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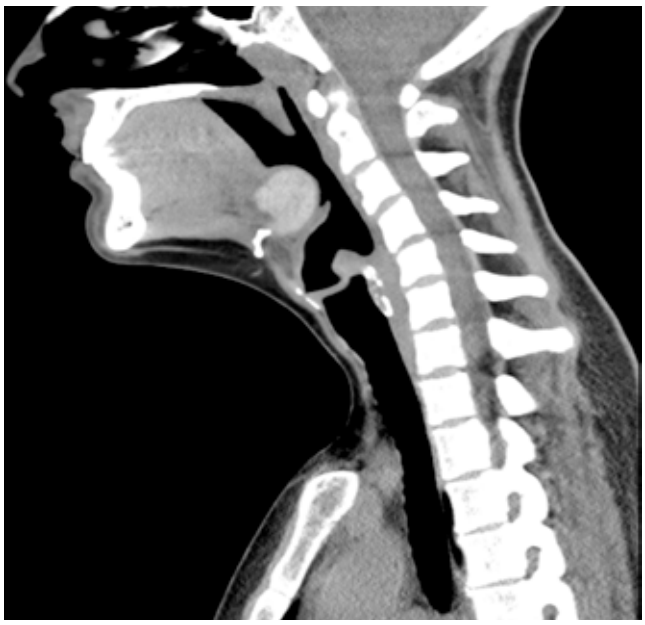

Undefined mass in head-neck region on iodine-123 scan: what is your diagnosis?

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Contents

EDITORIAL

Confronting complex infections in a tertiary healthcare setting

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Infections, particularly complicated urinary tract infections (cUTI), are responsible for a substantial part of emergency department visits in secondary and tertiary hospitals.[1,2] The Dutch Working Party on Antibiotic Policy (SWAB) has written guidelines for empiric antibiotic therapy for (c)UTIs based on antibiotic resistance rates to these drugs as monitored by Nethmap.[3] Are these guidelines, however, applicable to all Dutch healthcare settings? And more specifically, are these guidelines applicable to a tertiary healthcare setting, which often includes multimorbid patients with complicated UTIs? This is the focus of Wijting et al., who investigate both micro-organism distribution and susceptibility patterns.

In this observational retrospective cohort study, the authors show that the susceptibility rates of commonly isolated micro-organisms to empirical intravenous antibiotic therapy for patients with a cUTI in the emergency department of a Dutch university hospital is comparable to national epidemiologic data. Resistance to orally available antibiotics however, is higher for the most frequently cultured pathogens. A shortened time between presentation at the emergency department and last admission resulted in lower susceptibility rates of the isolated uropathogens to initiated antibiotic therapy, especially if readmission occurs within three months. Based on these data, the authors recommend treatment with empiric therapy as prescribed in national guidelines, which include cefuroxime (or a third-generation cephalosporin) and gentamicin. For strictly selected patients, e.g., with severely impaired renal function (eGFR < 30 ml/min) or renal transplants, they advise consideration of meropenem.

The article by Wijting et al. raises the concern of whether the tertiary healthcare setting is a risk factor for infections with resistant micro-organisms. Reports identifying independent risk factors for harbouring resistant micro-organisms, include the recent use of broad-spectrum antibiotics, health care exposures, and travel to parts of the world where multidrug-resistant organisms are more prevalent, as illustrated, for example, in the COMBAT study.[4-9] However, information is lacking regarding the Dutch tertiary healthcare setting as a risk factor. Thus, the authors provide valuable insight with their findings that susceptibility rates to cefuroxime/gentamicin drop well below 90% (the threshold that the authors also refer to for empiric treatment justification) in those who have been admitted to a tertiary healthcare setting within the previous 3 months, especially since these patients accounted for almost half of their studied population (40.3%). This could well reflect the increased risk of resistance attributable to tertiary healthcare settings and support the use of other antibiotic regimens to account for healthcare-associated flora. This includes for example, piperacillin-tazobactam/gentamicin, which is commonly used in these situations, although not discussed by the authors, and advised by institutional SWAB guidelines. A relevant follow-up question that Wijting et al. have not yet addressed in this study would therefore be to what extent antibiotic regimens should take the tertiary healthcare setting specifically into account in empirical therapy for cUTI in comparison to other healthcare settings. Such a follow-up study should also specifically define any identified highly resistant micro-organisms (HRMOs), such as pathogenic micro-organisms that are resistant to a combination of therapeutically-relevant antibiotics including first-line treatment choices.[10] The potential relevance of HRMOs in the tertiary healthcare setting as a risk factor for resistance is also illustrated by the difference in observed susceptibility to first-line orally available antibiotics such as fluoroquinolones or trimethoprim-sulfamethoxazol, compared to NethMap data. The risk of harbouring fluoroquinolone-resistant micro-organisms is driven by the prior use of fluoroquinolones.[11,12] Could the higher risk for fluoroquinolone resistance in the complex academic patient also be related to the academic setting or is it only

because of a higher chance of prior use of said antibiotics in these patients and settings? Nonetheless, additional studies including HRMOs would facilitate drawing better conclusions as to whether or not tertiary care is a risk factor for cUTIs with HRMOs, and what empirical regimen in which setting is best advisable, especially for those patients who are quickly readmitted.

We can extend the above concern to include other infections (e.g., pneumonia) after a recent admission to a tertiary healthcare setting, and the implications for definitions of hospital-acquired and healthcare-associated infections. The Dutch Working Party on Antibiotic Policy (SWAB) currently applies the definition of nosocomial acquired infection to infections acquired during a hospital stay (two days or more after admission) or acquired within 30-90 days after hospital discharge, regardless of the secondary/tertiary healthcare setting.[13] The potential difference in resistance rates between these healthcare settings touches a relevant point frequently encountered in daily medical consultation, which the authors also raised: until what point can we include cultural history into the choice of antibiotic therapy? Studies have already been published that carriership of a HRMO < 6 months is an independent risk factor for a repeat culture with HRMO, which will often lead to an HRMO-related infection.[12] The findings of Wijting et al. seem to support this statement with the lower susceptibility rates observed with a shorter time to readmission, although as mentioned, additional information on the HRMO in the studied population would be necessary. It is also important to note that previous resistance is a risk factor for resistance,[11,12,14] but a previously isolated susceptible micro-organism does not mean that the risk for resistance is lower. The fact that cultures have been previously taken increases the chance of antibiotic use, which is indeed, a risk factor for resistance. The question remains: should we extend the definition of terms such as healthcare-associated infections, or introduce a new definition to also account for the previous healthcare setting, in addition to the frequency and timing of admissions and culture history? This may be relevant for empiric treatments for certain patient categories with complex infections in the tertiary healthcare setting, including cUTIs, and warrants further investigation.

According to the authors, empiric antibiotic therapy is still sufficient for most cUTIs in a tertiary healthcare setting. Unfortunately, for patients most at risk for resistance (i.e., patients in tertiary healthcare settings with frequent readmissions or readmissions < 3 months) empirical therapy has the largest liability with perhaps even fewer safe options for specifying empirical regimens. In addition, options for oral antibiotics are limited, implying that these patients will have to be admitted and thus, potentially confronted with the tertiary healthcare setting as risk factor for additional HRMOs. What this will mean for the future is yet to be seen. Can we restrain this vicious circle with a policy of restricted antibiotic prescriptions? There is a need to continue to address this issue in order to combat antibiotic resistance, regardless of healthcare setting.

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ORIGINAL ARTICLE

Retrieval of chronic hepatitis B patients in the Utrecht region in the Netherlands

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ABSTRACT

Background: In the Netherlands, approximately 200 patients die annually from a chronic hepatitis B (CHB) infection, even though effective antiviral treatment is available. There are an estimated 49,000 Dutch CHB patients. Many of these patients have been lost to follow-up (LFU) over time. The study aimed to trace LFU CHB patients in the province of Utrecht and bring them back into care.

Methods: Positive hepatitis B surface antigen (HBsAg) tests from 2001-2015 were collected from the four hospitals in the Utrecht province and linked to medical records. The general practitioners (GPs) were requested in writing to evaluate LFU CHB patients and to refer patients when needed. In addition, GPs were asked to fill out a questionnaire on the patients' characteristics and to indicate reasons for not being able to perform an evaluation.

Results: A total of 2,242 chronic CHB patients were identified based on HBsAg-positive serology. After review of their medical records, 599 (27%) patients were eligible for retrieval. Of those, the GP response rate was 49% (n = 292) and 62 patients (10%) of the eligible CHB patients could be evaluated. Of these, 20 patients (3%) were referred to a hospital and 42 patients (7%) did not have an indication for referral.

Conclusion: Lost to follow-up CHB patients can be traced through screening of past positive HBsAg tests. There was willingness among GPs to participate in the retrieval of CHB patients. This may contribute to the reduction of the CHB-related burden of disease.

KEYWORDS

Chronic hepatitis; hepatitis B virus; retrieval; REACH

INTRODUCTION

In the Netherlands, approximately 200 people die annually from the consequences of hepatitis B virus infection.[1] With an estimated prevalence of 0.34% for chronic hepatitis B (CHB) in the Netherlands, there are roughly 49,000 patients who are chronically infected.[2] The current availability of new and effective treatment modalities for CHB leads to more patients being eligible for treatment, which reduces liver-related morbidity and mortality. However, many patients who were once diagnosed with CHB are no longer in care and are therefore unaware of these new treatments.[3] Several regional CHB retrieval projects described a loss to follow-up (LFU) rate up to 65%.[4-6] For this reason, in 2014, the Dutch National Institute for Public Health and the Environment (RIVM) requested that the various parties involved retrieve and evaluate patients once diagnosed with CHB and offer them treatment.[7] This aligns with the goals of the Dutch national plan on viral hepatitis and the World Health Organization (WHO) targets to prevent or even eliminate further distribution and burden of disease as a consequence of viral hepatitis.[8,9]

In September 2016, the University Medical Centre Utrecht (UMCU) partnered with hepatitis treatment centres and the Public Health Services (GGD) in the Utrecht region and initiated the REACH (REtrieval And Cure of Chronic Hepatitis C) project. This project entailed retrieval of patients with chronic hepatitis C who were no longer in care to provide them with a (serologic) evaluation and an appropriate treatment plan.[10] Following the REACH project, the GGD started with the retrieval of patients who were previously diagnosed with CHB but were LFU. In contrast to patients with hepatitis C, not every patient with hepatitis B qualifies for treatment. This made the retrieval project for these patients less applicable. As the

decision to begin treatment is dependent on multiple parameters such as the hepatitis B virus (HBV) viral load, liver fibrosis stage, and degree of inflammation, and adequate care for a patient with CHB includes not only treatment in a hepatitis treatment centre, but also periodic follow-up by the general practitioner (GP).[11,12] This article describes the results of this hepatitis B retrieval project in the Utrecht region in the Netherlands which constitutes the largest CHB retrieval project to date.

MATERIALS AND METHODS

The four hospitals in the Utrecht region (University Medical Centre Utrecht (in collaboration with Gelderse Vallei Hospital), Diakonessenhuis, St. Antonius Hospital, and Meander Medical Centre; all designated hepatitis treatment centres) participated in this project. For each hospital, a list was compiled of all patients with a positive HBsAg result in the period from 2001 to 2015. The chosen 15-year time period was based on the care provider's duty of care, which includes keeping patient medical records for 15 years after the end of treatment and informing the patient when new treatments become available. In accordance with this duty of care legislation and the Dutch Medical Treatment Act (WGBO), the medical microbiologists directly involved in the treatment were allowed to exchange information with the patient's GP.[7] Electronic medical records were reviewed to determine whether a patient qualified for (serologic) evaluation by the GP. Patients qualified if they (1) had a chronic hepatitis B infection (i.e., the last available HBsAg was positive and measured between January 1st, 2001 and December 31st, 2015); (2) were not currently undergoing treatment or being followed-up by a medical specialist (i.e., no appointment was scheduled after January 1st, 2016); (3) lived in the Utrecht region; and (4) the name and address of their GP was available. Other relevant information on demographic, clinical, and laboratory data, such as country of origin and hepatitis A status, were extracted from the electronic medical records. Of the patients who qualified based on the predefined inclusion criteria, the GP was requested in January 2018 in writing, to evaluate the patient in agreement with the 'guideline on viral hepatitis' from the Dutch College of General Practitioners (NHG) and to refer the patient accordingly if necessary (i.e., in case of raised alanine aminotransferase (ALT) levels, a positive HBeAg or an HBV-DNA ≥ 2000 IU/mL).[11] Moreover, GPs were asked to fill out a questionnaire with questions on patient characteristics (see table 1) and hepatitis A status, and to indicate reasons for not being able to perform a re-evaluation. If a patient was no longer registered at the GP's practice, the GP was asked to contact the investigator and, if known, provide the name of the current GP. Both data from the questionnaires and information from contact with the GPs via telephone or email were collected. The GPs were asked to evaluate the patient and/or return the questionnaire within six months. Thereafter, it was ascertained whether the patients who were referred by the GP did indeed visit the hospital.

The execution of this retrieval project took approximately 350 hours. The majority of time was spent on the review of the patients' electronic medical records. The Medical Research Ethics Committee (METC) of the University Medical Centre Utrecht (METC code 041, file number 12-409) declared that the Dutch Medical Research Involving Human Subjects Act (WMO) did not apply to this project and had no objection to the execution of this study.

