration

lysozyme in serum and urine and the occurrence of kidney damage. It seems evident that patients with mono- and myelomonocytic leukaemia almost invariably develop prominent proteinuria. Finally, azotemia develops in approximately 50% of all cases.[5]

Of note, the presence of lysozyme can be suspected when comparing urine albumin and urine total protein concentration, as lysozyme-induced nephropathy typically causes a nonalbumin proteinuria. In glomerular diseases, urine albumin comprises 60-70% of urine protein, whereas in patients with lysozymuria, albumin contributes < 25% to total protein. However, significant albuminuria may be present, due to toxic tubular damage caused by massive lysozyme reabsorption by the proximal tubulus. Thus, disproportionally high urinary protein excretion compared to albumin excretion may indicate lysozyme overproduction, although it is a trigger rather than a sensitive finding for the diagnosis of lysozyme-induced nephropathy. Lysozyme quantifying in urine is not available anymore in the clinical setting.

When diagnosed, a curative treatment for lysozyme-induced kidney damage in CMML is not known, however it is to be expected that treatment of CMML will also result in improved kidney function. Santoriello et al. described a case in which the serum lysozyme levels decreased to within normal ranges four months after CMML treatment was started, although this patient remained dialysis-dependent.[1] Borges et al. presented a case in which kidney function was ameliorated after treatment of CMML with azacitidine and prednisolone.[8]

In this case report, we highlight the relationship between CMML and kidney failure other than tumor lysis, because early recognition is essential in preventing further kidney damage. Kidney biopsy and quantifying of lysozyme in the serum are useful diagnostic procedures, once the suspicion of lysozyme toxicity is raised. There are no pharmacological options to solely lower serum lysozyme levels, and this is why the presence of lysozyme-induced nephropathy may be an argument to start CMML treatment in order to prevent progressive renal failure.

INFORMED CONSENT

Because our patient died before this case report was finished, we could not obtain informed consent.

DISCLOSURES

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CASE REPORT

Allergic acute coronary syndrome in exercise-induced anaphylaxis

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ABSTRACT

In this case report we present a 49-year-old male who was seen in the emergency department after collapsing due to anaphylactic shock, with ECG findings suggesting myocardial ischaemia. We linked both diagnoses to Kounis syndrome, which describes an acute coronary syndrome due to an allergic event. His circulatory collapse was explained by exercise-induced anaphylaxis.

KEYWORDS

Acute care, anaphylaxis, emergency department, exercise induced anaphylaxis, Kounis syndrome

What was known on this topic?
Most allergic events cause relatively mild or minor symptoms; however, in case of anaphylactic shock it could be life-threatening. Identification of the inducing agent by an allergy work-up is essential to prevent future events. Exercise could be a trigger of allergic shock; when associated with food ingestion it is referred to as food-dependent exercise-induced anaphylaxis.

What does this add?
Kounis syndrome is described as an acute coronary syndrome as a result of an allergic event. Patients with systemic allergic reactions associated with clinical signs and symptoms, laboratory or electrocardiographic findings of acute myocardial ischaemia should be suspected of having Kounis syndrome. Cardiological work-up is necessary.

INTRODUCTION

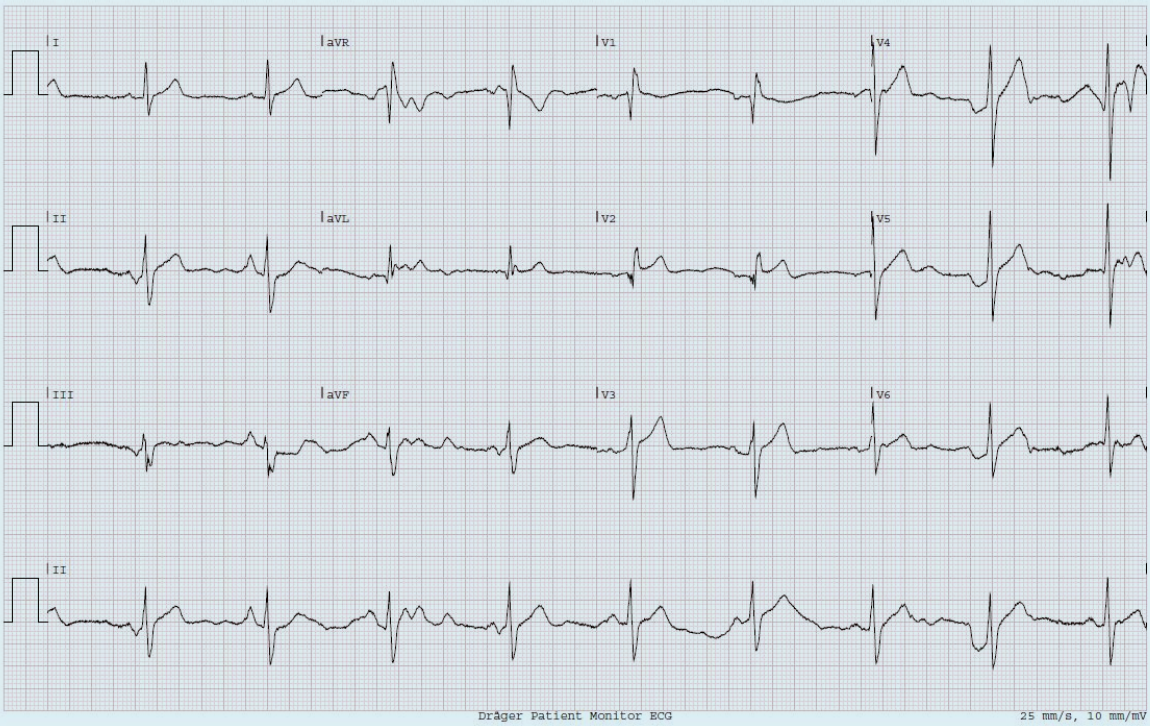
Exercise-induced anaphylaxis (EIA) is a rare condition in which an anaphylactic reaction occurs after physical exercise. Symptoms generally occur within 30 minutes, but may develop up to two hours after exposure to the specific trigger. In one-third of cases EIA is associated with cofactors, such as food intake.[1] This is known as food-dependent, exercise-induced anaphylaxis (FDEIA). In this uncommon condition an anaphylactic reaction will develop during or shortly after exercise, when a patient has eaten particular food prior to the activity. Exertion or ingestion of the specific food for which the patient is sensitised alone, do not cause any symptoms. FDEIA is uncommon but symptoms can be life-threatening.[1,2]
An acute coronary syndrome can occur as a result of an anaphylactic reaction: allergic myocardial infarction, referred to as Kounis syndrome.[2] A concurrence of acute coronary syndrome and anaphylaxis is rarely described but recognition is important in treatment. We present a case of wheat-dependent exercise-induced anaphylaxis (WDEIA) with secondary suspicion of Kounis syndrome.

