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Linoleum-cutting entitled 'Normen en waarden' by Manuel Kurpershoek. For details about the artist, his work, and how to order see elsewhere in this journal.

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Guidelines and shared care for asthma and COPD

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Shared-care constructions between general practitioners and pulmonary physicians are seemingly attractive for asthma and COPD patients. Thus they have to be implemented in further guidelines. However, anticipation that rapid changes will occur in treatment options towards optimal disease management justifies rapid adjustments in these strategies and requires investigations as to their ultimate benefit in disease outcome.

Many general practitioners (GPs) and pulmonary specialists in the Netherlands are faced with increasing numbers of patients attending their practices with symptoms and signs of asthma and/or chronic obstructive pulmonary disease (COPD). So far, asthma and COPD cannot be cured. Thus, GPs and pulmonary specialists have to pay attention to an individual's needs when providing care to improve the wellbeing and quality of life of these patients. Furthermore, they have to install an optimal individual treatment strategy to prevent exacerbations and deterioration of these diseases.

Asthma is one of the most common diseases encountered in clinical medicine, in both children and adults. It is one of the classic diseases recognised by Hippocrates over 2000 years ago, yet today it is still underdiagnosed. Main symptoms of asthma are attacks of breathlessness and wheezing that may occur both during the daytime and at night. Asthma is a variable disease in time and intensity that affects an individual's quality of life and cognitive performance, and it is associated with work and school absences, emergency consultations and hospital admissions. Asthma patients are predominantly under general practice care, and specialist visits only occur when the disease is

severe or treatment does not have the anticipated beneficial effects.

COPD is recognised to cause significant morbidity in adult individuals. The main symptoms are cough and shortness of breath. Furthermore, the disease is associated with reduced quality of life, work absence and increasing numbers of exacerbations and/or hospital admissions, especially in advanced disease. COPD is the only chronic disease worldwide with an increasing incidence and mortality. Several studies show stabilisation of mortality rates in men over the last decade, but a continued rise in women. In advanced disease, COPD patients improve with rehabilitation and oxygen treatment, yet mortality rates are high and cannot simply be prevented.

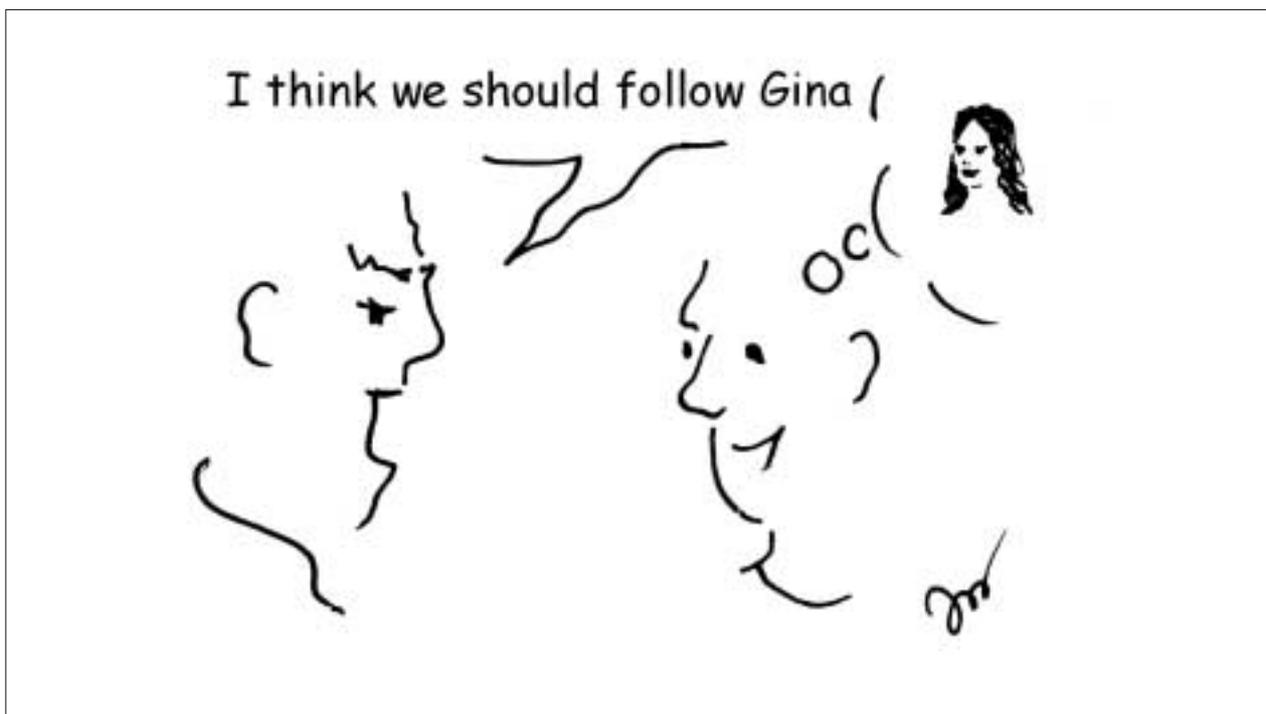
Management of asthma and especially COPD implies long-term follow-up with a periodical review of the patient's condition and comparison with the treatment objectives. To this aim primary care physicians and specialists have been given a framework for management by specific guidelines, the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Diseases (GOLD). These guidelines are based on the best-validated current concepts of COPD and asthma pathogenesis and the available evidence on the most appropriate management and prevention strategies. However, they do not encompass the notion how the interaction between GPs and specialists can be best applied in clinical practice.