Table 1. *Patient characteristics*

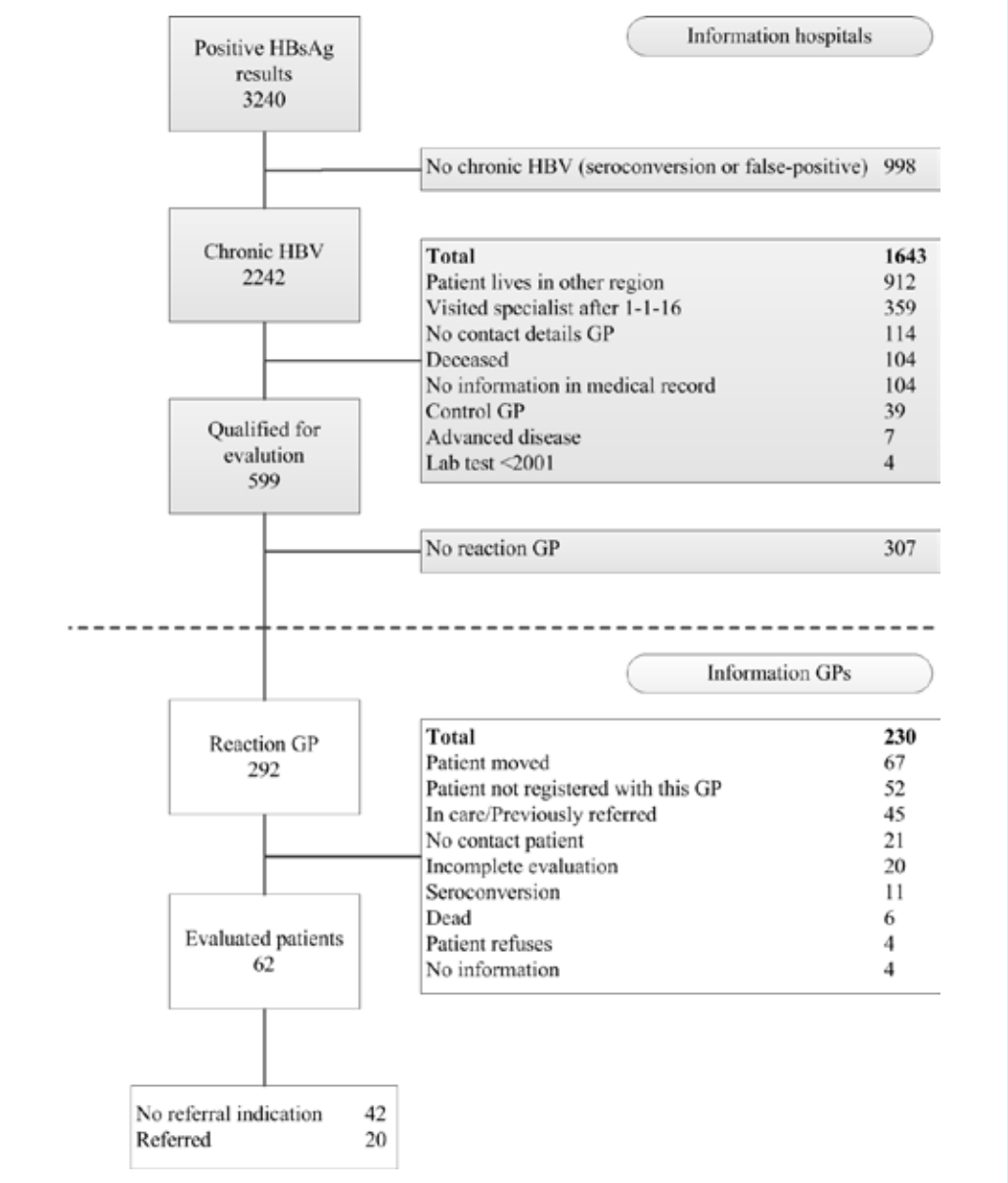
Patient characteristics	Patients who qualified for evaluation n = 599
Average age, years (SD, range)	46 (13, 11-91)
Male sex, n (%)	299 (50)
Country of origin, n with known country of origin	n = 316
The Netherlands, n (%)	55 (17)
Turkey, n (%)	42 (13)
China, n (%)	39 (12)
Morocco, n (%)	31 (10)
Suriname, n (%)	14 (4)
Other, n (%)	135 (43)
Hepatitis A, n immune / n with known hepatitis A status (%)	287/343 (84)

n = number; SD = standard deviation.

Statistical analysis

Continuous data are reported as means with standard deviation (SD) and discrete variables in absolute and relative frequencies. Descriptive statistics were generated with IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

Figure 1. *Flowchart patient selection process*



HBsAg = Hepatitis B surface antigen; HBV = hepatitis B virus; GP = general practitioner.

RESULTS

Initially, 3,240 unique positive HBsAg test results between the years 2001 and 2015 were extracted from the laboratory records of the four participating hospitals (figure 1). After review of the patients' medical records, 2,641 patients were not suited for retrieval: 998 patients (38%) did not have a chronic hepatitis B infection (e.g., seroconversion or false positive), 912 patients (35%) never lived in or no longer live in the Utrecht region, and 359 patients (14%) had visited a specialist for their CHB after January 1st, 2016 and were therefore not considered to be LFU.

A total of 599 evaluation requests and questionnaires were sent to GPs and 14 letters were resent after having received updated contact information of the GP. The demographic and clinical characteristics for the 599 patients who qualified for evaluation are summarized in table 1. The patients had an average age of 46 years (± 13 SD) and 50% were male. The country of origin was known in 53% (n = 316) and this group predominantly consisted of Dutch (17%, n = 55), Turkish (13%, n = 42), and Chinese (12%, n = 39) patients. The hepatitis A status was determined in 343 patients (57%) and 287 (84%) of those were found immune for this viral infection.

The GP response rate was 49% (n = 292) and the replies consisted of 147 filled out questionnaires and 145 emails and phone calls. Of those, 79% (n = 230) could not be evaluated, mainly because the patient had relocated (29%, n = 67) or was no longer registered with the GP (23%, n = 52), and follow-up information was unavailable. The remaining part (21%, n = 62) was evaluated by the GPs.

Of the evaluated patients, 42 patients (68%) did not have an indication to be referred to a hospital according to the NHG guideline and 20 patients (32%) were referred. Of the referred patients, 14 had visited a hepatitis treatment centre, an appointment was planned for two patients, and four patients had made an appointment but did not attend. Of the 14 patients who have already visited the outpatient clinic, one started treatment. For the other 13 patients, at the writing of this manuscript, there is either no indication to start treatment (n = 10) or they are still awaiting the results of additional laboratory testing (n = 3).

DISCUSSION

This study aimed to trace all LFU CHB patients in the Utrecht region in the Netherlands by means of screening past positive HBsAg results. At the end of the study, 10% of all LFU CHB patients eligible for retrieval had been evaluated by their GP and 3% were referred to a hepatitis treatment centre. The GPs were willing to participate in CHB care and retrieval as is reflected by the response rate of 49%. To our knowledge, this is the largest CHB retrieval project that has been conducted to date. Other Dutch CHB retrieval projects previously achieved response or evaluation rates of 44-70% but these cannot be directly compared with the current study due to different methods and LFU definitions that were used in each project.[4-6] In the study of Beekmans et al., 44% of the invited patients were finally evaluated at the hospital. However, deceased patients and patients with an unknown GP had been completely excluded from the analysis which could partly explain the higher success rate.[6] The study of Spruijt et al. reported a GP response rate of 70% but this involved both hepatitis B and C patients and also included false-positive results.[4] Beekmans et al. described that three CHB patients had an indication for antiviral therapy but not how many actually started treatment. One patient initiated treatment in the current study but this number may still increase since three patients were still awaiting the results of additional investigations.[6]

A total of 2,242 CHB patients were identified in the Utrecht province after evaluation of a 15-year time period. However, almost double the number of CHB-infected patients would be expected based on the prevalence of 0.34% and the Utrecht population size of almost 1.3 million inhabitants. Our numbers align with the nationwide notification data on CHB from the RIVM who also report a ~ 50% diagnosis rate when compared to the total population size estimates.[13] All though differences in our study population size may partly be explained by local CHB prevalence differences and the exclusion of GP laboratory records from this project, it also suggests that a substantial number of CHB infected remain undiagnosed.

Because this project focused on the Utrecht region, 912 (41%) of the identified CHB patients who currently reside outside of Utrecht were excluded. This high number of non-Utrecht residents is probably inherent to the large total adherence area of the four hospitals combined. Also, GPs described asylum seekers as a very dynamic population as they were often relocated after initial testing for CHB had been performed by a nearby asylum seekers' centre. Retrieval projects specifically targeting this risk group would therefore be a worthwhile future endeavour in our opinion. These could complement the Health Council's (HC's) recommendations to screen all asylum seekers from endemic countries for CHB.[14] First-generation migrants are also included in the HC's advice as they are, by far, the largest subgroup affected by CHB in the Netherlands.[2] More specifically, Turkey, Somalia, and China are the main countries of origin in Dutch CHB-infected first-generation migrants.[15] This is also reflected in our population eligible for retrieval which included 83% of non-Dutch individuals and Turkey and China as the largest migrant groups. Only the Somalis seemed underrepresented in our study population compared to the nationwide estimates, however this could be due to the high proportion of unknown countries of origin in our group.

This retrieval had a positive effect on the renewed linkage to care of CHB patients and possible treatment initiation among GPs in the Utrecht region. In addition, a reinstituted periodic follow-up of CHB patients without referral indication is also considered a positive outcome of this retrieval effort. Through this project, the GPs have become reacquainted with the 2016 updated NHG guideline on viral hepatitis which now recommends indefinite periodic control of ALT and HBsAg in "inactive CHB carriers".[11] We anticipate that an increased number of GPs will resume this regular follow-up of CHB patients after this reintroduction.

Another positive effect that was expected from this project is the raised awareness of CHB among GPs which may result in evaluation of other LFU CHB patients and also increased screening practices. Indeed, preliminary notification data of the GGD suggest enhanced screening efforts: the number of reported CHB in the six months after this project had increased to 44 in comparison with 32 notifications during the same period in 2017. However, subsequent studies may need to confirm this assumption by following-up with the participating GPs over a longer

period of time. A final positive side effect of this project was the multidisciplinary collaboration for this project, leading to a reinforcement of the regional healthcare network.

The main drawback of this project was that the GPs' laboratory records at the medical diagnostic centre Saltro, could not be included. Therefore, the LFU CHB patients who had never been referred to a hepatitis treatment centre could not be retrieved. Future retrieval initiatives should focus on tracing these specific LFU CHB patients and bringing them back into care.

For the benefit of future HBV retrieval efforts, the key lessons learned were distilled from this project. First, written evaluation invitations should be short and straightforward and additional information for research purposes is preferably requested separately in order to optimize the evaluation response rates. For further time saving purposes, the NHG referral guidelines may best be summarized in the invitation letter. Second, it could be beneficial to offer the GP remote (tele-) supervision from a hepatitis specialist since they often perceive hepatitis B serology as difficult to interpret and only have a few chronic HBV patients in their practice. Third, in order to optimize the GPs' response rate, it is essential to learn more about the GPs' perceived barriers and facilitators to participation in HBV retrieval projects.

CONCLUSION

Lost to follow-up CHB patients can be traced through screening of past positive HBsAg tests and GPs are willing to participate in the retrieval of CHB patients. This may contribute to the reduction of the CHB related burden of disease.

DECLARATIONS

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Conflict of interest statement

Dr. Arends reports fees from Abbvie, BMS, Gilead, Janssen, MSD and ViiV and research grants from Abbvie and BMS, outside the submitted work, all paid to his institution. Dr. Boland is Chairman of the Hepatitis Information Foundation, which is supported by AbbVie, Gilead, BMS and GlaxoSmith Kline. Fees go to the department of Medical Microbiology, UMC Utrecht. Dr. Hoepelman reports personal fees from Abbvie, BMS, Gilead and Janssen. All other authors declare that they have no competing interests with respect to the presented work.

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ORIGINAL ARTICLE

Metabolic syndrome is not uncommon in treatment-naïve rheumatoid arthritis patients

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ABSTRACT

Objectives: Rheumatoid arthritis (RA) is an independent risk factor for cardiovascular disease (CVD). Glucocorticoids are often used in the management of RA and might also contribute to the increased risk of metabolic syndrome (metS). Identifying metabolic alterations earlier and treating them together with disease-modifying therapy may be associated with better outcomes. Here, we aimed to investigate the frequency of metS and its components in treatment-naïve RA patients.

Methods: Fifty-three newly diagnosed treatment-naïve RA patients and 55 control subjects were enrolled. MetS was diagnosed using Adult Treatment Panel III report-defined criteria. We evaluated the metS-related metabolic and anthropometric alterations between the groups. RA patients were subdivided and those with and without metS were also compared with respect to disease-related parameters.

Results: MetS was more common in treatment-naïve newly diagnosed RA patients compared to controls (25 of 53 (47.1%) vs 9 of 55 (16.4%), respectively ($p = 0.001$; OR, 4.56; 95% CI 1.86-11.16). All evaluated anthropometric and metabolic parameters were similar in both groups. However, there was a trend to lower LDL and HDL cholesterol levels in RA patients. Furthermore, among those with metS, the number of fulfilled metS criteria items were higher in RA patients, compared to controls ($p < 0.001$). Interestingly, more RA patients fulfilled metS criteria with a glucose measurements item compared to controls ($p < 0.001$).

Conclusion: MetS was more common in newly diagnosed and treatment-naïve RA patients compared to controls. MetS, along with tendency to present paradoxical and atherogenic lipid profiles in RA patients, may be among the underlying mechanisms of increased CVD.

KEYWORDS

Rheumatoid arthritis, nutritional and metabolic diseases, cardiovascular diseases, disease activity, metabolic syndrome

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic auto-inflammatory disease with chronic joint damage and disability. Early diagnosis and proper treatment are the key factors for treatment success.[1] Cardiovascular disease (CVD) is the most commonly identified cause of death in RA.[2] In RA patients, metabolic features may be altered. These alterations may be the underlying mechanisms of increased CVD rate. Body composition changes, increased insulin resistancy, alterations in lipid parameters and adipokine levels would be the most significant impairments related to RA. Herein, some of these changes may also be seen in metabolic syndrome (metS).[3]

Not only traditional CVD risk factors, but also systemic inflammation may account for increased frequency of CVD events in RA.[4] Lipid parameters may change in both a quantitative and qualitative manner during inflammatory conditions. Furthermore, more atherogenic sub-fractions were highlighted during the disease.[5] These changes in lipid parameters are termed as lipid paradox. Metabolic alterations during active disease, including paradoxical changes in lipid profile, could increase the risk of cardiovascular mortality.