CASE

A 49-year-old male without a history of cardiovascular disease presented to our emergency department with an anaphylactic shock after physical exercise. After warming-up the patient developed urticaria on his chest and arms, abdominal pain, vomiting and diarrhoea. An ambulance was called and after arriving the patient's clinical status deteriorated. He developed angio-oedema and collapsed. The patient's vital signs included an oxygen saturation 88% on room air, and a blood pressure 92/55 mmHg. Epinephrine and clemastine were administered. An ECG showed incomplete right bundle branch block with mild elevated ST segments without reciprocal ST depression.

At the emergency department, the patient kept vomiting and the urticaria did not disappear. The oxygen saturation was 96% with 15 litres of oxygen and the blood pressure

Figure 1. *ECG taken in the emergency department, showing some conduction abnormalities*



12-lead ECG in the emergency department: sinus rate 50 beats per minute, right bundle branch block pattern, elevated ST segments in V1-V4 without reciprocal ST depression

normalised. There was no medical history of allergy. A detailed anamnesis could not reveal any potential causative trigger or allergen for this anaphylactic reaction. The clue that eventually led to the diagnosis of FDEIA came from the patient who remembered recently having a previous reaction with urticaria during a strenuous cycling trip.

The patient was stabilised with intravenous fluid therapy and antiemetic drugs. Cardiac biomarkers were measured because the prehospital ECG showed ST elevation in V2-V4, suggesting myocardial ischaemia. Unfortunately, this ECG is not available. The ECG taken in the emergency department (*figure 1*) showed some conduction abnormalities. There were no dynamic ST segment and T wave changes. Echocardiography performed at the bedside did not show any wall motion abnormalities. Laboratory testing showed high-sensitivity troponin T at 15 ng/l (normal range < 14 ng/l; after one hour 73 ng/l). Creatine kinase-MB was 3 µg/l (after one hour 3.7 µg/l), lactate 7.3 mmol/l (after one hour: 1.6 mmol/l). The level of serum tryptase 5.5 hours after onset of symptoms was 5.1 µg/l (normal range < 11.4 µg/l). Elevated serum tryptase levels could be caused temporarily by mast cell activation as in allergic reactions, or sustained elevated levels by mast cell diseases such as mastocytosis. In case of an allergic reaction, levels fall rapidly and are normalised three hours after the onset of the allergic symptoms.

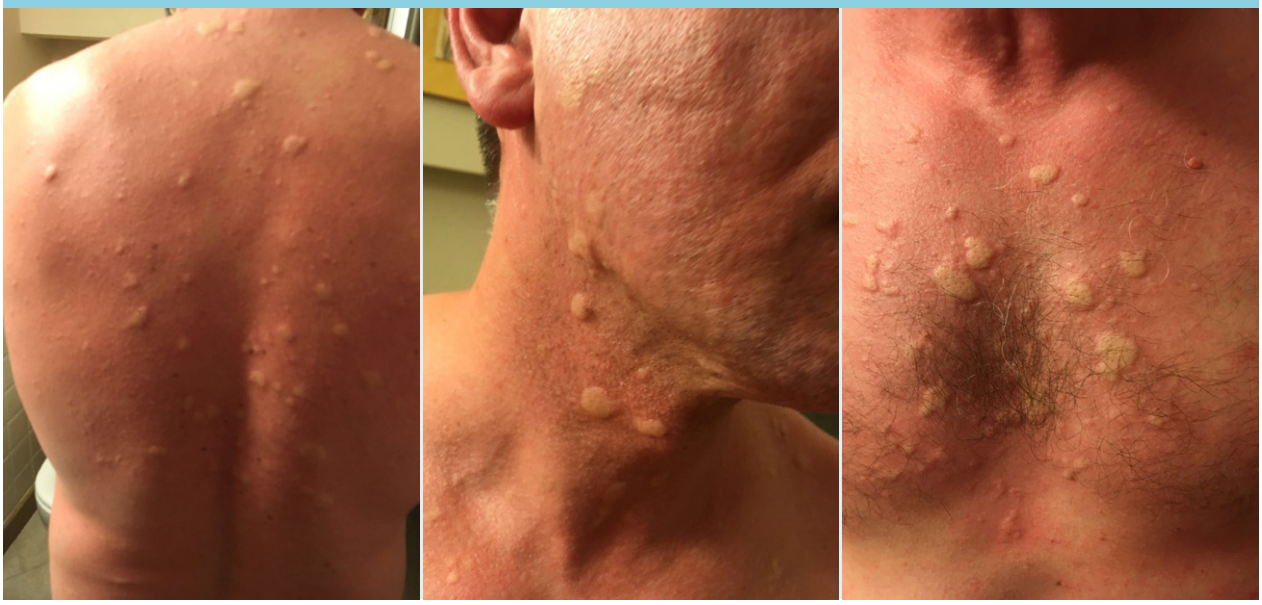
DISCUSSION

Food-dependent exercise-induced anaphylaxis

EIA frequently needs cofactors to provoke an allergic reaction. Known cofactors that should be inquired about are: food intake, alcohol, medication (e.g. NSAIDs), temperature, and menstruation cycle.[1,3] FDEIA will develop during or shortly after exercise when a patient has ingested a specific food for which he is sensitised up to a few hours prior to exercise. Sometimes, more cofactors are needed for a reaction. A detailed anamnesis is mandatory for the right evaluation and diagnosis.