Hence, it is of great interest that in the current issue of the Netherlands Journal of Medicine, Schermer and colleagues report their cross-sectional study with 29 participating pulmonary physicians. The study assessed whether the Dutch GP guidelines functioned according to the participating

pulmonary physicians' view on interaction between GPs and lung specialists with respect to optimal patient care. The asthma treatment available in 2003 is adequate for symptomatic control in many patients. Therefore, it is not surprising that strategies for collaboration between GPs and specialists were agreed quite easily. However, the approach in COPD is less clear. No studies have been performed as to the best consultation and back-referral strategies between GPs and pulmonary physicians. This will, however, prove very difficult to study. The lack of clear cut-off points for referral of patients may be largely attributed to the lack of knowledge on the best treatment strategies. In the past year a new

treatment has been introduced for COPD and it can be anticipated that more treatment strategies will follow. This will again change the approach for referral and back-referral.

The current study constitutes a good start for further optimisation of shared-care constructions between GPs and pulmonary physicians in clinical practice. Thus, it may have implications for future changes in asthma and COPD guidelines in the Netherlands. However, further studies are needed to establish whether this will also result in a better outcome for these diseases.



A high prevalence of culture-positive extrapulmonary tuberculosis in a large Dutch teaching hospital

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ABSTRACT

Background: In the Netherlands the incidence of tuberculosis (TB) has increased during the last decade. Growing immigration and international travel were important determining factors. To determine if this has resulted in altered clinical manifestations of the disease, we assessed the clinical spectrum of all TB cases diagnosed at our hospital in the period 1994 to 2000.

Methods: All culture-proven TB cases during the study period were retrospectively reviewed for clinical and demographic data.

Results: Sixty-five patients were identified. Solitary pulmonary TB was diagnosed in 33.9%, extrapulmonary TB in 51.8% and combined pulmonary and extrapulmonary TB in 14.3% of all cases. Patients were of foreign descent in 78.6% of all cases. Incidence peaked between 15 to 45 years. Decreased immunity was an important determining factor in the older patients. Presenting symptoms were mostly aspecific causing an important doctor's delay in establishing the diagnosis in 25%. Mortality was 3.6% and isoniazid resistance 3.6%

Conclusions: Our data suggest an increase in the percentage of extrapulmonary TB concomitantly with an increasing percentage of patients of foreign descent. Because of aspecific presenting symptoms, TB was often diagnosed late. Treatment is mainly hindered by non-compliance and a high index of suspicion is necessary in making the diagnosis.

INTRODUCTION

Tuberculosis (TB) remains one of the largest global health problems of our time. It accounts for approximately three million deaths each year and 1.7 billion people, one third of the world's population, are infected with *Mycobacterium tuberculosis*. This reservoir of infected persons results in eight million new cases of TB each year.¹⁻³ The spread of HIV/AIDS, the breakdown in health services and the emergence of multidrug-resistant *M. tuberculosis* are contributing to the impact of the disease.²⁻⁶ The growing epidemic led the World Health Organisation to declare TB a global emergency in 1993.

In the Netherlands the incidence of TB decreased during the course of the 20th century. However, in the last decade an important increase occurred, with numbers rising from 1227 TB cases in 1987 to 1535 cases in 1999.^{7,8} Immigration and international travel seem to be the most important determining factors.^{3,7,9,10} Besides alterations in incidence and demographic characteristics, the presentation of TB has changed. In the US the proportion of extrapulmonary TB remained fairly constant in the period 1977 to 1981. However, during subsequent years, as the incidence of pulmonary TB declined at a faster rate than that of extrapulmonary TB, the proportion of extrapulmonary TB gradually rose, with its incidence rising from 14.4% of all TB cases in 1977 to 17.5% in 1986.¹¹⁻¹³ In the Netherlands extrapulmonary TB accounted for 576 (31%) of all TB cases in 1999, compared with 383 cases (24%) in 1993. When nationality is taken into account, the incidence of extrapulmonary TB is much higher among patients of foreign descent than among natives of the Netherlands.⁷

In Rotterdam, and in other large cities, the incidence of TB is much higher than in rural areas. The higher incidence of TB and the growing number of newly diagnosed patients can be explained by the increasing number of people belonging to risk groups, such as immigrants and the socially marginalised.^{7,14} To test the hypothesis whether the clinical presentation of TB has changed in recent years due to its altered epidemiology, we retrospectively reviewed all cases of bacteriologically confirmed TB and compared our data with published series from the literature.