It is known that metabolic changes may be seen even in preclinical RA. Also, during the course of the disease, especially in cases with high disease activity, metabolic changes may be more significant.[6] Therefore, the European League Against Rheumatism (EULAR) task force recommends both controlling disease activity and treating

traditional CVD risk factors together for preventing disease-related disability and lowering CVD risk.[7]

MetS may be more frequent in patients with RA. Furthermore, it was found that throughout the disease course, overall risk for developing metS was higher in RA patients when compared to healthy controls.[8] So, detection of metabolic disorders at early stages of the disease along with effective disease activity control may reduce the risk of CVD.[9] It is also known that like full-blown metS, every particular metabolic alteration in metS might be associated with CVD related mortality.[10] Therefore, evaluating and treating every particular metabolic alteration may also be significant for lowering CVD risk in RA.

Glucocorticoids are usually used in the management of RA; however they may also contribute to the increased risk of metS. Furthermore, other disease-modifying treatments may also have effect on metS frequency. To ourknowledge, there has not been a study in the literature that evaluated the features of metS in treatment-naïve RA patients even before starting any disease-modifying anti-rheumatic drugs (DMARD) treatment. In this study, we examined the hypothesis that metS is more frequent in treatment-naïve RA patients than controls without inflammatory diseases, even before starting any DMARD treatment. Therefore, we could exclude the interference of standard DMARD treatment (including glucocorticoids) on metabolic and anthropometric components. Then, we compared the frequency of metS-related metabolic and anthropometric alterations between RA patients and healthy controls. Lastly, we evaluated the differences of disease-related parameters between the RA patients with or without metS.

MATERIAL AND METHODS

The study was performed in Kartal Dr. Lutfi Kirdar Training and Research Hospital between the dates of January 2017 to January 2018. We enrolled 53 patients with RA who fulfilled the 2010 American College of Rheumatology/EULAR RA Classification Criteria.[11] All patients were diagnosed with RA for the first time in our outpatient rheumatology clinic. None of the patients had received any treatment, including glucocorticoids due to their symptoms. All consecutive newly diagnosed RA patients accepted to enrol in the study. At the same time, we enrolled 55 age- and sex-matched subjects as a control group from the same outpatient clinic. None of the controls were previously diagnosed for rheumatologic diseases. Moreover, all of the controls presented at the hospital with the complaints of non-specific symptoms including arthralgia, non-specific pain, and constitutional symptoms. None of the subjects in control group had any pathologic findings in their physical examination. Likewise, none had increased acute phase reactants or positive serologic tests. For control group selection, we appointed 504 subjects as possible controls between the dates of January 2017 to January 2018. Then, we randomly enrolled 55 age- and sex-matched subjects as control group from among those 504 subjects. In this study, we diagnosed patients and controls as metS using 2001 Adult Treatment Panel III report (ATP III)-defined criteria for the metabolic syndrome.[12]

RA related features

RA patients were evaluated for duration between RA-related symptoms onset to diagnosis, visual analogue scale (patient global health), number of tender and swollen joints, rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), sedimentation rate, C-reactive protein (CRP), and disease activity. We measured disease activity with disease activity score 28 joint C-reactive protein (DAS28-CRP).[13]

Metabolic and anthropometric components

All study participants were evaluated for medical history of diabetes mellitus (DM), hypertension (HT), and coronary heart disease; metabolic parameters included triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), fasting glucose; anthropometric parameters included waist circumference, hip circumference, height and weight, and lastly systolic and diastolic blood pressure measurements. Blood pressure was measured in sitting position after 30 minutes of rest in a quiet environment using a mercury sphygmomanometer. Body mass index (BMI) was calculated as previously shown.[14] All anthropometric parameters measured according to Centers for Disease Control and Prevention Anthropometry Procedures Manual.[15] This study was approved by the Local Research Ethics Committee and carried out in compliance with the Helsinki Declaration. All the patients gave written informed consent.

Statistical analyses

Statistical analyses were carried out using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). In order to determine if the data were normally distributed, the Kolmogorov-Smirnov test was performed. All continuous variables distributed non-normally. The comparisons of the continuous variables between patients were performed by the Mann-Whitney U test. Moreover, comparisons of the categorical variables were implemented by Chi-square test. Cut off values for HDL, and hip and waist circumferences have gender differences for fulfilling ATP III criteria. Therefore, we compared these parameters for different genders separately. First, we compared the metS frequency, and metabolic and anthropometric parameters between RA and controls. Then, the RA patients were sub-divided

into two groups according to fulfilling ATP III criteria as those with metS and without metS.[12] Disease-related parameters were compared between these groups. The results are given as median (interquartile range). We performed Bonferroni correction for protecting type 1 error. In our study, we compared 35 different variables between the groups. Therefore, after correction, $p \leq 0.001$ was considered as statistically significant.

Table 1. *Metabolic syndrome-related parameters of the study participants*

	RA (n = 53)	Control (n = 55)	p
Gender (M/F)	12/41	12/43	0.91
Age (year)	51.0 (37.5-60.0)	51.0 (37.0-58.0)	0.80
Smoking (%)	5 (9.4)	16 (29.1)	0.01
MetS (%)	25 (47.2)	9 (16.4)	**0.001***
Body mass index (kg/m^2)	28.9 (25.2-32.4)	30.0 (27.3-31.6)	0.19
Waist circumference (cm)			
Male	96.5 (86.0-98.7)	100 (92.2-108.0)	0.18
Female	96.0 (86.0-103.0)	90.0 (79.5-95.2)	0.02
Hip circumference (cm)			
Male	100.5 (93.7-115.5)	107.0 (101.2-112.7)	0.56
Female	110.0 (100.2-117.7)	107.0 (100.5-114.0)	0.14
Fasting glucose (mg/dL)	97.0 (87.0-108.5)	94.0 (88.7-103.5)	0.75
Triglycerides (mg/dL)	114.0(87.0-162.2)	113.0 (89.7-169.0)	0.70
HDL (mg/dL)			
Male	41.5 (37.7-45.0)	48.5 (42.5-52.7)	0.05
Female	48.5 (41.0-56.7)	52.0 (47.0-59.3)	0.03
Total cholesterol (mg/dL)	191.0 (167.0-208.0)	218.0 (183.0-257.0)	0.002
LDL (mg/dL)	124.0 (103.5-151.0)	141.0 (109.0-166.2)	0.04
Hypertension (%)	16 (30.2)	9 (16.4)	0.08
Diabetes mellitus (%)	6 (11.3)	1 (1.8)	0.04
Coronary heart disease (%)	2 (3.8)	0(0)	0.23
Systolic blood pressure (mm-hg)	127.5 (110.0-140.0)	120.0 (110.0-140.0)	0.50
Diastolic blood pressure (mm-hg)	80.0 (70.0-90.0)	80.0 (70.0-82.0)	0.65
Total number of positive metS criteria	2.0 (2.0-3.0)	1.0 (1.0-2.0)	**< 0.001***
Numbers of patients who fulfil particular metS criteria (%)			
Waist circumference	31 (58.5)	25 (45.5)	0.17
Triglycerides	15 (28.3)	19 (34.5)	0.48
HDL	24 (45.3)	16 (29.1)	0.08
Blood pressure or HT	26 (49.1)	20 (36.4)	0.18
Fasting glucose or DM	23 (43.4)	1 (1.8)	**< 0.001***

M = male; F = female; HDL = high density lipoprotein; LDL = low density lipoprotein; metS = metabolic syndrome; HT = hypertension; DM = diabetes mellitus.
Numbers: median (range); $p \leq 0.001$ was shown with bold numbers

RESULTS

Demographic and disease-related features of the study participants

In both groups, male:female ratio was 1:3.5. The median age in both groups was 51.0 years. Furthermore, the median duration between symptom onset to diagnosis was 6.0 (2.25-14.2) months. Herein, 32/53 (60.3%) of the patients were diagnosed as RA within six months of symptom onset. Anti-citrullinated protein antibodies (ACPA) were positive in 25/53 (47.1%) of the patients. The median DAS28-CRP score of the patients was 5.3 (4.1-5.2).

Metabolic and anthropometric features of the study participants

The number of subjects with metS were 25/53 (47.1%) in the RA group and 9/55 (16.4%) in controls. MetS was found statistically more frequent in RA patients than controls ($p = 0.001$; OR, 4.56; CL%95 1.86-11.16). All anthropometric parameters were similar in both groups. Likewise, there were no statistically significant differences between groups according to lipid parameters. However, total cholesterol, and LDL and HDL levels were lower (but not significantly so) in RA patients as compared to controls. Furthermore, systolic and diastolic blood pressures, fasting glucose levels, and DM, HT, CVS disease frequencies were similar in both groups. There were five different components in ATP III criteria for metS. The only component with different frequency between RA and controls was fasting glucose/established DM item. The number of patients who fulfilled this particular criteria item was higher in RA patients ($p < 0.001$). RA patients fulfilled three of the remaining four components more frequently than the control group. However, these differences were not statistically significant. Herein, controls fulfilled the triglyceride item more frequently than RA patients. Additionally, RA patients fulfilled significantly higher number of particular criteria components as compared to controls ($p < 0.001$) (table 1).

Demographic and disease-related parameters between patients with or without metS

Demographic features, disease activity, frequency of sero-positivity, and duration between symptom onset to diagnosis were similar between the patients with or without metS. However, disease activity was non significantly higher in the patients with metabolic syndrome. Furthermore, patients with metS were older. Nevertheless, this difference was not statistically meaningful (table 2).

DISCUSSION

In our study, we showed that metS frequency in treatment-naïve, newly diagnosed RA patients was higher

Table 2. *Demographic and rheumatoid arthritis-related parameters of the patients*

	Patients with metabolic syndrome (n = 25)	Patients without metabolic syndrome (n = 28)	p
Gender (M/F)	6/19	6/22	0.82
Age (year)	56.5 (50.0-66.7)	42.0 (36.2-57.7)	0.02
Smoking (%)	2 (8.0)	4 (14.3)	0.35
Duration of symptom onset (month)	5.5 (2.0-14.2)	6.0 (3.0-21.0)	0.67
Number of tender joints	4.0 (1.2-10.7)	7.0 (2.0-10.0)	0.96
Number of swollen joints	1.5 (0.0-8.0)	1.0 (1.0-4.0)	0.96
VAS (patient global health)	60.0 (40.0-80.0)	60.0 (40.0-80.0)	0.85
DAS28-CRP	5.6 (4.8-6.2)	4.9 (4.0-5.5)	0.02
Sedimentation rate (mm/h)	29.0 (18.0-47.0)	30.0 (15.2-46.7)	0.55
CRP (mg/L)	5.6 (3.2-21.5)	6.4 (3.2-17.6)	0.94
ACPA positivity (%)	11 (44.0)	14 (50.0)	0.66
RF positivity (%)	12 (48.0)	14 (50.0)	0.65

VAS = Visual analogue scale; DAS28-CRP = Disease activity score 28 joint C-reactive protein; CRP = C-reactive protein; ACPA = Anti-citrullinated protein antibody; RF = Rheumatoid factor.
Numbers: median (range)

than the controls from the same outpatient clinic without inflammatory diseases. All anthropometric and metabolic parameter were similar in both RA patients and controls. However, HDL, total cholesterol, and LDL levels were not significantly lower in treatment-naïve RA patients than controls. Furthermore, the numbers of patients who fulfilled fasting glucose/established DM item were significantly higher in treatment-naïve RA patients. Our study is unique because most of the patients had early RA. Additionally, unlike other early RA cohorts, none of our patients had been previously treated.

MetS frequency in early RA patients was previously found between 16-31% depending on the criteria used for diagnosing metS.[6] In our study, 47.1% of the treatment-naïve RA patients fulfilled the ATP III metS criteria. This was statistically higher than metS frequency in our control group from the same outpatient clinic without inflammatory diseases (16.4%). Furthermore, 33.9% of the Turkish background population was diagnosed as metS according to a nationwide study.[16] Accordingly, these results might have showed that even in early, treatment-naïve and newly diagnosed RA patients, the frequency of metS would be higher than in the normal population. Likewise, it was shown that leptin/adiponectin ratio may increase even at the pre-RA stage. Increased inflammatory cytokines during active disease is thought to be responsible for increased leptin/adiponectin ratio.[17] Therefore, increasing levels of pro-inflammatory and pro-atherogenic adipokines and cytokines may relate to higher frequency of metS in early and treatment-naïve RA patients.

In our study, RA patients had lower HDL, LDL, and total cholesterol levels compared to controls. All differences were found non-significant after Bonferonni correction. However, our results may show tendency to lower cholesterol levels in treatment-naïve, newly diagnosed RA patients. HDL, LDL, and total cholesterol levels usually reduced depenent upon inflammation.[18] Lipid profile alterations in our study were also concordant with previous studies in RA patients.[19,20] As shown previously, decreased HDL, LDL, and total cholesterol levels have been accepted as CVD risk factors in RA patients.[3,21] Suppressing inflammation with synthetic or biological disease-modifying drugs (DMDs) may paradoxically increase the LDL and total cholesterol levels.[20] But, contrary to expectations, these metabolic effects of the DMDs lowers the risk of CVD.[22] Other than quantitative lipid changes, RA patients may have pro-atherogenic structural and functional changes in lipid sub-fractions. These changes may also be the reason for increasing CVD in RA. During active disease, even with low levels of LDL and total cholesterol, the frequency of CVD increases.[5] Here, HDL particles become less protective against atherosclerosis. Moreover, LDL particles become more oxidised and atherogenic.[5,23] Therefore, according to our results, as expected in an active disease state, newly diagnosed and treatment-naïve RA patients may have a tendency towards atherogenic lipid level alterations. All of these alterations were independent of the influence of DMDs.

Previous studies showed that RA patients had increased waist circumference, elevated blood pressure, and high fasting glucose levels compared to the healthy population.[6] Also, in an early RA cohort, high BMI and increased disease activity were found to be associated with metS.[24] We found that BMI of our patients and controls were similar.[25] In our study, we demonstrated that all anthropometric parameters were similar between the patients and controls. Furthermore, 23/53 (43.4%) of the patients compared to 1/55 (1.8%) of the controls fulfilled metS criteria for fasting glucose/DM, and both fasting glucose levels and DM frequency were similar between the groups. However, there was a tendency for higher fasting glucose levels in RA patients compared to controls, and DM frequency was non-significantly higher in patients than controls. It was shown that insulin resistance increases in RA patients.[26] Moreover, during high disease activity, pancreas beta-cell activity usually reduces.[25] In our study, we did not evaluate insulin sensitivity. Therefore, we could only speculate that increased insulin resistance may also be found in treatment-naïve RA patients. This may explain the alterations in glucose parameters.