Sensitisations tests, such as skin testing or food-specific IgE, should be performed to identify potential allergens. A challenge test could confirm the diagnosis but is challenging because of high false-negative results. The procedure is not standardised and does not replicate daily life. Without the right diagnosis, the patient runs the risk of a potential life-threatening reaction.[1,3]

Figure 2. *Positive provocation test after eating bread and dancing*



In our patient we suspected exercise-induced anaphylaxis provoked by wheat (WDEIA) because he ate wheat before this anaphylaxis and the previous cycling trip when he developed urticaria. IgE against omega-5 gliadin can confirm WDEIA. Omega-5 gliadin is one of the most common allergens involved in WDEIA; approximately 80% of the patients have IgE reacting to omega-5 gliadin.[4]

In our patient, an omega-5 gliadin sensitisation was found (5.23 kU/l), and a food-exercise challenge test was planned. However, our patient already challenged himself accidentally by eating bread followed by dancing before his appointment in the outpatient clinic. This was followed by allergic symptoms (*figure 2*). Because we had already demonstrated a specific IgE to omega-5 gliadin and the patient had already reacted three times within the same pattern of food ingestion plus exercise, we confirmed the diagnosis of WDEIA without performing a challenge test. He was advised to avoid exercise > 4 hours after ingestion of wheat; an adrenaline auto-injector (AAI) was prescribed and he was instructed on how to use it.

Patients with EIA must always carry an AAI with them and self-administer adrenaline intramuscularly as soon as symptoms occur during exercise, and call for help. We strongly advise to exercise only in the attendance of someone who is familiar with the potential risks of exertion and knows how to use an AAI.[1,3,4]

Kounis syndrome

Our patient had abnormal electrocardiogram findings and elevated troponins, both findings could be consistent with an acute coronary syndrome (ACS). Kounis syndrome is defined as the concurrence of ACS (coronary spasm, acute myocardial infarction, and stent thrombosis) in the setting of mast cell and platelet activation from allergic or anaphylactic reactions.[2] Coronary vasospasm is the result of a systemic allergy-induced mast cell activation and a release of inflammatory mediators.[5] Therefore ACS can occur as a result of the anaphylactic reaction.

Three types of allergy-induced coronary vasospasm are recognised: vasospasm with or without a rise in cardiac biomarkers in patients without coronary artery disease (type I), coronary vasospasm in patients with pre-existing coronary plaques in whom the release of inflammatory mediators may induce plaque erosion or rupture and therefore myocardial ischaemia (type II) or even stent thrombosis as a result of the induced vasospasm (type III). If patients have allergic symptoms accompanied with cardiac symptoms, such as chest pain, Kounis syndrome should be considered. It is important to recognise and distinguish Kounis syndrome from normal ACS because the identification of the allergic trigger could prevent recurrences and the approach to treatment is different. In case of anaphylaxis, it is important to recognise Kounis syndrome because underlying coronary artery disease must be ruled out. The combination of allergic and cardiac symptoms should trigger physicians to perform acute accessory cardiac evaluation including biomarkers (troponins, CK-MB), electrocardiography (ST-T segment changes) and echocardiography (regional wall motion abnormalities). An urgent coronary angiogram can be considered to distinguish between type I and II. During follow-up patients should be monitored for underlying coronary artery disease. Cardiac magnetic resonance imaging and myocardial scintigraphy can help to confirm the diagnosis.[5-7]

Treatment of Kounis syndrome could be challenging because of the concurrent allergic and cardiac symptoms. Supplemental treatment includes antihistamines, corticosteroids, and epinephrine. Coronary artery vasodilators, such as nitrates, need to be considered first but should be avoided in case of anaphylaxis, because it causes hypotension. However, when blood pressure is satisfactory, sublingual or even intravenous nitroglycerin seems reasonable and safe.[6] In a type I variant, treatment of the anaphylactic reaction alone with antihistamines and corticosteroids can resolve the acute coronary symptoms. In case of myocardial infarction (type II) revascularisation is the preferred emergency reperfusion strategy. Remember that epinephrine increases the heart rate and blood pressure and therefore oxygen demand, and this may worsen ischaemia in patients with coronary vasospasm. Besides, coronary artery vasospasm can also be induced by epinephrine when administered in acute anaphylaxis.[2,5] Be aware that opiates, given to relieve stress and chest pain, increase mast cell degranulation and vasodilatation and thus may worsen anaphylaxis and coronary vasospasm. Therefore, we would suggest to avoid the use of morphine. Fentanyl is preferable because it shows only a slight activation of mast cells.[6]

After a short admission to the hospital, our patient was discharged home safely to be followed up closely as an outpatient. Cardiac magnetic resonance imaging did not reveal subsequent coronary artery disease.

CONCLUSION

Both described diagnoses are rare but should be recognised by physicians, especially those specialised in acute care.