PATIENTS AND METHODS

Rijnmond-Zuid Medical Centre, location Clara, is a 553-bed hospital and serves a community of 147,197 persons, accounting for 205,316 outpatient contacts each year. Patients come from Rotterdam (592,673 inhabitants), as well as from the surrounding areas. It is the largest haemodialysis centre in the area and approximately 40 residents are being trained. The hospital is not a centre for HIV/AIDS. These patients are referred to the nearby university hospital. By screening the database of the microbiology laboratory of our hospital, we identified all patients who had one or more positive culture results for *Mycobacterium* species and were treated between 1 January 1994 and 31 August 2000. TB cases which were not bacteriologically confirmed were not included. We reviewed the records of all thus identified patients for demographic and clinical data, such as age, gender, country of birth, presenting symptoms, localisation of TB and comorbidity. Treatment and follow-up were studied, as well as *Mycobacterium* species and resistance to antituberculosis drugs. Pulmonary TB was defined as a positive culture from sputum or bronchoalveolar lavage (BAL) fluid. Pleural and mediastinal TB were considered as extrapulmonary localisations of TB.

During the study period two solid culture media were used, the agar-based Middlebrook 7H11 and the egg-based Löwenstein-Jensen media. Histological material was evaluated with both a fluorochrome stain with phenolic auramine and a Ziehl-Neelsen stain. Other specimens were evaluated with Ziehl-Neelsen staining only.

RESULTS

Bacteriological studies

Between January 1994 and August 2000 a total of 63 patients with a positive culture for *Mycobacterium* species were identified. Seven cultures were atypical *Mycobacteria*. These patients were not included in the study. Of the seven cases of atypical mycobacterial infections, one patient was a two-year-old girl, who developed an abscess on her shoulder after local BCG vaccination. Culture demonstrated an

M. bovis BCG. After surgical incision and drainage the patient recovered and no further treatment was necessary. Three patients had a positive culture for *M. avium*. All three patients had either chronic obstructive pulmonary disease (COPD) with chronic corticosteroid use or an underlying malignancy. *M. avium* caused no serious pulmonary illness and the patients received no antimycobacterial treatment. Two of the other patients had an infection with *M. malmoense* and one had *M. kansasii*. Mycobacterial infection caused pulmonary illness in these three patients and all were treated with tuberculostatic drugs. Again, a malignancy or COPD with chronic corticosteroid use were present in these patients. In 56 patients a *Mycobacterium* from the *M. tuberculosis* complex was identified. Two patients had an infection with *M. bovis*. A patient from Morocco presented with a painless swelling of a cervical lymph node. The lymph node was excised and histological examination showed a caseating granuloma. Biopsy culture and Mantoux testing were positive. The other patient was a native from the Netherlands and presented with slowly progressive shortness of breath, weight loss and non-productive cough. She had been treated for TB some fifty years before. Chest X-ray demonstrated unilateral pleural effusion. Pleural biopsy showed granulomatous, caseating inflammation. *M. bovis* was isolated from pleural fluid. Culture was positive for *M. tuberculosis* in 54 patients. Seven patients carried a strain of *M. tuberculosis* which was resistant to one antituberculosis drug: two to isoniazid (INH), one to rifampicin, three to streptomycin and one to pyrazinamide. No multidrug resistance was observed. Of the seven subjects with drug resistance, six were of foreign descent. None of these patients had a history of previous TB treatment.

A total of 66 positive cultures were obtained. Nine patients had a positive culture from two or more localisations. *M. tuberculosis* was most frequently cultured from lymph nodes (25.8%), sputum (22.7%) and BAL fluid (18.2%). The remaining positive cultures were obtained from an abscess (12.1%), pleural fluid (7.6%) or another source in 13.6%. Of the 15 sputum culture-positive patients, seven were smear-positive (Ziehl-Neelsen method) and five were smear-negative. Of the 12 positive BAL cultures, microscopic examination was positive in four patients and negative in six. Information on microscopic examination could not be retrieved in five patients.

Demographics

Twenty-seven patients were male with a mean age of 40.2 years (range 18 to 75 years) and the 29 females had a mean age of 40.7 years (range 13 to 83 years). Of all 56 patients, 21.4% were natives of the Netherlands and 78.6% of foreign descent. Patients from Turkey, Morocco and Surinam, the three largest ethnic groups in the Netherlands, accounted for 5.4, 10.7 and 12.5% of all

cases, respectively. Of the remaining patients 21.4% were of African (other than Morocco) and 25% of Asian descent. Two patients were of European origin.

Clinical manifestations

As illustrated in *table 1*, presenting symptoms were often aspecific (cough, fever and wasting). Of all patients, solitary pulmonary TB accounted for 19 cases (33.9%). A total of 29 patients were diagnosed with extrapulmonary TB, representing 51.8% of all cases. In eight patients (14.3%) a diagnosis of both pulmonary and extrapulmonary TB was made. Localisation and frequency of extrapulmonary TB are summarised in *table 2*.