The frequency of metS was increased, in particular, in established RA patients with higher disease activity.[27,28] In our study, new diagnosed patients with metS had higher disease activity compared to the non-metS group. However, this difference was not significant after Bonferroni correction. Tumour necrosis factor may be increased during active inflammatory states. Both high inflammatory conditions and high tumour necrosis factor levels may alter body mass, lipid, and adipokine profiles. Even though rheumatoid cachexia is more frequent in uncontrolled RA, visceral fat mass may increases during active disease. It was found that visceral fat mass is associated with hypertension, higher fasting glucose, and metabolic syndrome.[29]

This study had some limitations. First, a limited number of patients was enrolled to the study; however, all patients were treatment-naïve and newly diagnosed. Second, we did not evaluate the pathophysiological aspects of the actual metabolic alteration that we illustrated in the study. These included insulin sensitivity, levels of adipokines, and pro-inflammatory cytokines. Therefore, we could only speculate how these metabolic changes would have emerged. Lastly, even though both metabolic and anthropometric components were similar between the groups, we found a metS more frequently in RA patients than controls. This may be because we diagnosed metS with by individual patient's performance with criteria and

performed conservative statistical methods for comparing variables. Therefore, it would be harder to demonstrate significance of the differences with this method.

In conclusion, the frequency of metS in new diagnosed RA patients was higher than in controls without inflammatory diseases from the same outpatient clinic. Additionally, there were a tendency towards atherogenic lipid changes in treatment-naïve RA patients. Therefore, evaluating metabolic alterations since the diagnosis, controlling the disease activity, and treating metabolic alterations along with standard disease-modifying therapy may be the first steps for reducing CVD risk in RA patients.

DISCLOSURES

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

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ORIGINAL ARTICLE

Urinary tract infections in a university hospital: pathogens and antibiotic susceptibility

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ABSTRACT

Background: A substantial group of patients visit the emergency department (ED) with complaints of urinary tract infections (UTI). Treatment advice is based on national and local public health surveillance data. It is unclear whether this advice is adequate for hospitals with selected patient populations, such as university hospitals.
Methods: We performed a retrospective study on patients visiting the ED of the Erasmus University Medical Center (Erasmus MC) in the Netherlands from January 1st, 2013 until December 31st, 2014 with a suspected complicated UTI (cUTI) and positive urinary cultures. Patient data, data concerning the ED visit and microbiological data were analysed.
Results: 439 patients visited the ED, of whom 429 had a cUTI. Our results were compared with NethMap data. Distribution of uropathogens was comparable with the overall distribution in the Netherlands. Antibiotic susceptibility was comparable for intravenous antibiotics, but was lower for oral antibiotics. Susceptibility for empiric antibiotic therapy (i.e., cefuroxime and gentamyicin) was 96.2%. Pathogens differed from the index culture in 56.2% (104/185) of the urinary cultures available from the previous year. Using logistic regression, we found that a shorter time between last admission to the initiated antibiotic regimen was associated with lower susceptibility of cultured uropathogens.
Conclusion: The distribution and antibiotic susceptibility of uropathogens for intravenous antibiotics in a Dutch university hospital is comparable with overall distribution in the Netherlands. Empiric antibiotic therapy in our local guideline appears to be an adequate antibiotic regimen for cUTI and we therefore recommend treating patients accordingly. Extension of the chosen regimen based on earlier cultured pathogens is advised, and narrowing of the antibiotic regimen strongly discouraged.

KEYWORDS

Urinary tract infections, emergency departments, antibiotic resistance

INTRODUCTION

Background and rationale

Urinary tract infection (UTI) is suspected in a substantial group of patients visiting the emergency department (ED). In the United States, UTIs accounted for approximately 2% of ED visits in 2014 for a total of 2.3 million people.[1] This percentage is similar in the Netherlands.[2] There is continuous debate about the appropriate antibiotic treatment for patients with UTI, despite guidelines on the subject. The Dutch guidelines for antibiotic therapy are based on national resistance data on pathogens causing UTI.[3] It is questionable if, and to what extent, these data are applicable to the patient population encountered in specialized hospitals, such as university hospitals.
Patients in university hospitals often have a complex medical history and in particular, patients from nephrology and urology departments are more frequently treated for UTIs with antibiotics. These patients are at risk for colonization with antibiotic-resistant uropathogens. When UTI occurs, it is likely that the uropathogens are less susceptible to routinely prescribed antibiotics.[4-6] Data comparing the distribution and antibiotic susceptibility of uropathogens in Dutch university hospitals with the overall distribution in the Netherlands are currently lacking.
Dutch national guidelines advise to treat complicated UTIs (cUTI) with amoxicillin or a second-generation cephalosporin combined with an aminoglycoside, or with a third-generation cephalosporin.[3] A cUTI is defined by the 'The Dutch Working Party on Antibiotic Policy'

(SWAB) as all UTIs with the exception of cystitis in non-immunocompromised, non-pregnant women with no anatomical and functional abnormalities of the urogenital tract and no signs of tissue invasion, and in men younger than 40 years without a medical history, no previous lower urinary tract symptoms and no findings at physical examination.[3] In the Erasmus University Medical Center Rotterdam, the Netherlands (Erasmus MC), cefuroxime combined with gentamicin is the antibiotic regimen of choice for cUTI based on local resistance data. This regimen can only be administrated intravenously, which requires hospitalisation, regardless of the patient's clinical condition. Furthermore, side effects of gentamicin include nephrotoxicity and ototoxicity.[7] Although this risk is particularly applicable after multiple doses in patients with renal insufficiency, aminoglycosides are frequently left out, resulting in inappropriate treatment.[8-10] The duration of hospital stay or even prevention of admission may be achieved if hospitals can identify patients who can be safely treated with other specific antibiotic-regimens, based on their medical history and available data from previously obtained cultures.

When initiating adequate antibiotic therapy, physicians should take the increase of antibiotic resistance into account. However, there are currently not enough data to enable a more tailor-made decision for the first choice of the antibiotic regimen. Recently, a study in a university hospital in Israel showed that patients who had a culture with a resistant uropathogen had high rates of a repeat resistant uropathogen in a subsequent culture.[11] This chance of a repeat resistant uropathogen was reduced with time, or with an intervening culture without resistant uropathogens. Data that enables extension or narrowing of the empiric regimen in a university hospital ED population are not available. However, these data would substantially contribute to more efficient antibiotic treatment and prevention of antibiotic resistance.[12]

Objectives

The primary goal of this research was to study the distribution of uropathogens and their antibiotic resistance patterns in a university hospital population. Second, we investigated susceptibility to the empiric regimen consisting of cefuroxime and gentamicin in this population, and studied the probability of extending or narrowing of this regimen, based on previously cultured pathogens.

MATERIALS AND METHODS

Study design, setting, and patients

We conducted an observational retrospective study in the Erasmus MC. This is the largest university hospital of the Netherlands with approximately 32,000 adult ED visits per year. All urinary cultures with at least one pathogen and an available antibiogram taken from patients visiting the ED from January 1st, 2013 until December 31st, 2014 were obtained from the Department of Medical Microbiology and Infectious Disease.

Urine samples were cultured by standard microbiological culture techniques. Bacterial species were identified by Matrix Assisted Laser Desorption/Ionisation Time-of-Flight Analyzer Mass Spectrometry (MALDI-TOF MS) analysis (Microflex, Bruker Daltonics, Bremen, Germany). Susceptibility testing was performed with VITEK®2 (bioMérieux, Marcy l'Etoile, France). Antibiotic resistance was determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints.[13] Only samples from patients 18 years or older having a UTI were included (i.e., index culture). Patients were only included once, and the first obtained sample of each patient in the abovementioned period was used. Uropathogens were considered to be identical (i.e., the same uropathogen), if the index culture and previously cultured uropathogens as well as its antibiotic susceptibility were identical.

Variables

For each patient, demographic data (e.g., age, sex, previous medical history) and data concerning their ED visit, such as history, vital parameters (e.g., blood pressure, heart rate, respiratory rate, oxygen saturation, temperature), laboratory results (e.g., C-reactive protein (CRP), leukocyte count, and presence of pyuria, defined as leukocytes in urine dipstick), results of blood cultures, previous urinary cultures acquired within 12 months prior to the ED-visit with antibiogram available, data on initiated antibiotics, and disposition were obtained from electronic patient records. In patients who were previously hospitalised in the Erasmus MC, the dates of the last admission and discharge were obtained, and time since last admission and duration of the last admission were calculated. The number of admissions in the last year was also obtained. Comorbidities considered relevant were renal transplantation, urological anomalies (e.g., recent urological interventions, neo-bladder reconstruction, urological tract anomalies), and immunocompromised status (defined as patients with congenital or acquired immunodeficiency, patients undergoing active treatment for malignancies, patients using immunosuppressive medication). Patients were grouped in 'never hospitalised within the Erasmus MC' (Erasmus MC-naïve), and 'previously hospitalised in the Erasmus MC'. Previously hospitalised patients were categorised based on the time between the last admission, either > 12 months or ≥ 12 months ago. We made a subset of patients recently hospitalised (defined as < 3 months). Data on hospitalisation in other hospitals or residing in a nursing home were not available.

We combined the SWAB definition[3] and the Centers for Disease Control and Prevention (CDC) definition[14] to define a cUTI: an urinary culture with no more than two species of organisms identified, at least one of which is a bacterium of ≥ 10^3 colony forming units (in contrast to the ≥ 10^5 colony forming units, as defined in the CDC definition) and one of the following criteria: 1) a positive blood culture from the same moment with the same micro-organism as in the urinary culture; 2) a body temperature > 38.0 °C; 3) symptomatology of a UTI (e.g., dysuria, urinary frequency or urgency, suprapubic or costovertebral tenderness); or 4) according to the treating physician (i.e., UTI reported as (most likely) diagnosis in discharge letter). A UTI was considered to be complicated when there were signs of systemic illness. Patients met our definition of cUTI when they were fulfilled at least one of the following: being male and older than 39 years,[3] having a body temperature > 38.0 °C, meeting two or more systemic inflammatory response syndrome (SIRS) criteria (of note, missing SIRS criteria were coded as negative),[15] having costovertebral tenderness, being ill according to the treating physician, having a CRP > 60 mg/l,[16] having a blood culture with the same pathogen as in the urine culture, having a renal transplantation in medical history, being immunocompromised, or the decision for hospitalisation by the treating physician. Cefuroxime combined with gentamicin was considered empiric therapy in the ED, and we therefore described the proportion of patients having a UTI in whom empiric therapy would have been an adequate antibiotic regimen without resistance of the causing pathogen against these agents. We also described the population of pathogens cultured with their susceptibility to different, frequently prescribed antibiotic regimens, including susceptibility to cefuroxime and gentamicin, in Erasmus MC-naïve versus previously hospitalised patients (< 12 versus ≥ 12 months ago). We compared the index culture and its susceptibility for the prescribed antibiotic regimen with previously cultured pathogens. Lastly, we compared prevalence susceptibility of uropathogens for frequently prescribed antibiotics in our population with national antibiotic susceptibility.[17]

Statistical analyses

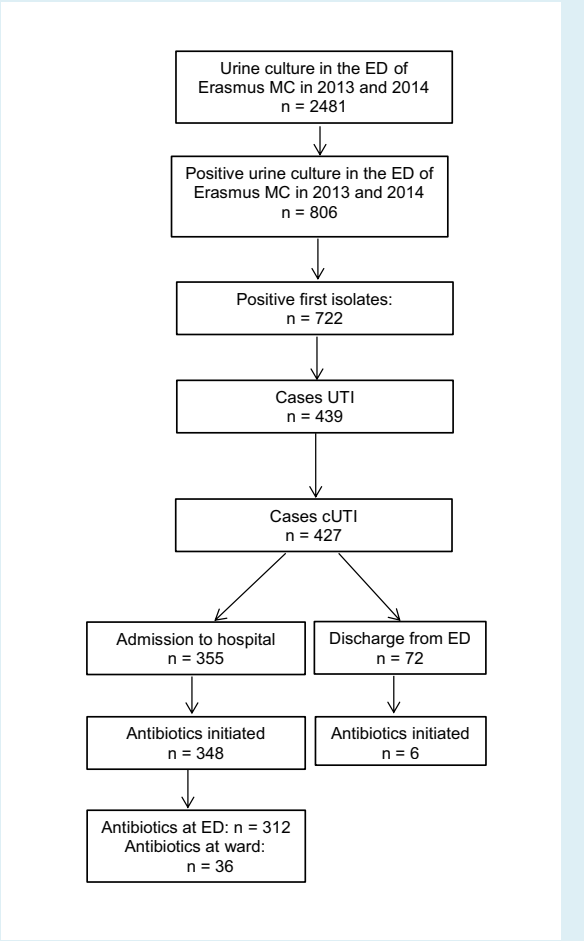
We presented patient characteristics as mean and interquartile range (IQR), or as an absolute number (proportion) with percentage (%) and 95% confidence interval (95% CI). Categorical variables were compared using the Pearson chi-squared test. We performed one sample T-tests for the comparison of proportions and 95% CIs of susceptibility in our population with Dutch national susceptibility data (NethMap).[17] We performed univariate and multivariate logistic regression analysis on susceptibility of the found bacteria for initiated therapy, empiric therapy and cefuroxime monotherapy over days since last admission. Other factors included in the models were sex and age. Results are presented as odds ratios (ORs) and 95% CIs. All analyses were conducted with IBM SPPS Statistics for Windows version 21 (IBM Corp., Armonk, N.Y., USA). A p-value < 0.05 was considered significant.