In case of anaphylaxis, physicians should be motivated to search for the causative allergen. Exercise, with or without cofactors, could be a specific trigger for serious allergic insults. Finding the allergen helps patients to avoid specific triggers and is the best prevention of life-threatening situations. Kounis syndrome is the association of an acute coronary syndrome with anaphylaxis. Physicians should be aware when a patient presents with both allergic and heart symptoms. The allergic trigger could be the cause of the cardiac symptoms in case of Kounis syndrome. An allergy work-up and additional testing for underlying coronary artery disease should follow.

DISCLOSURES

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

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PHOTO QUIZ

Itching dermatitis on the leg of a 46-year-old HIV-positive man from Jamaica

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CASE REPORT

A 46-year-old HIV-positive man having sex with men in Jamaica presented to the infectious disease outpatient clinic with itching skin lesions on his lower left leg. The skin lesions had appeared after he arrived in the Netherlands, a few weeks earlier. The patient reported no primary chancre, fever or other skin or mucosal abnormalities. His last unprotected sexual contact was in Jamaica, three months before initial presentation. The alcohol use of the patient was three units/week and his nutritional state was normal. His HIV viral load was undetectable using antiretroviral therapy consisting of emtricitabine, tenofovirdisoproxil and nevirapine and he had an adequate immune status with a CD4 count of 563 x 10^6/l. Other laboratory tests showed no diabetes or hepatitis. A serological test for syphilis was performed during the first visit to our outpatient clinic. The fluorescent treponemal antibody absorption test, Treponema pallidum haemagglutination assay 1:40960, and Rapid Plasma Reagin (RPR) test 1:1 were positive. The patient recalled a previous syphilis treatment with

Figure 1. *Skin lesions medial view*

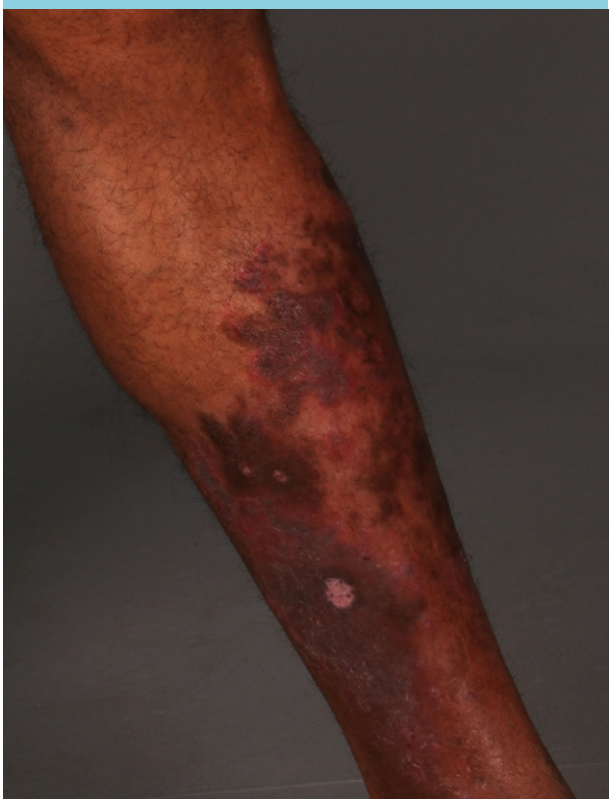
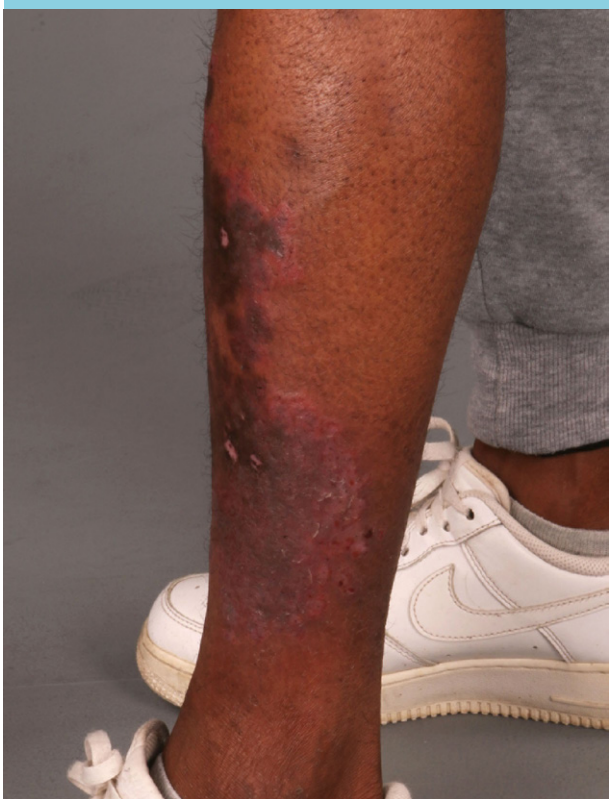


Figure 2. *Skin lesions lateral view*



multiple injections in Jamaica, one and a half years ago. Unfortunately, no additional information on clinical stage or laboratory results from this episode were available. The results were interpreted as a treated *T. pallidum* infection and follow-up serological testing was planned.
The lesions on the lower left leg were described as localized areas of lichenified eczema with scaly surfaces. At first, the clinical diagnosis was lichen simplex chronicus and treatment with a potent topical steroid class IV was started. After eight weeks, the lesions did not respond to the treatment and the lesions became progressive with multiple ulcerations (*figures 1 and 2*). Two skin biopsies were taken.

WHAT IS YOUR DIAGNOSIS?