Table 1
Presenting symptoms in 56 patients with tuberculosis

SYMPTOM	NUMBER	PERCENT
Cough	28	50.0%
Fever	23	41.1%
Wasting	23	41.1%
Lymph node swelling	15	26.8%
Malaise	11	19.6%
Dyspnoea	9	16.1%
Haemoptysis	6	10.7%
Abscess	5	8.9%
Abdominal complaints	5	8.9%
Bone pain	5	8.9%
Night sweating	5	8.9%
Chest pain	3	5.4%
Other	6	10.7%

Table 2
*Localisation and frequency of tuberculosis in 56 patients**

ORGAN SYSTEM	NUMBER	PERCENT
Pulmonary	19	33.9%
Pleural	7	12.5%
Lymphatic	18 [§]	32.1%
Cervical	14	25.0%
Mediastinal	5	8.9%
Intra-abdominal	4 [‡]	7.1%
Colon	1	1.8%
Small bowel	1	1.8%
Peritoneum	3	5.4%
Skeletal	6	10.7%
Vertebral column	4	7.1%
Clavicle	1	1.8%
Knee	1	1.8%
Skin/abscess	5	8.9%
Cerebrum	1	1.8%
Total	62	

* Six patients had two EP localisations of TB, [§] one patient had both cervical and mediastinal lymphatic TB, [‡] one patient had both small intestinal and colonic TB.

Tuberculin status

Of the 56 patients, 12 underwent tuberculin testing (Mantoux method). Nine patients were considered to have a positive result (>10 mm induration) and three were negative. Of these three patients one had pulmonary TB, one had tuberculous peritonitis and one tuberculous pleuritis. Immune suppression was present in one of the three patients, who was suffering from multiple myeloma and was treated with prednisone and melphalan. He had a history of pulmonary TB some 50 years before.

History of previous TB

Six patients had in the past been treated for TB. In two patients (aged 36 and 72 years) TB had been diagnosed in another hospital several years before. Due to non-compliance both had been treated inadequately. Four patients (two aged 67, one 75 and one 80 years) were treated for TB in a sanatorium some 30 to 50 years earlier. One of them received prednisone and melphalan shortly before reactivation of TB occurred. All four patients were natives of the Netherlands.

Associated medical problems/underlying diseases

Of all patients, 39 had no underlying disease or any other medical problems. Six patients had diabetes mellitus, three patients had a malignancy and four patients were receiving cytostatic or immunosuppressive treatment. Five patients were on chronic intermittent haemodialysis. Five patients had other associated medical problems such as drug or alcohol abuse. No patients were found to be positive for HIV or suspected of having HIV/AIDS. It should be noted that routine HIV screening was started after 1996.

Delay in diagnosis

In 60.7% of all cases a diagnosis of TB was made within four weeks following admission. In 14.3% the diagnosis was established between four and eight weeks. In 17.9% (ten cases) it took between eight weeks and six months before a definitive diagnosis of TB was made. Of these ten patients, two had pulmonary TB, six had extrapulmonary TB and two had both types of TB. In 3.6% (two cases) it took between six months and a year before a diagnosis of TB was made. Both had extrapulmonary TB. It took more than a year to establish the diagnosis in two patients. One patient had extrapulmonary TB and one pulmonary TB.

Treatment

Fifty-five patients (98.2%) received INH and 54 (96.4%) rifampicin. Thirty-eight patients (67.9%) were treated with ethambutol and 48 (85.7%) with pyrazinamide. None of the patients were treated with streptomycin. Sixteen patients (28.6%) received antituberculous treatment for a duration of six to nine months and 26 patients (46.4%) were treated for nine to 12 months. One patient was treated for more than

one year. Five patients had not completed the full course of treatment by the time of writing. Of six patients exact information on the duration of treatment could not be retrieved. Four patients suffered from polyneuropathy, five had liver enzyme abnormalities and five patients had other complications. Two patients died. One patient had multiple myeloma with renal insufficiency complicated by pneumonia. Culture from BAL fluid revealed *M. tuberculosis* post mortem. The second patient was on chronic intermittent haemodialysis and developed a tuberculous chest abscess. On top of uraemic and diabetic polyneuropathy he developed a severe polyneuropathy due to tuberculostatic drugs leading to respiratory insufficiency. After five months of mechanical ventilation the patient died of sepsis.

Follow-up

Of all patients, 31 (55.5%) completed their full course of antituberculosis treatment without any complications. Non-compliance occurred in 11 (19.6%) patients, leading to complete loss to follow-up in six patients and prolongation of treatment in five.