RESULTS

Inclusion of patients

A total of 2481 urinary cultures were obtained in the ED between January 1st, 2013 and December 31st, 2014, of which 806 (32.5%) contained at least one pathogen. After selecting first isolates, 722 (89.6%) cultures of unique patients remained. Of these patients, 439 (60.8%) had a UTI according to the predefined criteria and 427 had a

Figure 1. *Flow diagram on selection of patients*



ED = emergency department; UTI = urinary tract infection; cUTI = complicated urinary tract infection.

cUTI. A total of 355 (83.1%) patients were admitted to the hospital, and in 348 (98.0%), antibiotics were initiated. The flowchart of these results and medical decisions with respect to hospital admission and initiation of antibiotics is shown in figure 1.

Patient characteristics

Of the 427 patients with cUTI, a majority were male (223 patients, 52.2%), with a median age of 59 years. The vast majority of patients had relevant comorbidities (72.8%) and 63.2% were hospitalised the prior year. Only

Table 1. *Patient characteristics*

	Patients with cUTI (n = 427)
Sex, male [n (%)]	223 (52.2)
Age [mean (SD)]	59 (17)
First responsible specialism at ED [n (%)]	
Internal medicine	221 (51.8)
Surgery	97 (22.7)
Urology	48 (11.2)
Emergency medicine	6 (1.4)
Other	55 (12.9)
Comorbidities [n (%)]	
Yes	311 (72.8)
Status after renal transplantation	106 (24.8)
Urological problem	193 (45.2)
Immunocompromised status	185 (43.3)
No	115 (26.9)
Time since last admission	
< 3 months [n (%)]	172 (40.3)
3- 6 months [n (%)]	33 (7.7)
7-9 months [n (%)]	21 (4.9)
10-12 months [n (%)]	25 (5.9)
≥ 12 months [n (%)]	106 (24.8)
Never admitted [n (%)]	70 (16.4)
Length of last hospitalisation, months*[median (IQR, Range)]	3 (IQR 15, Range 123)
Duration of last hospitalisation, days*[median (IQR, Range)]	5 (IQR 7, Range 125)
Number of hospitalisations in the last year*[median (IQR, Range)]	1 (IQR 3, Range 13)
Clinical presentation at ED	
Ill according to physician's discretion [n (%)]	130 (30.4)
Pulse rate, b/min [median (IQR)]	99 (85-112)
SBP, mmHg [median (IQR)]	130 (114-146)
DBP, mmHg [median (IQR)]	75 (65-85)
Breathing frequency, n/min [median (IQR)]	20 (16-25)
Body temperature, °C [median (IQR)]	38.2 (37.2-38.8)
C-reactive protein, mg/l [median (IQR)]	60.0 (23.8-122.2)
Leukocyte count, 10^9/l [median (IQR)]	11.5 (8.1-15.8)
Pyuria [n (%)]	354 (82.9)
Number of micro-organisms in urinary culture [n (%)]	
1	392 (91.8)
2	35 (8.2)
Micro-organism in urinary culture [n (%)]	**n = 462**
Escherichia coli	237 (51.3)
Klebsiella pneumoniae	44 (9.5)
Enterococcus faecalis	45 (9.7)
Proteus mirabilis	31 (6.7)
Pseudomonas aeruginosa	26 (5.6)
Group B Streptococcus	12 (2.6)
Other	67 (14.5)

cUTI = complicated urinary tract infection; n = number; SD = standard deviation; ED = emergency department; SBP = systolic blood pressure; DBP = diastolic blood pressure; IQR = inter quartile range.
*Data available for n =357.

12.2% of the patients were not previously admitted to Erasmus MC. Most frequently cultured pathogen was *E. coli* (51.3%). Other frequently cultured micro-organisms were *K. pneumoniae*, *E. faecalis*, *P. mirabilis*, *P. aeruginosa*, and *S. agalactiae* (*Group B Streptococcus*) (9.5%, 9.7%, 6.7%, 5.6% and 2.6%, respectively). Patient characteristics are shown in table 1.

Antibiotic susceptibility

In all patients who were hospitalised after their ED visit with a cUTI, we found susceptibility to cefuroxime and/or gentamicin in 96.2% (228/237) for *E. coli*, 90.9% (40/44) for *K. pneumoniae*, and of 100% (31/31) for *P. mirabilis*. These rates are comparable to NethMap-data.[17] Susceptibility to meropenem was 100%, except for *P. aeruginosa* (susceptibility rate 92.3% (24/26)). Compared to the general resistances rates in the Netherlands, we found more resistance of *E. coli* and *K. pneumoniae* for trimethoprim-sulfamethoxazole and more resistance of *E. coli* and *P. mirabilis* for ciprofloxacin. All susceptibility patterns can be found in table 2A.

Using multivariate logistic regression, we found that a shorter time between the last admission to Erasmus MC was associated with lower susceptibility rates for initiated antibiotic therapy (OR 1.22; 95% CI 1.04, 1.43; p = 0.015). We also found that a shorter the time since the last admission was associated with lower susceptibility for cefuroxime (OR 1.31; 95% CI 1.14, 1.49; p < 0.001). We found no association between age and sex and susceptibility (OR 1.30; 95% CI 0.73, 2.31; p = 0.364, and OR 0.98; 95% CI 0.97, 1.01; p = 0.19, respectively). We also found no association between the time in days between the last admission to Erasmus MC and susceptibility for empirical therapy (i.e., cefuroxime and gentamicin) (OR 1.17; 95% CI 0.95, 1.45; p = 0.14).

We tested non-linearity by adding a quadratic term to the natural logarithm of days since the last admission to

Table 2A. *Susceptibility rates of cultured pathogens for frequently prescribed antibiotics in patients hospitalised in Erasmus MC and in the Netherlands, as reported by Nethmap*

Cultured pathogens n = 462		*E. coli* (n = 237)	*Nethmap E. coli*	*K.pneumoniae* (n = 44)	Nethmap *K. pneumoniae*	*P. mirabilis* (n = 31)	Nethmap *P. mirabilis*	*P. aeruginosa* (n = 26)	Nethmap *P. aeruginosa*	*E. faecalis* (n = 45)	Other (n = 67)
Amoxicillin-clavulanic acid	N % 95% CI	194 81.9% (76.9-86.8)	64%	36 81.8% (70.0-93.7)	81%	28 90.3% (79.3-100)	92%	-	-	45 (100)	*
Cefuroxim	N % 95% CI	199 84.0% (79.3-88,7)	87%	36 81.8% (70.0-93.7)	84%	31 100%	99%	-	-	-	*
Meropenem	N % 95% CI	237 100%	100%	44 100%	100%	31 100%	100%	24 92.3% (81.3-100)	99%	-	*
Ciprofloxacin	N % 95% CI	180 75.9% (70.5-81.4)	86%	36 81.8% (70.0-93.7)	87%	19 61.3% (43.1-79.4)	88%	21 80.8% (64.5-97.0)	89%	-	*
Gentamicin	N % 95% CI	222 93.7% (93.2-98.3)	95%	40 90.9% (82.1-99.8)	95%	27 87.1% (74.6-99.6)	94%	24 92.3% (81.3-100)	97%	-	*
Trimethoprim-sulfa-methoxazole	N % 95% CI	139 58.6% (52.3-65.0)	77%	31 70.5% (56.4-84.5)	85%	19 61.3% (43.1-79.4)	73%	-	-	-	*
Nitrofurantoin	N % 95% CI	226 95.4% (92.7-98.1)	98%	-	-	-	-	-	-	45 (100)	*
Cefuroxime/ gentamicin	N % 95% CI	228 96.2 (93.7-98.6)	98%	40 90.9 (82.1-99.7)	96%	31 100%	100%	-	-	-	*

n = number; % = percentage; 95% CI = 95% confidence intervals.
*Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.

Erasmus MC. We detected no non-linearity, which implies there is no specific cut-off period for losing non-susceptible uropathogens.
Susceptibility for amoxicillin-clavulanic acid, cefuroxime, gentamicin, trimethoprim-sulfamethoxazole, and cefuroxime/gentamicin was lowest if last admission < 3 months ago, and highest for never admitted patients (tables 2B-2E).

Table 2B. *Susceptibility rates of cultured pathogens for frequently prescribed antibiotics of patients who were admitted < 3 months to Erasmus MC*

Cultured pathogens n = 189		***E. coli* (n = 84)**	***K. pneumoniae* (n = 18)**	***P. mirabilis* (n = 12)**	***P. aeruginosa* (n = 15)**	***E. faecalis* (n = 23)**	**Other (n = 45)**
Amoxicillin-clavulanic acid	N (%)	62 (73.8)	13 (72.2)	11 (91.7)	-	23 (100)	*
Cefuroxime	N (%)	66 (78.6)	12 (66.7)	12 (100)	-	-	*
Meropenem	N (%)	84 (100)	18 (100)	12 (100)	13 (86.7)	-	*
Ciprofloxacin	N (%)	58 (69.0)	14 (77.8)	7 (58.3)	12 (80.0)	-	*
Gentamicin	N (%)	76 (90.5)	15 (83.3)	11 (91.7)	14 (93.3)	-	*
Trimethoprim-sulfamethoxazole	N (%)	41 (48.8)	13 (72.2)	6 (50.0)	-	-	*
Nitrofurantoin	N (%)	81 (96.4)	3 (17.6)	-	-	23 (100)	*
Cefuroxime/gentamicin	N (%)	79 (84.0)	15 (83.3)	12 (100)	14 (93.3)	-	*

n = number; % = percentage.
*Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.

Table 2C. *Susceptibility rates of cultured pathogens for frequently prescribed antibiotics of patients who were admitted < 12 months to Erasmus MC*

Cultured pathogens n = 270		***E. coli* (n = 130)**	***K. pneumoniae* (n = 25)**	***P. mirabilis* (n = 23)**	***P. aeruginosa* (n = 16)**	***E. faecalis* (n = 30)**	**Other (n = 45)**
Amoxicillin-clavulanic acid	N (%)	101 (77.7)	18 (72.0)	21 (91.3)	-	34 (100)	*
Cefuroxime	N (%)	103 (79.2)	18 (73.0)	23 (100)	-	-	*
Meropenem	N (%)	130 (100)	25 (100)	23 (100)	14 (87.5)	-	*
Ciprofloxacin	N (%)	94 (72.3)	20 (80.0)	13 (56.5)	13 (81.3)	-	*
Gentamicin	N (%)	118 (90.8)	22 (88.0)	20 (87.0)	15 (93.8)	-	*
Trimethoprim-sulfamethoxazole	N (%)	61 (46.9)	18 (72.0)	13 (56.5)	-	-	*
Nitrofurantoin	N (%)	125 (96.2)	7 (29.2)	-	-	34 (100)	*
Cefuroxime/gentamicin	N (%)	121(93.1)	22 (88.0)	23 (100)	15 (93.8)	-	*

n = number; % = percentage.
*Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.

Table 2D. *Susceptibility rates of cultured pathogens for frequently prescribed antibiotics of patients who were admitted ≥ 12 months to Erasmus MC*

n = 117		*E. coli* (n = 65)	*K. pneumoniae* (n = 15)	*P. mirabilis* (n = 6)	*P. aeruginosa* (n = 6)	*E. faecalis* (n = 7)	Other (n = 17)
Amoxicillin-clavulanic acid	N (%)	53 (81.5)	14 (93.3)	5 (83.3)	-	7 (100)	*
Cefuroxime	N (%)	58 (89.2)	14 (93.3)	6 (100)	-	-	*
Meropenem	N (%)	65 (100)	15 (100)	6 (100)	6 (100)	-	*
Ciprofloxacin	N (%)	50 (76.9)	12 (80.0)	4 (66.7)	5 (83.3)	-	*
Gentamicin	N (%)	62 (95.4)	14 (93.3)	5 (83.3)	5 (83.3)	-	*
Trimethoprim-sulfamethoxazole	N (%)	41 (63.1)	9 (60.0)	4 (66.7)	-	-	*
Nitrofurantoin	N (%)	61 (95.3)	4 (26.7)	-	-	7 (100)	*
Cefuroxime/gentamicin	N (%)	65 (100)	12 (92.3)	6 (100)	5 (83.3)	-	*

n = number; % = percentage.
*Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.

Table 2E. *Susceptibility rates of cultured pathogens for frequently prescribed antibiotics of patients who were never admitted to Erasmus MC*

n = 74		*E. coli* (n = 42)	*K. pneumoniae* (n = 4)	*P. mirabilis* (n = 2)	*P. aeruginosa* (n = 4)	*E. faecalis* (n = 8)	Other (n = 14)
Amoxicillin-clavulanic acid	N (%)	40 (95.2)	4 (100)	2 (100)	-	8 (100)	*
Cefuroxime	N (%)	38 (90.5)	4 (100)	2 (100)	-	-	*
Meropenem	N (%)	42 (100)	4 (100)	2 (100)	4 (100)	-	*
Ciprofloxacin	N (%)	36 (85.7)	4 (100)	2 (100)	3 (75)	-	*
Gentamicin	N (%)	42 (100)	4 (100)	2 (100)	4 (100)	-	*
Trimethoprim/ sulfamethoxazole	N (%)	29 (69.0)	4 (100)	2 (100)	-	-	*
Nitrofurantoin	N (%)	40 (95.2)	1 (25)	-	-	8 (100)	*
Cefuroxime/gentamicin	N (%)	42 (100)	4 (100)	2 (100)	4 (100)	-	*

n = number; % = percentage.
*Due to the large variation in 'other' uropathogens, overall susceptibility in this group was not representative and therefore not mentioned.

In 427 patients with a cUTI, 462 pathogens were cultured (427 single isolates, 35 double isolates). Of 185 index cultures, previous cultures were available. Of all urine cultures obtained within the last year, 56.2% (104/185) contained pathogens different from the index culture. In 71.2%, the current pathogen was susceptible for the initiated antibiotic therapy, compared to 91.4% if the pathogen matched previous cultures ($p < 0.001$, see table 3).
Of the 427 patients with cUTI, 61 were Erasmus MC-naïve, 251 were admitted < 12 months, and 106 were admitted ≥ 12 months ago. In patients admitted < 12 months ago, uropathogens carried higher resistance rates for the initiated treatment than those of patients who were last hospitalised ≥ 12 months ago, or were never hospitalised (24.3% vs 12.3% vs 12.9%, respectively; $p = 0.002$, see table 4). Majority of the patients admitted < 12 months ago were admitted in the last three months (68.9%).