See page 417 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 415)

ITCHING DERMATITIS ON THE LEG OF A 46-YEAR-OLD HIV-POSITIVE MAN FROM JAMAICA

DIAGNOSIS

The differential diagnosis of the skin lesions was malignant syphilis (also known as lues maligna or ulceronodular syphilis), tertiary gummatous syphilis or an endemic treponematose. Histopathology showed an interstitial lymphohistiocytic infiltrate with formation of non-necrotizing granulomas. Giemsa, Ziehl-Neelsen and Grocott stainings were negative. The culture showed no growth of mycobacteria and fungi. During follow-up, the RPR increased to 1:256. The polymerase chain reaction (PCR) test for *treponema pallidum* conducted on the skin biopsy was positive. A Treponema IgG immunoblot was performed and all bands were positive. Combined with the rise of the RPR titer, this confirmed the diagnosis of an active syphilis infection.

Malignant syphilis is a rare form of secondary syphilis often accompanied with the prodromal phase of fever, headache and myalgia.[1,2] The first systematic studies of malignant syphilis were performed by Haslund[3] and Neisser[4], who differentiated malignant syphilis as a severe form of secondary syphilis from the gummas of tertiary syphilis. The following diagnostic criteria for malignant syphilis are defined as: strongly positive RPR titer, a severe Jarisch-Herxheimer reaction, characteristic macroscopic and microscopic morphology and rapid resolution of the lesions with antibiotics.[5] The macroscopic characteristics are pleomorphic papulopustules, beginning ulcerations and deep ulcerations covered with crusts. The microscopic characteristics are an interstitial lymphohistiocytic and plasma cell-rich infiltrate with formation of non-necrotizing granulomas, sometimes in the presence of spirochetes. We diagnosed our patient with malignant syphilis because of the lamellar crusting, multiple ulcers, strongly positive RPR titer, a positive *treponema pallidum* PCR test of suspected syphilis lesions and rapid resolution of the lesions after antibiotic treatment.[2]

Although tertiary gummatous syphilis was considered as a differential diagnosis, we consider this less likely in our patient. Lamellar crusting is not a feature of tertiary syphilis and gummatous disease generally takes years to decades to develop after initial infection, although progression may occur faster in HIV-positive patients.[6]

In our patient, neurosyphilis was excluded with a cerebrospinal fluid examination and cardiovascular syphilis was excluded with an ultrasound of the heart.

Endemic treponematoses consisting of *Treponema pallidum* subsp *pertenue* (yaws), *T. pallidum* subsp *endemicum* (bejel), and *T. carateum* (pinta) were also considered as differential diagnoses. It is very difficult to distinguish venereal syphilis from the endemic treponematoses by serology only. However, yaws and bejel were less likely due to the patient's country of origin and travel history. Pinta can be present in the Americas, including the Caribbean, but primary skin lesions due to pinta do not ulcerate. Furthermore, the rapid resolution of the lesions after treatment is not typical for pinta.

Penicillin is the best treatment for malignant syphilis: 10 to 14 days of IV treatment[7-10], as well as 2.4 MIU intramuscularly, weekly for three weeks[11-13], have shown good response. Malignant syphilis is considered as form of secondary syphilis, so with a confirmed infection within one year, a single dose of 2.4 MIU penicillin could also be considered. In our patient, neurosyphilis was not present, but the duration of infection and previous treatments were not documented. Therefore, we treated the patient with benzathin benzylpenicillin, 2.4 MIU intramuscularly for three consecutive weeks. The lesions disappeared completely in the following weeks leaving only hyperpigmentation.

In conclusion, atypical skin disorders in a patient with syphilis may be a form of malignant syphilis, especially in a HIV co-infected patient. The characteristic macroscopic and microscopic morphology, strongly positive RPR titer and rapid resolution of the lesions with antibiotics may lead to this rare diagnosis.

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PHOTO QUIZ

Out of pace: An uncommon cause of atrioventricular block

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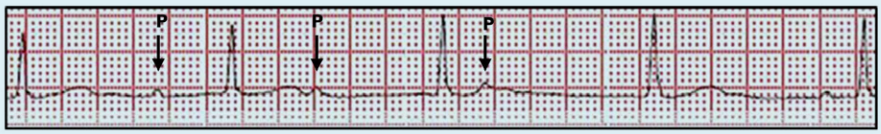
CASE REPORT

A 57-year-old female with a history of hypertension presented to the emergency department with extreme fatigue and dizziness. She had no complaints of chest pain or palpitations. Her current medication consisted of irbesartan and hydrochlorothiazide. She had a 7 pack-year history of smoking, drank alcohol occasionally, and she had no history of drug use. Her social pastimes included frequent walks in the woods. Family history for cardiovascular disease was negative. On physical examination the blood pressure was 126/65 mmHg, and she had a marked bradycardia with a heart rate of 47 beats/min. Other cardiac, pulmonary and neurological examinations were unremarkable. Routine laboratory tests showed a haemoglobin level of 8.0 mmol/l, leukocytes of 10.1 x 10^9/l, and a slightly elevated C-reactive protein of 21 mg/l. High-sensitive troponin was not elevated. There were no electrolyte abnormalities and thyroid studies showed no signs of hypothyroidism. Electrocardiography showed a third-degree AV block with nodal escape rhythm with a rate of 48 beats/min (*figure 1*). Chest X-ray was normal, transthoracic echocardiography did not show any structural abnormalities and a cardiac computed tomography scan showed no signs of obstructive coronary artery disease. Additional laboratory tests excluded the diagnoses of sarcoidosis, syphilis and amyloidosis.

WHAT IS YOUR DIAGNOSIS?

See page 419 for the answer to this photo quiz.