DISCUSSION

The increased TB incidence in the Netherlands during the last decade was mainly caused by immigration from countries of high TB prevalence.^{7,8} The aim of our study was to assess the clinical spectrum of TB and to determine whether these epidemiological and demographic changes have led to a different clinical presentation of the disease. We found 78.6% of all patients with culture-proven TB to be of foreign descent, which is a high percentage compared with the national data. In 1998, patients of foreign descent accounted for 60% of all TB cases in the Netherlands.⁷ In a recent study conducted at Amsterdam's university hospital, patients of foreign descent were found to account for 70% of all TB cases.¹⁰ In comparison, Smelt *et al.* found 25% of TB patients to be of foreign descent in their study conducted in the early eighties.¹⁵ The national data of 1985 showed 30% of all TB cases to be of foreign descent.⁷ Our results reflect the demographics of the Rotterdam area, where people of foreign descent made up approximately 40% of the total population in 2000 (source: www.cbs.nl) and are consistent with the view that TB is becoming increasingly concentrated in urban areas.¹⁶⁻¹⁸

The age distribution showed a peak in (young) adults and in the elder population. Patients in the younger age group were most often of foreign descent and had primary infections without associated medical problems. Elderly patients were mostly born in the Netherlands. Reactivation of TB accounted for 80% of all TB cases in Dutch patients of over 60 years of age. Decreased immunity, due to underlying diseases or immunosuppressive treatment, was

an important determining factor in this age group and is consistent with the view that the elderly are a population at risk for TB.^{19,20}

Presenting symptoms were mostly aspecific as described by other authors.^{12,16,18} This can be attributed in part to the remarkably high number of solitary extrapulmonary TB (51.8%) in our population. Another 14.3% of all patients had extrapulmonary combined with pulmonary TB. In the Netherlands, the incidence of extrapulmonary TB was 36% in 1998 with combined pulmonary and extrapulmonary TB accounting for 8% of all cases.⁷ Extrapulmonary TB is more frequent among patients of foreign descent (40%) than among natives of the Netherlands (30%).⁷ Table 3 summarises the results of 20 studies from various parts of the world.^{10-13,15,17-19,21-32} On average the percentage of extrapulmonary TB varies between 20 and 40%. The higher percentage we observed could be explained by the large number of patients of foreign descent and the fact that in the Netherlands immigrants routinely undergo screening for pulmonary TB by means of chest radiography. Extrapulmonary TB will not often be diagnosed in this way.

An important doctor's delay in diagnosis occurred in 25% of the patients. We found three main reasons for this delay. Sometimes inconclusive histology or negative culture results together with aspecific presenting symptoms led the clinician to consider diseases other than TB, such as sarcoidosis, Brucellosis or cat-scratch disease. After failure to respond to the instituted therapy, and repeated biopsies and cultures, TB was diagnosed. A second group of patients experienced delay because of concomitant diseases masking TB. Respiratory tract infections caused by pathogens other than *Mycobacteria* were most often implicated. Treatment failure or recurrence of symptoms led to reconsideration of the differential diagnosis and a more thorough search for TB. Finally, a low index of suspicion by general practitioners or other medical specialists caused late referral to the departments of pulmonology or internal medicine. Weir *et al.* observed a similar range in delay in diagnosis, which varied from days to years, with a median of two months.¹³ A lack of experience with TB on the part of physicians due to its decreasing incidence in the postsanatorium era has been implicated.²⁴ The elderly and patients not belonging to traditionally high-risk populations appear to be at greatest risk of having unsuspected disease.¹⁹

Sputum culture was positive in 55.6% of cases of pulmonary TB and culture from BAL fluid in the remaining 44.4%. Approximately 40% of patients with pulmonary TB were found to be smear positive on direct microscopic examination. Reviews on sputum analysis in the diagnosis of TB have found the incidence of smear positivity ranging from 32 to 55.3% and culture positivity from 70 to 96% of patients.^{18,33}

Table 3

Trends since 1962 in the prevalence of extrapulmonary (EP) TB in various parts of the world

NO.	AUTHOR	REFERENCE	COUNTRY	STUDY PERIOD	N	% EP TB
1	Alvarez <i>et al.</i>	11	USA	1968-1977	1593	4.5
2	Weir <i>et al.</i>	13	USA	1970-1980	104	37.0
3	Goldstein <i>et al.</i>	21	Canada	1977-1980	487	12.9
4	Rose <i>et al.</i>	17	USA	1980	70	3.5
5	Page <i>et al.</i>	22	USA	1976-1981	108	31.0
6	Mehta <i>et al.</i>	12	USA	1977-1981	7172	11.3
7	Byram <i>et al.</i>	23	United Kingdom	1973-1982	1673	20.0
8	Porat <i>et al.</i>	24	Israel	1979-1982	26	69.0
9	Brett <i>et al.</i>	25	New Zealand	1980-1982	235	11.0
10	Smelt <i>et al.</i>	15	The Netherlands	1980-1984	76	35.5
11	Counsell <i>et al.</i>	19	USA	1983-1987	38	18.0
12	Hurley <i>et al.</i>	26	Australia	1962-1989	482	42.9
13	Pang <i>et al.</i>	27	Australia	1980-1989	485	21.5
14	Svane <i>et al.</i>	28	Norway	1974-1993	32	65.6
15	Kuyvenhoven <i>et al.</i>	29	The Netherlands	1993	1582	24.5
16	O'Reilly <i>et al.</i>	18	Ireland	1991-1995	107	22.0
17	Juffermans <i>et al.</i>	10	The Netherlands	1993-1995	100	43.0
18	Gilad <i>et al.</i>	30	Israel	1992-1997	249	20.0
19	Melzer <i>et al.</i>	31	United Kingdom	1996-1997	47	57.0
20	Bonadio <i>et al.</i>	32	Italy	1996-1998	88	15.9
21	Hesselink <i>et al.</i>		The Netherlands	1994-2000	56	51.8