DISCUSSION

Our study shows that susceptibility rates to empirical intravenous antibiotic therapy in our cohort of patients visiting the ED of a Dutch university hospital are

Table 3. *Comparison of previously isolated and new pathogens in urinary cultures and susceptibility to initiated antibiotics*

	Previously isolated pathogen within any culture within the last 12 months. (n = 81)	New pathogens compared to any culture within the last 12 months. (n = 104)	No previous cultures (n = 277)
Current Pathogen S to initiated AB, n (%)	74 (91.4)	74 (71.2)	0 (0)
Pathogen R to initiated AB, n (%)	4 (4.9)	27 (26.0)	0 (0)
No AB initiated, n (%)	3 (3.7)	3 (2.9)	0 (0)
No previous culture, n (%)	*	*	277 (100)

n = number; % = percentage; S = susceptible; R = resistant; AB = antibiotics.

Table 4. *Comparison of susceptibility of pathogens in urinary cultures to initiated antibiotics in relation to time since last admission*

	Last admission < 3 months (n = 172)	Last admission < 12 months (n = 251)	Last admission ≥ 12 months (n = 106)	Never admitted (n = 70)
Pathogen S to initiated AB, n (%)	131 (76.2)	190 (75.7)	93 (87.7)	61 (87.1)
Pathogen R to initiated AB, n (%)	36 (20.9)	52 (20.7)	8 (7.5)	4 (5.7)
No AB initiated, n (%)	5 (2.9)	9 (3.6)	5 (4.7)	5 (7.1)

n = number; % = percentage; S = susceptible; R = resistant; AB = antibiotics.

comparable to national epidemiological data. However, resistance to orally available antibiotics is higher for the most frequently cultured pathogens. A shorter time between presentation in the ED and the last admission was associated with lower susceptibility of uropathogens for initiated antibiotic therapy.

As in most studies, we found higher susceptibility rates for meropenem than for cefuroxime and/or gentamicin, which is aligned with NethMap 2018,[17] and are most likely the result of restricted use of carbapenems, since they are considered last-resort antibiotics. In line with the principles of antimicrobial stewardship, carbapenems should continuously be prescribed with caution.[18]

We also found that susceptibility of prevalent uropathogens to frequently prescribed oral antibiotics was lower than nationwide susceptibility rates, especially for ciprofloxacin and trimethoprim-sulfamethoxazole. This difference is most explicit within the subgroup of patients who were admitted within one year before presentation at the ED. It is likely that this discrepancy is due to the specific patient population encountered in university hospitals. Patients who are using immunosuppressive medication or who have anatomical anomalies frequently require treatment with antibiotics and are more often admitted. These patients are not only at risk for UTIs in general, but also for UTIs with more uncommon and more resistant uropathogens.[19,20] Notably, the NethMap report calculates resistance percentages for all hospitals combined and not for university hospitals separately, which probably resulted in higher susceptibility rates.

More than half of the cultured uropathogens differed from previously cultured uropathogens. This finding suggests a high prevalent heterogeneity of uropathogens in single individuals. There was significantly higher resistance for initiated antibiotics in patients who were admitted < 12 months ago, compared to patients admitted ≥ 12 months ago. This confirms the evidence that patients who are frequently admitted to the hospital carry more resistant uropathogens than patients who are less frequently or never admitted.[11,21] We were not able to define a safe cut-off point, since we found a linear association over time, and the longer the time since last hospitalisation, the smaller the risk. A cross-sectional study of Teunis et al. on duration of carriership of multi drug resistant *E. coli* in a subset of a general adult population showed that the estimated time to lose carriership was approximately 400 days.[22] In the prospective COMBAT (Carriage Of Multiresistant Bacteria After Travel) study, 633 individuals acquired multi drug

resistant *E. coli* during travel, in whom median duration of colonization after travel was 30 days, and of whom 11.3% remained colonized 12 months after return; however, this was performed predominantly with individuals without comorbidity and infections.[23] In clinical practice, the results of previously obtained cultures contribute to the decision to initiate an antibiotic regimen, but information from earlier obtained cultures should be applied with caution. Based on our data, we suggest treatment with empiric therapy, including gentamicin, in all patients – also those who were admitted recently. Antibiotic regimen should be extended and not narrowed, based on cultures obtained in the year before presentation at the ED.

In kidney transplant recipients or patients with severe pre-existent renal insufficiency (eGFR < 30 ml/min) there is continuous discussion on the safety of gentamicin. Evidence for significant nephrotoxicity after a single dose of aminoglycosides is controversial,[7,24] but most physicians are cautious with prescribing aminoglycosides in patients with kidney transplants or severe renal insufficiency.[21,25] However, these patients accounted for a substantial part of our study population, and for this group, monotherapy with cefuroxime or ciprofloxacin is not advisable, since susceptibility rates were below the threshold of 90%. In these selected groups another empiric regimen, like meropenem, may be justified. Especially in tertiary hospitals, where decision-making regarding the choice for antibiotic treatment in an aging, multi-morbid patient population is often complex, antimicrobial stewardship is recommended. However, we also show that guidelines on empiric therapy based on local resistance data are effective, as long as they are followed.

Due to the retrospective nature of our study we encountered several limitations. We selected patients based on positive urinary cultures and subsequently selected patients with cUTIs. In a small but substantial group, this led to misclassification of cUTI: antibiotics were initiated in only six of the 72 patients who met our criteria for cUTI and who were discharged from the ED. Patients with cUTI without positive urinary cultures, for example, due to pre-treatment with antibiotics or due to a negative urinalysis and no subsequent culture, were not selected. This might have led to a selection bias. However, our data (i.e., the cultured uropathogens and their antibiotic susceptibility) were selected are used in the national NethMap data. We also have no information on antibiotic treatment of patients in general practice or in other hospitals, and if antibiotics would have been used, this could potentially have caused an increase in resistance in our population.

Also, important differences between our data and NethMap 2018 results are seen in the susceptibility rates of *E. coli* and *K. pneumoniae* for amoxicillin-clavulanic acid. This is a result of a new test panel for Gram-negative bacteria, resulting in higher minimal inhibitory concentrations for amoxicillin-clavulanic acid and higher resistance levels from 2016 onwards. For our data, susceptibility rates from the period 2013-2014 are applicable. Therefore, we compared our data with NethMap reports for this period and our resistance percentages for amoxicillin-clavulanic acid are comparable.[17]

In conclusion, the distribution and antibiotic susceptibility for intravenous antibiotics of uropathogens in a Dutch university hospital is comparable with overall distribution in the Netherlands. Cefuroxime in combination with gentamicin is therefore an adequate antibiotic regimen for cUTI, and we recommend treating patients accordingly. Extension of the chosen regimen based on earlier cultured pathogens is advised, and narrowing of the antibiotic regimen strongly discouraged, especially the omission of gentamicin. In a strictly selected population (e.g., recently admitted renal transplant recipients, pre-existing severe kidney insufficiency), prescription of meropenem as an alternative empiric therapy could be considered.

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CASE REPORT

Multiple chronic conditions: the need for integrated secondary care

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SUMMARY

Current hospital-level care is "mostly disease-specific and monodisciplinary-oriented". These three case reports show different journeys that patients with multiple chronic conditions experienced in Dutch secondary outpatient care, and aim to demonstrate why an integrated care approach might be beneficial for this group of patients.

KEYWORDS

Hospital-level care, multimorbidity, multiple chronic conditions, integrated care, secondary care

What was known on this topic?
The current secondary care organization appears to be insufficient for patients with multiple chronic conditions who visit multiple hospital physicians. Integrated care is viewed as a potential solution, but methods to implement this approach in secondary care are scarce.

What does this add?
The creation of an individualized management plan by an appointed care professional could be a method to implement a more integrated care approach. Moreover, it aims to stress the importance of coordinating and tailoring care for these patients by presenting their individual, secondary care journeys.

INTRODUCTION

With the aging population, the prevalence of patients with multimorbidity or multiple chronic conditions (MCC) is expected to rise.[1,2] This could have consequences for the current healthcare system: patients with MCC use more healthcare resources than patients with a single condition: they have more contact with healthcare providers; they are prone to polypharmacy (simultaneous use of ≥ 5 medications); and they have a higher risk of hospitalisation and complications.[3-6] For healthcare providers as well as for patients, keeping a real-time overview of appointments, recommendations, diagnostics, and current medication might be difficult and time-consuming. As a result, the provided care might be insufficient.[7] In addition, current hospital-level care is "mostly disease- or organ-specific and monodisciplinary-oriented".[1] There are multiple programs that recommend an integrated care approach for patients with MCC, however the implementation and efficacy still fall short.[1,8] In daily clinical practice, the need for a tailor-made, integrated approach is becoming more urgent, and the following case reports aim to illustrate why.[1] The last two cases also intend to show how an individualized management plan by an appointed care professional might be a method to achieve more integrated secondary care.

CASE PRESENTATION

Case 1

An 81-year-old male patient, with a history of mixed dementia (Alzheimer/vascular), an ischemic stroke and a moderate-severe valvular aortic stenosis (AS), suffered from acute vision loss of the left eye and visited the ophthalmologist and rheumatologist in September 2017. Because of an elevated erythrocyte sedimentation rate level, temporal arteritis was considered (although the

echo of the arteria temporalis was negative); a biopsy was performed and 60 mg prednisone was pragmatically started. As a consequence, his glucose levels started fluctuating, and the prednisone dosage was decreased by half. Temporal arteritis was excluded based on the biopsy and the diagnosis Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) was made. The rheumatologist recommended quick reduction of prednisone. However, this was accidentally not executed. One week after the last rheumatology consultation, the patient was admitted to the internal medicine department for a blood transfusion, analysis of anaemia with black stool, and dysregulated diabetes. A colonoscopy showed a cecum carcinoma.

For assessment of frailty in light of this new diagnosis, the internist referred the patient to the geriatrician. The geriatrician concluded that the patient was frail, based on the pre-existing cognitive disorder, moderate functional level, and moderate-severe AS. The frailty and high risks of invasive treatments were discussed. At first, the patient and his family members had different treatment preferences, so the geriatrician informed the general practitioner and advised to discuss the situation with the family. Two days later, the patient and his family visited the surgeon and they unanimously chose to defer surgery and to start with palliative radiotherapy.

During the palliative phase, a transthoracic echocardiogram was performed. The ophthalmologist also diagnosed ocular hypertension during a check-up, started pressure reduction treatment, and requested that the general practitioner optimize blood pressure and glucose levels. In March 2018, the patient moved to hospice care.

Case 2

We report the case of an 80-year-old female patient, with a history of more than 30 treatments at the pain clinic (for arthrosis and chronic back pain due to a prior hernia surgery); chronic, low-dose prednisone use for acute febrile neutrophilic dermatosis since 2008; and intrinsic asthma with recurrent exacerbations since 2013.

In 2015, gradual decline started on several physical health domains and contact with care providers increased. The gastroenterologist performed a colonoscopy for anaemia and found arteriovenous malformations, which were treated with argon plasma coagulation (APC). A gastroenterologist referred the patient to an internist because of an elevated M-protein, who diagnosed her with multiple myeloma. During follow-up, the internist diagnosed an auto-immune haemolytic anaemia and increased the prednisone dosage. Two weeks later, the gastroenterologist performed another colonoscopy with APC because of recurring blood loss. This was complicated by a cecum perforation for which she received surgery. Postoperatively, she was readmitted twice with an exacerbation of her asthma. After three months, she fell, due to muscle weakness, broke her hip, and received a surgical hip repair. Afterwards, she was readmitted with another exacerbation of her asthma, and the cardiologist diagnosed a valvular AS.

Following this complicated course, the general practitioner referred the patient to the geriatrician for a comprehensive assessment and coordination of care. The patient's main complaints were pain, dyspnoea, fatigue, and loneliness, and she was using 14 medications. The geriatrician consulted all physicians about their diagnostic/treatment plans. The gastroenterologist, anaesthesiologist, cardiologist, and orthopaedic surgeon decided to delay more diagnostics/treatment/check-ups because of the risks and lack of results; the haematologist planned periodical blood tests that could be performed by the general practitioner; the ophthalmology and pulmonology check-ups were evaluated and coordinated. Several medications were changed. The geriatrician advised psychological guidance for coping with physical decline. After six months, the patient's secondary care could be transferred to the general practitioner.

Case 3

A 77-year-old female patient had been consulting a rheumatologist for gout and rheumatoid arthritis; an internist for recurrent erysipelas, diabetes mellitus (DM), and renal function deterioration; and a gastroenterologist for follow-up of a Side-Branch Intraductal Papillary Mucinous Neoplasm of the pancreas (SB-IPMN).

In January 2018, she visited a dermatologist because of itching, which had possibly started after switching insulin analogues. The dermatologist diagnosed asteatotic eczema, influenced by anaemia, uraemia, and DM and prescribed an ointment and a corticosteroid cream. In February, she visited the internist at the emergency department, because of acute redness of both lower legs and pain in the left upper leg and groin. She was diagnosed with cellulitis, received an antibiotics prescription and went home. The following day, she visited the internist again; earlier, she had been referred by an acting general practitioner to evaluate whether her fatigue, weight loss, and itching could be paraneoplastic. The internist ordered an abdominal ultrasound and thoracic X-ray to exclude lymphoma, and concluded that the itching might be medically induced. The internist also referred her to the neurologist because of muscle weakness of the left leg.

At this point, the general practitioner referred the patient to the geriatrician for a comprehensive assessment and coordination of care, because of the multitude of physicians and polypharmacy. The itching and functional decline also caused a sleep disorder and anxiety, and her informal caregivers were overburdened. The pharmacologist advised to stop medication by trial-and-error to investigate their effect on the itching. The geriatrician advised psychological

treatment and consulted the other involved physicians: the dermatologist ended the follow-up; the referral to the neurologist was cancelled and the general practitioner agreed to coordinate the follow-up with the internist and rheumatologist. The patient was referred to rehabilitation care to relieve the burden on the informal caregivers since the itching was not completely abrogated.