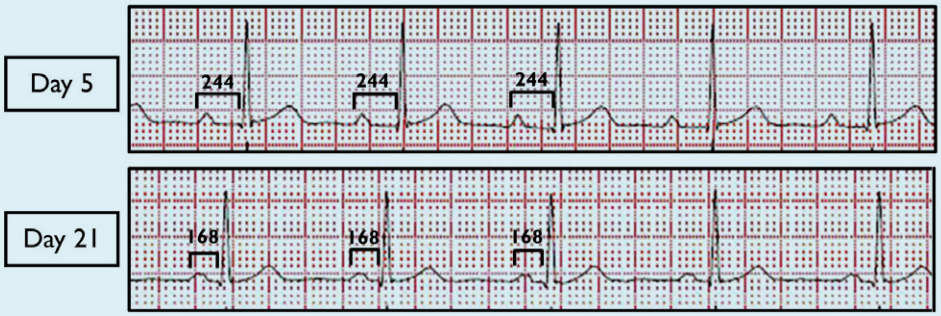
Figure 1.



ANSWER TO PHOTO QUIZ (PAGE 418)

OUT OF PACE: AN UNCOMMON CAUSE OF ATRIOVENTRICULAR BLOCK

Figure 2.



DIAGNOSIS

ELISA and Western blot analysis revealed seropositivity for *Borrelia burgdorferi* (IgM and IgG) confirming the diagnosis of Lyme carditis.

Lyme carditis represents a rare manifestation of Lyme disease, a tick-borne disease caused by *Borrelia burgdorferi*. Cardiac involvement in Lyme disease is estimated to occur in 0.3-4% of infected adults without appropriate antibiotic treatment in Europe.[1] Atrioventricular (AV) block, being the most common presentation of Lyme carditis, can fluctuate rapidly, and progress from a prolonged PR interval to a His-Purkinje block within minutes to hours and days. It is considered that Lyme carditis occurs as a result of an inflammatory response to the presence of bacteria in cardiac tissue, most commonly in the AV node. Symptoms of Lyme carditis include syncope, shortness of breath, palpitations and chest pain, although AV block can be the sole manifestation of Lyme disease. Our patient could not recall any signs of tick bite or skin lesions representing erythema migrans. If promptly recognised, adequate treatment may completely reverse the AV block, thereby preventing fatal arrhythmias and the unnecessary implantation of a permanent pacemaker. Treatment of patients with AV block or other cardiac manifestations associated with early Lyme disease consists of oral or parenteral antibiotic therapy for 14 to 21 days. All patients with third-degree AV block should be hospitalised and continuously monitored.[2,3] Our patient was immediately treated with intravenous ceftriaxone. Five days after treatment was started, the AV conduction improved from a third-degree AV block to a first-degree AV block with a PR interval of 244 milliseconds (*figure 2*). Once the ECG showed improvement and she became asymptomatic, intravenous antibiotics were switched to oral doxycycline, and the patient was discharged. After 21 days of treatment with antibiotics, ECG showed complete normalisation of the AV block with a normal PR interval of 168 milliseconds (*figure 2*).

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PHOTO QUIZ

A woman with a purplish-red skin lesion on the neck

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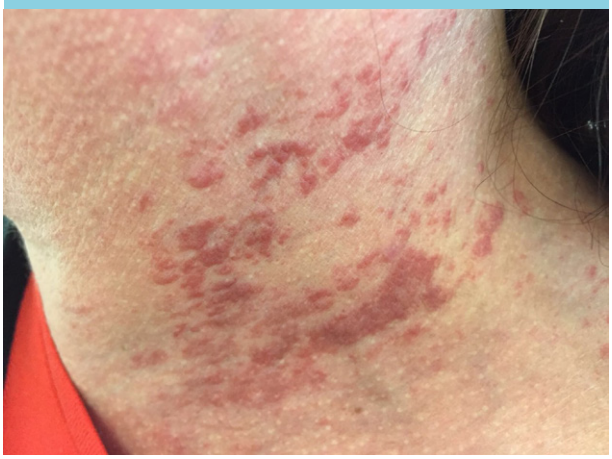
CASE REPORT

A 48-year-old woman visited the clinic with a 15-year history of a purplish red skin disorder on the left side of her neck. The lesion was asymptomatic and had slowly increased in size and thickness over the years. Because of her medical history of rheumatoid arthritis, she is on the following immunosuppressive medications: adalimumab, prednisone, azathioprine and hydroxychloroquine. On the left side of the neck a palm size area of multiple discretely arranged erythematous, violaceous coloured papules and plaques was seen *(figure 1)*. An ultrasound showed that the lesion was restricted to the cutis.

Figure 1.



WHAT IS YOUR DIAGNOSIS?

See page 421 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 420)

A WOMAN WITH A PURPLISH-RED SKIN LESION ON THE NECK

DIAGNOSIS

We suspected a vascular malformation, with Kaposi sarcoma, angiosarcoma or haemangioma as our differential diagnosis. Histopathological examination revealed scattered multiple 'cannonball-like' lobules of closely packed capillaries without atypical endothelium. In the periphery characteristic crescent-shaped thin-walled vessels were present *(figure 2)*. Immunohistochemical staining for HHV-8 was negative, ruling out Kaposi sarcoma. These findings led us to the diagnosis of tufted angioma (TA). The patient did not want any treatment, because of the asymptomatic and benign nature of the skin lesion. After another follow-up of one year the lesion remained unchanged.