The percentage of INH-resistant *Mycobacteria* was low (3.6%) and comparable with the national number of 6 to 7%.⁷

All strains of single-drug resistant *Mycobacteria*, except for one, were isolated from immigrants from areas of high TB prevalence. None of these patients had been treated for TB in the past. Non-compliance was an important problem and all cases occurred in patients of foreign descent. Side effects of antituberculosis drugs caused non-compliance in two patients. In addition, one patient experienced worsening of a psychiatric disorder, causing loss to follow-up. Close cooperation with the public health service often led to early detection of defaulting and to measures ensuring completion of treatment, such as directly observed therapy (DOTS). Recently, Borgdorff *et al.* found an overall risk of defaulting from TB treatment of approximately 10% per year.³⁴ Recent and illegal immigrants showed higher rates of defaulting. The high percentage of patients of foreign descent may explain the relatively high percentage of non-compliance in our study. Shortening the duration of standard treatment from nine to six months, as was recommended in 1996,^{8,35,36} more frequent application of DOTS and improved coordination with the public health service in the follow-up of high-risk patients, may further improve treatment outcome in the future.

CONCLUSIONS

Extrapulmonary tuberculosis was present in 51.8% of all cases, which was high compared with earlier surveys showing percentages ranging between 10 and 40%. This change in the incidence of extrapulmonary TB occurred concomitantly with an increase in the percentage of TB patients of foreign descent (78.6% versus around 30% in the mid-80s). Mortality of TB was 3.6%. Extrapulmonary TB was often diagnosed late because of mostly aspecific presenting symptoms. This resulted in a greater than expected doctor's delay. Treatment was mainly hindered by non-compliance. Drug resistance was not a major problem during treatment. Although TB remains a relatively rare disease, a high index of suspicion is necessary in making the diagnosis.

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Referral and consultation in asthma and COPD: an exploration of pulmonologists' views

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ABSTRACT

Background: The burden of asthma and chronic obstructive pulmonary disease (COPD) on national healthcare systems is expected to increase substantially in future years. Referral guidelines for general practitioners (GPs) and pulmonologists may lead to more efficient use of healthcare facilities. We explored the prevailing views of pulmonologists regarding referral and once-only consultation in asthma and COPD, and compared these views with recently published transmural referral guidelines for GPs and pulmonologists.

Methods: Cross-sectional multiple case study. Twenty-nine Dutch pulmonologists working at non-university hospitals or specialised chest clinics participated in group discussion sessions.

Results: The outcome of the discussions and recently published referral guidelines for GPs and pulmonologists showed considerable similarity, but also some marked discrepancies. During the discussions, the main points of disagreement among the pulmonologists were: 1) should GPs or pulmonologists add long-acting β_2 -agonists to asthma treatment regimens; 2) should the current cut-off point 'predicted FEV₁ <50%' for referral of COPD patients be increased to 60 or 70%; and 3) should an annual exacerbation rate of two episodes a year be used as an undifferentiated referral criterion for COPD patients? For asthma, proposed back-referral (i.e. from pulmonologist to GP) criteria rested on: required dose of inhaled steroids, persistent need for long-acting β_2 -agonists, duration of clinical stability and persistence of airway obstruction. Back-referral criteria for COPD rested on age, blood-gas abnormalities and ventilatory limitations. Primary care

monitoring facilities and 'shared-care' constructions were considered to be facilitating conditions for back-referral.

Conclusions: This explorative study provided insights into how pulmonologists visualise a rational referral policy for patients with asthma or COPD. These insights can be taken into consideration in future revisions of referral and back-referral guidelines for GPs and pulmonologists.

INTRODUCTION

Over the next few years, it is expected that a sharp increase will occur in the incidence and prevalence of asthma and chronic obstructive pulmonary disease (COPD) in many Western countries.¹⁻⁴ Consequently, patients with these chronic pulmonary diseases will make steadily increasing demands on healthcare services. General practitioners (GPs) and pulmonologists will soon become aware of this, owing to the increasing time investment in these categories of patients. One of the major challenges for the near future is to achieve efficient use of available care facilities for asthma and COPD patients. Adequate referral policies from the GP to pulmonologist and back-referral to the GP form an inextricable part of this challenge. Although the theme 'referral in asthma and COPD' has been receiving increasing attention in the literature over the past few years and various guidelines have been put forward that contain concrete referral criteria,⁵⁻⁹ no research has been performed into the effectiveness of (alternative) referral policies for the two diseases. Nevertheless it is