DISCUSSION

The three cases presented here are examples of journeys that patients with MCC can experience while receiving secondary care. These case reports aim to show that during a patient's journey, it can become difficult for both the patient with MCC and the involved physicians to maintain an overview. All patients had a history of MCC and experienced causal or synergistic morbidity, causing the number of involved physicians and contacts with care providers to increase.[9] The treatment of MCC might become complicated at some point, for example, when there is another new, acute condition.[10] Moreover, the treatment by one specialist might interact with other diseases or medication prescribed by another specialist.[1] However, it is a common situation that every hospital physician only carries out the diagnostics and treatments within their own area of expertise;[1] the patient with MCC is expected to keep an overview of their care. Yet, with increasing numbers of involved care providers and complexity, this task can become increasingly demanding.[11] These case reports try to illustrate that patients with MCC might need a different, more integrated care approach. Care fragmentation and low continuity of care have been associated with overuse of medical procedures.[12] By designing an individualized management plan and discussing this with involved physicians, the geriatricians in the last two cases seemed to prevent unnecessary diagnostics, treatments, and check-ups. Moreover, early discussions about care planning have shown to enhance patient satisfaction and improve quality of care.[13] Individual care planning, comprehensive assessment, and care coordination are important elements of an integrated approach for patients with MCC.[8,14] The United Kingdom's National Institute for Health and Care Excellence guideline about this topic recommends the design of an individualized management plan, yet it has left implementation the responsibility of local organizations.[8] In the World Health Organization's report, several models of integrated care are described: individual models, group- and disease-specific models, and population-based models.[14] Individual models focus on high-risk patients, for example, with multiple conditions, through individual care plans and case-management. In the last two case reports, the geriatrician performed a comprehensive assessment, and coordinated and managed care for these older adults. However, as Tinetti, Fried and Boyd (2012) described in their article: depending on patient characteristics and type and complexity of the health problems, an individual, integrated approach could also be delivered by other care providers or specialists.[15] Recognizing the need for this approach could be a starting point for exploring implementation options with all disciplines involved, and stimulate the development and realization of group-specific or even population-based integrated care models within the hospital.

In conclusion, these case reports aimed to illustrate why an integrated approach in secondary care can be beneficial for patients with MCC. A starting point and method of implementation could be comprehensive assessment and the design of an individualized management plan by an appointed care professional in the hospital, in cooperation with the general practitioner and other physicians involved in treatment. The appointed care professional should be able to manage and coordinate care and to perform a comprehensive assessment of the patient's care and needs. General practitioners are an obvious candidate, but other care providers or specialists with the right competencies might be able to manage this as well. Future research should further elucidate which groups of patients with MCC might benefit from which integrated care approach, how to identify these groups, and which methods could be used to further incorporate integrated care in the current hospital system.

DISCLOSURES

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CASE REPORT

Large-vessel vasculitis associated with PEGylated granulocyte-colony stimulating factor

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KEYWORDS

Granulocyte-colony stimulating factor (G-CSF), large-vessel vasculitis (LVV), giant cell arteritis (GCA), pegfilgrastim

ABSTRACT

A 71-year-old female with advanced endometrial cancer was treated with pegfilgrastim. She developed a fever within seven days, and contrast-enhanced computed tomography scans repeated within three days revealed rapidly progressive thickening of the aortic wall. When clinicians administer PEGylated granulocyte-colony stimulating factor (G-CSF) to cancer patients, drug-associated vasculitis should be suspected. This report discusses the manifestation of G-CSF-associated large-vessel vasculitis (LVV).

What was known on this topic?
Granulocyte-colony stimulating factor (G-CSF)-associated large-vessel vasculitis (LVV) is a rare disease; however, it needs to be distinguished from other forms of LVV, including cancer-associated vasculitis. G-CSF-associated LVV shows rapid progressive thickening of the aortic wall.

What does this add?
A case of PEGylated G-CSF-associated LVV has been previously reported. We report a case of PEGylated G-CSF-associated LVV with rapidly progressive thickening of the aortic wall as observed with contrast-enhanced computed tomography (CECT). Patients with PEGylated G-CSF-associated LVV could be treated with prednisolone.

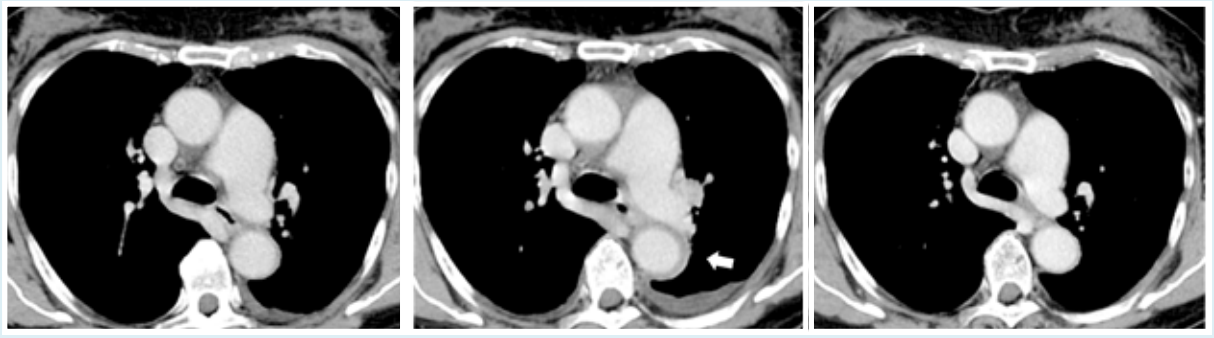
INTRODUCTION

Large-vessel vasculitis (LVV) is a chronic, idiopathic, granulomatous vasculitis of medium and large arteries.[1] LVV is thought to develop in a subacute manner, over several weeks or months. When clinicians find LVV in patients with solid cancers, they are likely to suspect cancer-associated vasculitis.[2] On the other hand, when clinicians find aortitis during chemotherapy treatment in such patients, they might recognise pegfilgrastim as the cause of inflammation. Pegfilgrastim is a PEGylated form of granulocyte-colony stimulating factor (G-CSF) that induces long-acting neutrophil proliferation and maturation. Due to its mild adverse effects, pegfilgrastim is considered relatively safe, and its adverse effects include back pain, headache, and fever, similar to those of filgrastim.[3] Recently, we found a rare case of LVV that developed during the administration of PEGylated G-CSF.

CASE REPORT

A 71-year-old Japanese female with stage IV endometrial cancer was treated with a single dose of pegfilgrastim for chemotherapy-induced neutropenia. Positron emission tomography (PET)-computed tomography (CT), performed three weeks before treatment, revealed no uptake in the aortic wall. After four days of treatment, a fever of 39.0 °C developed without any other symptoms. Her blood pressure was normal, and no blood pressure differences were observed between both arms. Her physical examination was unremarkable. Her laboratory results showed a total white blood cell count of 12.2 x 10^3 /μL (normal range 3.0-8.5 x 10^3/μL), with an absolute neutrophil count (ANC)

Figure 1. *CT scan of a patient with large-vessel vasculitis (LVV) associated with pegfilgrastim treatment. (A) Four days after pegfilgrastim administration. (B) Seven days after pegfilgrastim administration. An arrow indicates high-attenuation wall thickening. (C) CT scan after four weeks from the start of prednisolone treatment*



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of 10.2 x 10^3/μL, C-reactive protein of 278.5 mg/l (normal range 0-2.0 mg/l), and erythrocyte sedimentation rate of 111 mm/h (normal range 3-15 mm/h). Her blood culture tests were negative. The first contrast-enhanced CT (CECT) scan, which was performed four days after pegfilgrastim administration, showed no remarkable changes (figure 1A). Three days later, the follow-up CECT scan revealed high-attenuation wall thickening of the aortic arch and descending thoracic aorta (figure 1B). We could not detect such changes in her carotid arteries and abdominal aorta. Based on the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitis, she was diagnosed with giant cell arteritis (GCA)-like LVV.[4] After the administration of oral prednisolone (PSL) at 60 mg per day, both her symptoms and abnormal CECT findings were resolved within four weeks (figure 1C). During the diagnosis and treatment of LVV, there was no evidence of changes in the endometrial cancer spreading, remission, or invasion of other organs.

Table 1. *Previous reports of large vessel vasculitis associated with G-CSF drugs*

Case	Age	Sex	Disease	G-CSF, dose	Therapy duration of G-CSF	Time to onset of aortitis	CRP (mg/l)	Treatment	References
1	52	Male	None	Filgrastim, (no data)	4 days	6 months	no data	PSL 40 mg/day	7
2	78	Male	Cyclic neutropenia	Filgrastim, 500 μg	3 days	no data	142.8	PSL 40 mg/day	8
3	61	Female	Ovarian cancer	Lenograstim, (no data)	no data	6 days & 1 day	229.0	Cessation of treatment	9
4	77	Female	Ovarian cancer	Non-PEGylated G-CSF, 75 μg	6 days	8 days	84.30	Cessation of treatment	10
5	54	Male	Lung cancer	Non-PEGylated G-CSF, 300 μg	8 days	13 days	68.28	Cessation of treatment	11
6	67	Female	Lung cancer	Pegfilgrastim, 3.6 mg	1 day	8 days	202.0	PSL 80 mg/day	6
Our case	71	Female	Endometrial cancer	Pegfilgrastim, 3.6 mg	1 day	7 days	278.5	PSL 60 mg/day	-

G-CSF = granulocyte-colony stimulating factor; CRP = C-reactive protein; PSL = prednisolone; PEG = polyethylene glycol.

DISCUSSION

G-CSF-associated LVV is a rare disease. The frequency of aortitis in patients treated with G-CSF is 0.47% (16 out of 3409), as documented in the Japanese Adverse Drug Event database.[5] In the present and previous cases,[6] LVV appeared after administration of pegfilgrastim. We evaluated seven cases of patients with G-CSF-associated-LVV, shown in table 1.[6-11] Patients with solid cancers (cases 3, 4, 5, 6, and our case) developed vasculitis within 13 days of G-CSF administration. As seen in our case, the progression of vasculitis was rapid and developed within one week (figures 1A-B). Among these five cases, two PEGylated G-CSF-treated patients (2 out of 2) were treated with PSL, while three non-PEGylated G-CSF-treated cases (3 out of 3) went into remission without PSL after cessation of G-CSF. Therefore, PEGylated G-CSF-associated LVV could be treated using corticosteroids.

G-CSF drugs may affect various sized vessels in the body, including large vessels. Cutaneous leukocytoclastic vasculitis, mesenteric vasculitis, and polyarteritis nodosa (PAN) have also been reported in patients treated with G-CSF.[12,13,14] Notably, cases of cutaneous vasculitis recurrence upon re-exposure to G-CSF have been reported in detail.[14] Among these cases, measurement of ANC counts showed that the ANC in most cases increased above 800/μL at the time of recurrence, whereas cutaneous vasculitis showed no recurrence when ANC was maintained between 200/μL and 800/μL. Therefore, G-CSF-associated vasculitis is aggravated by neutrophil mobilisation.

When clinicians administer G-CSF treatment, including the PEGylated form pegfilgrastim, drug-associated LVV should be suspected in cancer patients. A radiological examination (e.g., CECT scan) may be suitable for detecting thickening in the aortic wall. The manifestation of G-CSF-associated LVV was rapid progressive aortic wall thickening, which might be distinguished from other forms of LVV.

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Statement of Ethics: According to the instructions of the Ethical Committee for Epidemiology of Hiroshima University, ethics board approval is not required for case reports, but the patient's informed consent is needed. We obtained the patient's written informed consent to publish this case report. The Ethical Committee for Epidemiology of Hiroshima University will obey the guidance published by the Ministry of Health, Labour and Welfare, Japan for the ethical regulations for case reports.

DISCLOSURES

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CASE REPORT

A rare bloodstream infection: *Bacillus mycoides*

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KEYWORDS

Bacillus mycoides, bacterial spores, bloodstream infection, environmental causes

ABSTRACT

A 65-year-old male was admitted to the Intensive Care Unit after being resuscitated because of a hypoxic cardiac arrest caused by influenza. Blood cultures taken at time of admission surprisingly grew *Bacillus mycoides*, a spore-producing apathogenic agriculture bacterium. We collected culture samples at his barge. Although we did not culture *Bacillus mycoides*, we did find multiple other *Bacillus* species. We hypothesised that our patient was colonised from the freights of his barge, and bloodstream infection occurred during resuscitation with either the bacterium itself or its spores. To our knowledge, this is the first report on bloodstream infection with *Bacillus mycoides* in a human patient.

What was known on this topic?

Bacillus mycoides, a spore-producing Gram-positive rod-shaped bacterium, is an apathogenic bacterium. It is part of the *Bacillus cereus sensu lato* (or *Bacillus cereus* group), together with species including *Bacillus cereus* and *Bacillus anthracis*.

What does this add?

To our knowledge, this is the first report on bloodstream infection with *Bacillus mycoides* in a human patient. In such rare cases of infection with *Bacillus mycoides*, exposition of agricultural origin should be taken into consideration.

Bacillus mycoides is able to produce spores and grows haemolytically on blood agar plates (bèta-haemolysis). This latter property differentiates it from *Bacillus anthracis*, which grows non-haemolytically.

INTRODUCTION

In this case report, we present a rare bloodstream infection: *Bacillus mycoides*, a spore-producing apathogenic agriculture bacterium.

Medical investigation in the field is not common practice in the Netherlands in cases of unexpected or rare pathogens, except for environmental assessment and source investigation by the municipal health service and the Dutch National Institute for Public Health and Environment (RIVM) in cases of tuberculosis, legionellosis and Q-fever.[1-3]

CASE REPORT

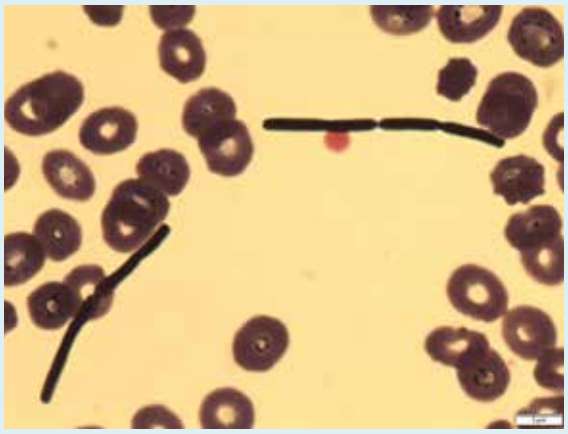
A 65-year-old male was admitted to the Intensive Care Unit (ICU), after an out-of-hospital cardiac arrest. Medical history revealed hypertension, cutaneous lupus erythematodes, chronic hyponatremia and Waldenström disease. Known prescribed medications were clobetasol balm, dabigatran, hydroxychloroquine, hydroxocobalamin injections, lercanidipine, lisinopril and pantoprazole. He was not recently treated with systemic immunomodulatory medication. He had not responded to the invitation for the annual Influenza vaccination.