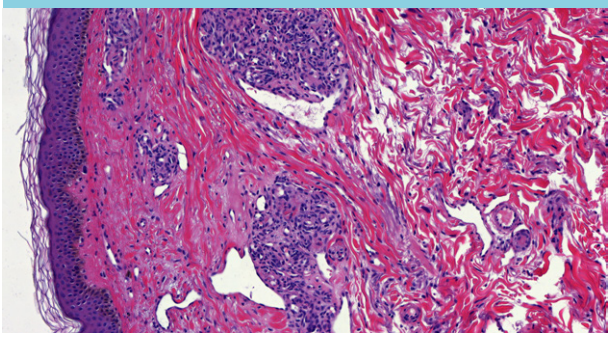
TA predominantly affects children, but can also rarely manifest in adulthood as reported in this case. More than 200 cases of TA, both congenital and late-onset cases, have been reported. In approximately 50% of these cases, TA is present within the first year of life and around 15% of the cases are present at birth.[1] One series of 41 cases reports that 34% of patients with TA were >10 years. All studies report that both sexes are equally affected.[2]

The lesions are predominantly located on the upper part of the trunk, neck or proximal extremities. The face or scalp can also be affected. It clinically presents with erythematous or purple macules, papules or plaques and is usually asymptomatic but can be painful, and in some cases hyperhidrosis and hypertrichosis are described.[1]

The differential diagnosis of TA comprises vascular lesions including infantile haemangiomas, congenital haemangiomas, vascular malformations and in acquired cases capillary haemangioma, Kaposiform haemangio-endothelioma and (malignant) neoplasms such as Kaposi sarcoma and angiosarcoma. Congenital TA can be associated with Kasabach-Merritt syndrome, a life-threatening complication, characterised by profound thrombocytopenia and consumption coagulopathy.

Tufted angioma may persist unchanged but also spontaneous regression has been described, after six months to two years.[3] It is a benign disorder and treatment is generally not needed. Several options such as surgical excision, cryosurgery, systemic steroid therapy, intralesional steroid injection, propranolol, interferon alpha therapy, radiotherapy and pulse dye laser have been proposed with different clinical outcomes.[4,5]

Figure 2.



The exact causes of TA have not yet been established, however some suggestions towards the role of immune suppression and the development of TA have been described.[4] One case of acquired TA occurred five years after renal transplantation. In one patient TA occurred after liver allograft transplantation and also a patient with Crohn's disease receiving immunosuppressive therapy has been described. We report similar findings in our case with adult onset development of a slowly increased and persistent TA in a patient on immunosuppressive therapy. However, no definitive conclusions can be made yet based on these few reports.

CONCLUSION

Tufted angioma has to be included in the differential diagnosis of congenital and acquired vascular disorders in both children and adults.

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LETTER

Assessment of physicians' cognitive biases

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INTRODUCTION

In healthcare, a certain level of confidence is necessary to make decisions. However, most beliefs are distorted by deep-seated overconfidence. Previous studies have assessed the level of overconfidence across industries and shown how workers are affected by it.[1] As overconfidence is a cognitive bias that hampers making appropriate decisions and potentially puts the patient at risk, we investigated whether physicians are also prone to overconfidence.

The same holds true for anchoring. Anchoring is the cognitive bias which results from the tendency to rely too heavily on the first piece of information a person receives when making a judgement. The information anchors in your mind and influences your judgement.

We hypothesized that physicians suffer from cognitive biases of overconfidence and anchoring. To test this hypothesis, we applied a previously validated "Confidence Quiz" among healthcare practitioners.[1]

METHODS

We used a confidence quiz to assess the level of overconfidence among physicians. Physicians were recruited after six consecutive workshops on leadership. Participants were asked to simply provide a low guess and a high guess for each of the 10 questions in the quiz (*table 1*), to indicate that they were 90% sure the true value would lie between the guesses. Hence, participants needed to provide answers so that nine out of 10 answers would be within their low and high guess interval. Of note, to assess your own confidence, please complete the quiz. The answers can be found in the appendix (the questions and answers have been updated for the year 2017). To investigate the effect of anchoring, one question (number 7) was introduced with either low, normal or high information. The question asked "how many passengers have died worldwide due to a commercial airplane accident in the previous 5 years (2013-2017)?" The question was

Table 1. *90% confidence interval questionnaire*

Question	
1	What is the gestation period of an African elephant in days?
2	What was the number of red blood cell transfusions in 2017 in the Netherlands?
3	What was the total national healthcare expenditure in 2017 in the Netherlands?
4	How often was TBC reported in 2017 in the Netherlands?
5	What was the proportion of health expenditure of GDP in 2017 in the Netherlands?
6	How many consultants were registered in 2017 in the Netherlands?
7	How many passengers have died worldwide due to a commercial airplane accident in the previous 5 years (2013-2017)?
8	What is the longest delay in minutes before starting CPR in which there was full recovery after an out-of-hospital cardiac arrest?
9	What is the number of states in Europe?
10	What is the national percentage of patients readmitted in 2017 within 30 days in a non-academic teaching hospital?

introduced with option A (high anchoring): "On March 8th 2014 239 passengers died in the crash of flight Malaysia Airlines"; or B (normal anchoring): "On December 28th 2014 162 passengers died in the crash of AirAsia"; or C (low anchoring): "On February 16th 2014 18 passengers died in the crash of Nepal Airlines".

All answers were filled in anonymously. Only answer sheets that were completed were included in the analysis. All anonymous data were extracted and processed by two independent researchers using the statistical software R. The responses of the numerical questions are expressed as mean ± standard deviation (SD). We compared groups with Wilcoxon test (nonparametric statistics). For multiple groups (n = 3) we used the Kruskal Wallis test.

RESULTS

In total, 318 physicians participated in the workshop and 261 physicians completed the quiz. The majority of participants had a background in internal medicine (65%), surgery (7%) or anesthesiology (8%); 77% of the respondents were residents and 21% consultants. The majority of respondents were female (65%).

Overconfidence

None of the 261 respondents achieved a 90% confidence score on the quiz (*table 2*). The reported confidence was around 25%, with intensive care and anesthesiology backgrounds resulting in higher confidence (35%). No effect was seen regarding level of experience, gender or age.

Anchoring

Physicians were susceptible to anchoring effects (*figure 1*). Questions with high anchoring resulted in significantly higher values compared to questions with low anchoring ($p < 0.001$).