reasonable to assume that if GPs follow an efficient referral policy, then superfluous specialist care will be prevented, while patients who do require specialist care will receive it all the sooner. If, at the same time, pulmonologists endeavour to refer patients back to their GPs as soon as they consider it medically justified, then optimal use will be made of their valuable time. Guidelines that dictate when referral is indicated contribute to more effective care. However, incorrect guidelines or recommendations that are poorly linked with daily practice can have an unfavourable effect.¹⁰ Therefore, the Dutch professional organisations of GPs and pulmonologists recently developed two transmural 'agreements', in which concrete recommendations are made about referral and back-referral of patients with asthma and COPD.^{11,12} As there is very little evidence-based information on which to base concrete referral criteria, these agreements (developed in the light of empirical findings and expert consensus) are the highest attainable at the present time. In the development of guidelines, it is of decisive importance to have intimate knowledge of daily practice; experts are often inclined to make too little allowance for this. In addition, it is important to be able to anticipate how new guidelines will be accepted by the workforce.¹³ A series of postgraduate courses enabled us to study the views of pulmonologists, regarding referral, back-referral and once-only consultation in asthma and COPD. The aim of the study was to make an inventory of prevailing views within this professional group and to compare these views to the expert consensus recently reached in the national transmural agreements for asthma and COPD.^{11,12}

METHODS

Between March 1999 and April 2000, four group discussion sessions were held with pulmonologists working at non-university hospitals or specialised chest clinics in four different regions of the Netherlands, to make an inventory of prevailing views on 'referral' and 'back-referral' of patients with asthma or COPD. Pulmonologists acting as regional contact persons were approached to evaluate the level of interest in postgraduate courses in this field. Participants in the four discussion groups were representatives from partnerships in the regions concerned. A total of 29 pulmonologists from 18 partnerships (approximately 10% of all registered pulmonologists active in the Netherlands) took part. In each discussion group one GP with a special interest in asthma and COPD was present to explain the guidelines issued by the Dutch College of General Practitioners (NHG),⁷⁻⁹ and the utility and applicability of these guidelines in daily practice. Prior to each discussion session, the pulmonologists were asked to fill in a short questionnaire on personal characteristics, their own criteria for back-referral of asthma and COPD patients, and local working agreements with GPs.

To ensure that a number of previously determined issues would be dealt with during the course of the discussions, two standardised cases were developed: one for asthma (see *table 1*) and one for COPD. Step by step, a specific part of the initial case description was modified using a standard set of overhead sheets. In this semi-structured manner, two of the authors (F. Smeenk and C. van Weel) were able to bring various issues under discussion that play a role in referral and back-referral in asthma and COPD. Criteria from the general practice guidelines were incorporated into the discussions. The asthma case was always discussed first, followed by the COPD case. This approach was tested and modified in a pilot discussion session held with pulmonologists working in the Nijmegen region. With the pulmonologists' consent, the discussions were recorded on audiotape. After the recordings had been typed out, two of the authors (T. Schermer and F. Smeenk) independently extracted conclusions from the discussions and classified them per theme. The themes for

Table 1
Asthma case used to structure group discussion sessions

INITIAL CASE DESCRIPTION

A 24-year-old non-smoking female cashier with a history of childhood asthma and atopic rash consults a GP. Renewed onset of respiratory symptoms (intermittent dyspnoea attacks, max. once a week) at age 20. Adequate symptom relief on salbutamol on an as-needed basis.
Should a GP refer this patient to a pulmonologist?

FIRST MODIFICATION

Additional diagnostic information is available: FEV₁ 2.56 l (73% of predicted value), FEV₁ reversibility after salbutamol 20% of predicted value, allergic response to house dust mite and pollen.
Should a GP refer this patient to a pulmonologist?

SECOND MODIFICATION

Frequency of respiratory symptoms increases from once a week to daily and symptoms are more severe. Salbutamol is needed every day.
Should a GP refer this patient to a pulmonologist?

THIRD MODIFICATION

Respiratory symptoms and salbutamol use are less frequent (once a week) with addition of budesonide 400 µg twice a day. Tapering off the budesonide dose is unsuccessful.
Should a GP refer this patient to a pulmonologist?

SUBSEQUENT MODIFICATIONS COVER THE FOLLOWING ISSUES

Persistent or deteriorating airway obstruction

(High) dose of inhaled corticosteroids

Addition of a long-acting β₂-agonist

Rapid deterioration of asthma condition

Frequent asthma exacerbations

Current smoking

Food allergy

Occupational exposure

asthma were medication and treatment targets, titration of the dose of inhaled corticosteroids, diagnosis and monitoring, and asthma exacerbations. The themes for COPD were lung function, exacerbations, treatment options, and diagnosis. Spirometry in general practice was considered as a separate theme. The results section describes the content of the discussions held in one or more of the sessions. The most important conclusions about referral and once-only consultation are summarised in tables. Explicit mention is made of all divergent views that became apparent during the discussion sessions. For the sake of simplicity, 'he' (read: he or she) is used in the text to refer to GPs, pulmonologists and patients.