He had been coughing for several days, when a friend found him in a dyspnoeic state inside the cabin of his barge. He had not been in contact with the water. When ambulance personnel arrived, he succumbed and they had to resuscitate him inside the cabin because of pulseless electrical activity. Struggling to accomplish intravenous access, they placed an intra-osseous needle (ION). Return of spontaneous circulation was gained after 20 minutes. On presentation at the Emergency Department, his blood pressure was 146/83 mmHg, his heart rate 103 beats/minute, his oxygen saturation 98% on mechanical ventilation with fraction of inspired oxygen 35%, and his

temperature 37.7 °C. Central venous and arterial lines were placed and the ION was removed. Electrocardiogram and cardiac ultrasound did not show signs of myocardial ischemia or pulmonary emboli. Chest X-ray showed redistribution and pleural effusion suspect for pulmonary oedema, and no clear signs of pneumonia. Since the patient developed pulseless electrical activity while in a dyspnoeic state, we assumed he had suffered from a hypoxic cardiac arrest.

He was admitted to the ICU for post-resuscitation therapeutic thermoregulation. Influenza A virus testing proved positive and treatment with oseltamivir was initiated. He gradually regained consciousness and was extubated at day four. That same day, to our surprise, four different blood cultures taken at time of admission proved positive for spore-producing Gram-positive rod-shaped bacteria. There were no clinical signs of bacteraemia: temperature was normal, circulation stable without support, and laboratory results showed declining leukocyte counts and C-reactive protein. Considering *Clostridium*, we started treatment with penicillin. To exclude and treat possible indwelling catheter infection, we removed the central venous lines and replaced the arterial line under penicillin treatment. Cultures of these lines remained negative. At day five, *Bacillus mycoides* were identified by matrix-assisted laser desorption/ionization (MALDI-TOF) (figure 1). Growth on blood agar plates showed haemolysis. Despite being known as an apathogenic bacterium, we chose to treat this *Bacillus* because of the bloodstream infection and switched antibiotic treatment to vancomycin because of penicillin resistance. We excluded any endogenous infection focus with CT scan of the thorax/abdomen. Blood cultures taken at day six and seven remained negative, as were sputum cultures throughout admission. Our patient recovered well, though still suffering the sequelae of postanoxic encephalopathy. He was discharged from the ICU at day seven.

Figure 1. *Gram stain of blood culture with Gram-positive rod-shaped bacteria: Bacillus mycoides*



DISCUSSION

In order to understand the cause of events which led to this unexpected and uncommon bloodstream infection, we had to investigate the origin of this case of *Bacillus mycoides*.

The *Bacillus cereus sensu lato* (or *Bacillus cereus* group) is comprised of eight different Gram-positive species: *Bacillus cereus sensu stricto*, *Bacillus thuringiensis*, *Bacillus weihenstephanensis*, *Bacillus mycoides*, *Bacillus pseudomycoides*, B*acillus cytotoxicus*, and *Bacillus anthracis*. They have the ability to express a number of enterotoxins and as spore-formers, they can present an increased risk to food safety since spores may survive food-processing controls such as pasteurisation. *Bacillus cereus* is among the most important enterotoxigenic foodborne pathogens, generally causing either emetic or diarrheal symptoms.[4] Though isolated and uncomplicated in the majority of cases, it is increasingly being reported to be a cause of serious and potentially fatal non-gastrointestinal tract infections, such as endocarditis, osteomyelitis, and severe cutaneous infections.[5] The other well-known pathogen species from this group is *Bacillus anthracis*, the etiological agent for anthrax.[6]

Bacillus mycoides is probably the least recognized species; in contrast to *Bacillus cereus* and *anthracis* it is not pathogenic and it does not have the insecticidal activity of *Bacillus thuringiensis* (figure 2, panel A).[6] *Bacillus mycoides* is ubiquitous in the soil and rhizosphere. Like *Bacillus subtilis*, some *mycoides* isolates have beneficial plant growth and biocontrol activity,[7] and hence, are found in natural compost and anti-fungal bio-pesticides (figure 2, panels B, C, D). Since it is not a human pathogen, infections with *Bacillus mycoides* are rare. B*acillus mycoides* is able to produce spores, and grows haemolytically on blood agar plates (bèta-haemolysis). This latter property differentiates it from *Bacillus anthracis*, which grows non-haemolytically.[8] In retrospect, it could have helped us differentiate between B*acillus mycoides* and *Clostridium difficile* (because the latter also grows non-haemolytically), when haemolytical growth would have been observed prior to identification by MALDI-TOF.

We concentrated on the agricultural origin of *Bacillus mycoides*. Our patient was not a gardener; he did not work with plants, compost, or manure other than the freights of his barge. Since he had been transporting agricultural freights for years (wheat, corn, and residual waste of palm/turnip/soy meant for cattle feeding), it is likely that *Bacillus species* like *subtilis* and *mycoides* and their spores entered

Figure 2. *Examples of insecticide, natural compost, and bio-pesticides, containing Bacillus thuringiensis (panel A), Bacillus subtilis (panels B, C), and Bacillus mycoides (panel D).*

A B C D

the barge, either as natural component of soil and plant roots, or as part of compost or pesticides.

The bacteria and their spores then colonised the skin of our patient. During resuscitation, the bacteria or their spores were introduced transdermally into the bloodstream through placement of either the ION or the venous and arterial lines. In order to test this hypothesis, we were granted permission to take culture samples from the hold and the water supply system of the barge (figure 3). Although subsequent cultures did not show *Bacillus mycoides*, we did find multiple other *Bacillus species*, in particular, *subtilis* and even *cereus* (table 1). Routine surveillance cultures of the patient's skin and throat did not grow *Bacillus*. However, because *Bacillus mycoides* is a spore-producing bacterium, the infection could also have originated from just the spores present on the ship and the patient's skin.

CONCLUSION

To our knowledge, this is the first report on bloodstream infection with *Bacillus mycoides* in a human patient. It seems likely that colonisation and subsequent transdermal bloodstream infection (with either the bacterium itself or its spores) originated from the ship's holds and freights. In such rare cases of infection with *Bacillus mycoides*, exposition of agricultural origin should be taken into consideration. Medical investigation in the field (patient homes, companies, public places) can contribute to the diagnostic process.

DISCLOSURES

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

Figure 3. *Pictures of our visit to the barge, in order to collect cultures from the hold and the water supply system. The 55-meter-long barge, with 560 tons of cargo capacity (panel A), the interior of the hold (panel B), one of several drainpipes (panel C).*

A B C

Table 1. *Results of the cultures collected at the barge*

Culture location barge	Microorganism	Quantity
Floor of the hold #1	Bacillus *cereus* *Serratia fonticola* *Serratia liquefaciens* Mixed flora	+ +++ +++ +++
Floor of the hold #2	*Bacillus circulans* *Bacillus pumilus* Mixed flora	++ + +++
Floor of the hold #3	*Bacillus pumilus* Mixed flora	++ ++
Floor of the hold #4	Mixed flora	++
Floor of the hold #5	Mixed flora	++
Floor of the hold #6	*Bacillus cereus* *Staphylococcus xylosus* Mixed flora	+ + +++
Wall of the hold #1	*Bacillus circulans* *Bacillus pumilus* Mixed flora	++ ++ ++
Wall of the hold #2	*Bacillus subtilis* Mixed flora	+ +
Wall of the hold #3	*Bacillus licheniformis* *Bacillus subtilis* Mixed flora	+ + +
Wall of the hold #4	*Bacillus circulans* *Bacillus pumilus* *Pseudomonas stutzeri* Mixed flora	+ ++ +++ +++
Drain pipe of the hold #1	Mixed flora	+++
Liquid drain pipe #1	Mixed flora	+++
Drain pipe of the hold #2	*Bacillus pumilus* Mixed flora	++ ++
Liquid drain pipe #2	Mixed flora	+
Sample outside water surrounding barge	Mixed flora	+++
Sample fresh water tank barge	Mixed flora	+

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PHOTO QUIZ

Undefined mass in head-neck region on iodine-123 scan

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Figure 1. *A CT scan of the head and neck shows a contrast enhancing mass at the base of the tongue*

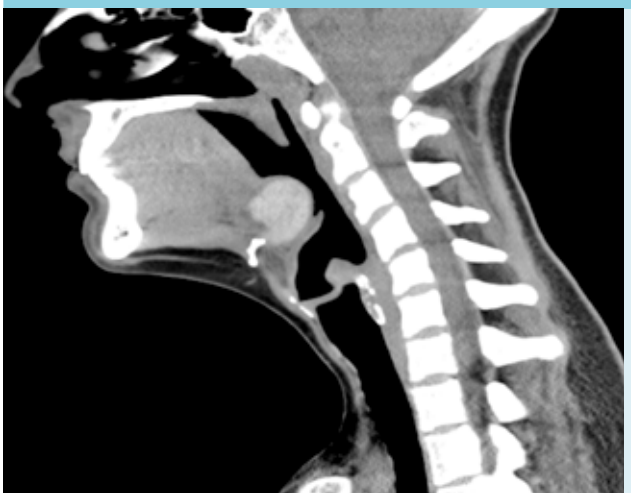
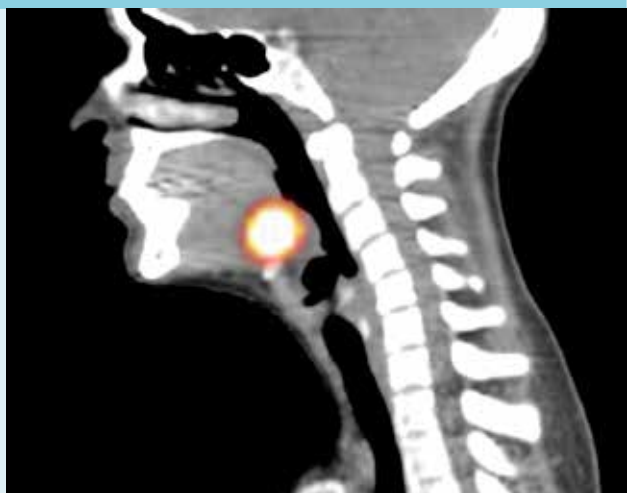


Figure 2. *An Iodine-123 SPECT CT scan shows high uptake in the mass*



CASE REPORT

A 30-year-old Caucasian woman was referred to the ear-nose-throat outpatient clinic complaining of dysphagia, otalgia and fever for four days. She did not have any relevant medical history. Under the suspicion of a pharyngeal abscess, a computed tomography (CT) scan was made, confirming the diagnosis; however, a contrast-enhancing mass at the base of the tongue was also visible (figure 1). An iodine-123 single photo emission tomography (SPECT)/CT scan was made, showing high iodine uptake in the lesion at the base of the tongue (figure 2).

What is your diagnosis?

See page 232 for the answer to this photo quiz

ANSWER TO PHOTO QUIZ (PAGE 231)

UNDEFINED MASS IN HEAD-NECK REGION ON IODINE-123 SCAN

DIAGNOSIS

This patient has an ectopic lingual thyroid, as there is high iodine uptake in the lesion, indicating that the lesion consists of thyroidal tissue. In addition, no iodine uptake was seen in the eutopic gland region, which means that the lingual thyroid is the only thyroid gland present. Thyroid function tests showed slightly elevated thyroid-stimulating hormone (TSH) serum concentrations (6.5 mU/l; reference range 0.27-4.2 mU/l) with normal free T4 serum concentrations (15.7 pmol/l; reference range 10.0-26.0 pmol/l). Thyroid antibodies were negative. During follow-up, thyroid function normalized (TSH 3.8 mU/l and free T4 16.2 pmol/l).

Thyroid gland ectopia is a condition which results from a developmental abnormality. During embryology, the thyroid descends from the pharyngeal gut towards the anterior neck region.[1] When descending fails, the thyroid will be localized in the descending path (lingual, sublingual, prelaryngeal or even substernal).[2] In most cases, the ectopic thyroid is the only gland present.

Thyroid ectopia is mostly asymptomatic. The incidence might be as high as 1 in 200,000 people.[1] When symptomatic, most patients present with symptoms due to any kind of obstruction such as cough, dysphagia, and dyspnea.[2] Most of the symptoms occur during childhood, adolescence, pregnancy, or menopause; this might be the result of increasing physiological demands for thyroid hormone, causing TSH concentrations to increase, resulting in enlargement of the gland. The ectopic thyroid is usually small and does not always have the capacity to fulfil the body's physiological needs. Approximately half of the patients are euthyroid; 40% have subclinical hypothyroidism and about 6% have overt hypothyroidism. The ectopia usually represents normal thyroid tissue, however nodular disease has also been described.[1]

Diagnosis should be made with nuclear imaging. It is a sensitive and specific modality for identification of thyroid tissue and thus for differentiation between thyroid ectopia and other masses in the head-neck region.[1,2]

Asymptomatic patients do not require therapy. Standard care for hypothyroidism should be initiated.[2] Not much is known about thyroid function of these patients during pregnancy. Regular measurements of thyroid function tests, follow-up by an endocrinologist and supplementation of levothyroxine in case of overt hypothyroidism is suggested. For patients who are euthyroid, but have mild symptoms due to obstruction, no consensus on optimal treatment is currently available. In addition to surgical intervention and radioactive iodine therapy,[2,3] combination treatment with levothyroxine and iodine might be beneficial. In a multicentre trial, this strategy has been shown to to reduce nodular volume in euthyroid patients.[4] Based on rationale, this strategy might also reduce obstructive complaints in patients with thyroid ectopia. However, this has not been formally tested in the setting of a clinical trial. Further evaluation of different therapeutic strategies in these patients is needed.

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