Table 2. *Overconfidence among healthcare practitioners*

	Percentage of misses		Size**
	Ideal*	Actual	
Total	10%	73%	2610
Residents	10%	73%	2050
Consultants	10%	74%	560
Internal medicine	10%	74%	1720
Surgery	10%	65%	170
Intensive care	10%	65%	210
Other	10%	75%	510

*The ideal percentage of misses is 100% minus the confidence interval. Thus, a 10% ideal means that physicians were asked for 90% confidence intervals.
**The total of number of judgements made across persons and questions.

DISCUSSION

To our knowledge, this is the first assessment of the level of overconfidence among physicians. All participating physicians overestimated their accuracy and were prone to over-precision. Physicians rank in the same range of overconfidence as advertisers, computer specialists and security analysts. None of the participants scored a correct 90% in the 10-question quiz, compatible with the less than 1% correct confident score reported in the literature.[1] Previous studies in medicine have mostly looked at diagnostic error rates compared with self-reported confidence.[2] Of interest, in a vignette study, self-reported confidence levels were around 70%.[3] We show that the level of overconfidence is much higher than a physician's own belief.

We could not find large differences in personal characteristics or specialty training. Because internal medicine residents were overrepresented, differences could have been blurred in our study. Previous studies however have also shown that confidence or recognition of uncertainty do vary with physician experience.[2,4]

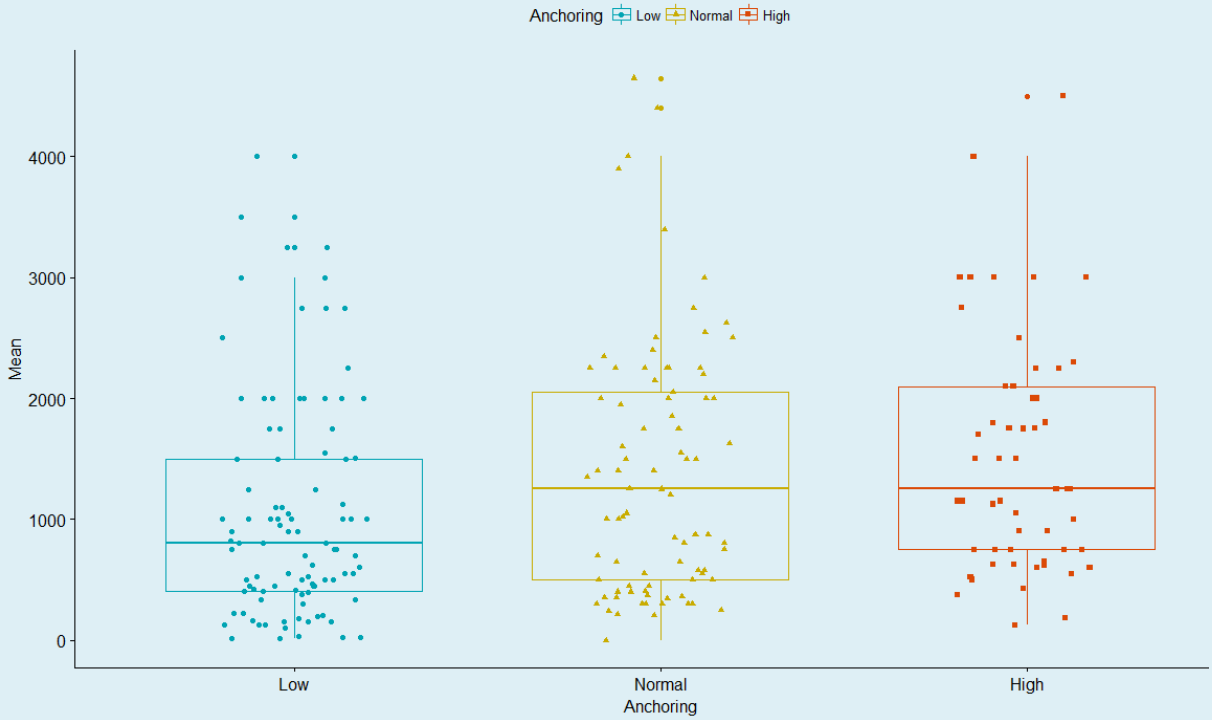
Overconfidence is caused by various biases or heuristics (mental shortcuts), especially the availability heuristic. In general, our decision system benefits from heuristics to find solutions when faced with complex problems or incomplete information, but in certain cases, they lead to systematic errors or cognitive biases. We specifically tested the anchoring phenomenon, a form of availability bias. Numerical information in the quiz allowed the participants to adjust their estimates accordingly, thereby demonstrating the effect of anchoring. Mamede et al. has shown before that an availability bias may occur in diagnosis as a consequence of recent experiences with similar cases.[5] Anchoring may lead to premature closure in the diagnostic process.

In summary, this study shows that physicians are highly susceptible to overconfidence and anchoring. Overconfidence may put patients at risk by influencing reasoning and decision making. Therefore, we believe it is important for physicians to become aware of this highly prevalent cognitive bias. Taking the Confidence Quiz can be a first step in creating this awareness.

DISCLOSURES

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

Figure 1. *The effect of anchoring on healthcare practitioners. To investigate the effect of anchoring, one question (number 7) was introduced with either low, normal or high information. The question asked "how many passengers have died worldwide due to a commercial airplane accident in the previous 5 years (2013-2017)?" The questions were introduced with option a (high anchoring): "On March 8th 2014 239 passengers died in the crash of flight Malaysia Airlines"; or b (normal anchoring): "On December 28th 2014 162 passengers died in the crash of AirAsia"; or c (low anchoring): "On February 16th 2014 18 passengers died in the crash of Nepal Airlines". In question 7 high anchoring resulted in a significantly higher answer compared to low anchoring ($p < 0.001$). Data are reported as mean passengers who died during commercial flights with individual data points.*



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