RESULTS

Characteristics of the pulmonologists

All 29 pulmonologists were working at non-university hospitals or specialised chest clinics (28 men, one woman; mean age 46 ± 5.2 years; mean time since specialist qualification 14 ± 6.7 years). All indicated that they were

familiar with the asthma and COPD guidelines issued by the Dutch College of General Practitioners. The pulmonologists estimated that on average, formal back-referral to general practice occurred in 51% (range 15 to 82%) of their asthma and COPD patients. Table 2 presents the criteria used for back-referral, subdivided into 'global' and 'specific' criteria. Existing arrangements with GPs regarding the reason for referral and consultation were once-only consultation to determine diagnosis (38%), assistance with spirometry interpretation (20%), shared-care (20%) and local protocol for referral/back-referral (7%).

Issues on referral and consultation in asthma

Medication and treatment targets

Referral by GP to pulmonologist: In the case of intermittent or mild asthma with (reversible) airway obstruction, GPs have sufficient means at their disposal to initiate treatment. If the treatment does not lead directly to visible improvement, a GP should not be too hasty in referring the patient to a pulmonologist: a minimum evaluation period of six months was recommended. If the *a priori* set treatment targets (table 3) are not reached within this period, then the GP can

Table 2

Global and specific criteria used by participating pulmonologists (n=29) to refer asthma and COPD patients back to general practice care

ASTHMA		COPD	
GLOBAL CRITERIA	SPECIFIC CRITERIA	GLOBAL CRITERIA	SPECIFIC CRITERIA
Stable asthma condition (13, 45%)	PC ₂₀ >8 mg/ml (4, 7%)	Stable COPD condition (13, 45%)	FEV ₁ >60% of predicted value and clinically stable (2, 7%)
Lung function parameters (7, 25%)	Stable lung function >1 year (4, 7%)	Lung function parameters (7, 25%)	FEV ₁ /VC >50% of predicted value (2, 7%)
Well-regulated medication use (4, 14%)		Competence of GP in question (2, 7%)	
Competence of the GP in question (2, 7%)			

Figures in brackets represent the number and proportion of participants that indicated the particular criterion, respectively.

Table 3

Treatment targets and indications for (once-only) consultation with a pulmonologist in adult patients with asthma, according to the national guidelines of the Dutch College of General Practitioners⁸

TREATMENT TARGETS IN PATIENTS

No, or only minor asthma symptoms, acceptable night's rest, (nearly) normal daily activities

As few interventions as possible, minimal or no side effects of asthma medication

Prevention or timely treatment of asthma exacerbations

Achieving and preserving optimal lung function

INDICATIONS FOR (ONCE-ONLY) CONSULTATION WITH A PULMONOLOGIST

Persistent use of high-dose inhaled steroids without being able to taper off; treatment targets cannot be achieved on this regimen

Continuous use of high-dose inhaled steroids or moderately high dose of inhaled steroids combined with a long-acting β_2 -agonist

increase the dose of inhaled steroids or add a long-acting β_2 -agonist. If no progress is made during the new evaluation period with this combination therapy, then referral to the pulmonologist is indicated. The phase in which lung medication is initiated depends on the degree to which the GP decides to extend the medication himself. In one of the discussion groups, the prevailing view was that (partial) substitution of an inhaled steroid for a long-acting β_2 -agonist should be performed by the pulmonologist, not by the GP. In any case, before deciding to administer long-acting medication, the GP should first reconsider his diagnosis of asthma. If after repeating the anamnesis and supplementary peak flow measurements there is still doubt about the accuracy of the diagnosis, then a once-only diagnostic consultation with the pulmonologist can be requested.

Tapering off the dose of inhaled steroids

Referral by GP to pulmonologist: The maintenance dose of inhaled steroids is in itself a factor that should play a role in the GP's decision as to whether or not to refer the patient. Upper dose limits of 800 to 1000 μg of budesonide or beclomethasone, or 500 μg of fluticasone a day, as recommended in the current Dutch GP guidelines, were considered to be acceptable referral criteria by the pulmonologists. At higher doses, the risk of systemic side effects can form an indication for referral.

Several of the pulmonologists had the impression that GPs are often reluctant to administer long-term maintenance treatment with inhaled steroids; they seem to have the tendency to prematurely taper off the dose. Once again, the factor time should play a role. If a GP decides to taper off a moderately high maintenance dose (800 to 1000 μg a day) in a stable asthma patient, but is unable to do so over a period of two years, then the risk of long-term side effects can form an indication for referral. Most pulmonologists were of the opinion that if the GP is certain of the diagnosis and has excluded all possible trigger factors, he can first add a long-acting β_2 -agonist and then subsequently try to taper off the dose. If it still proves impossible to reduce the dose of steroids, then a once-only consultation with the pulmonologist can be requested to check whether any trigger factors have been missed. Several of the discussions revealed that owing to the fact that referral information from the GP does not always offer sufficient footing, it might not be possible to gain an adequate overview during a once-only consultation.

Back-referral from pulmonologist to GP: During consultation with an asthma patient, the pulmonologist provides further confirmation of the diagnosis and treatment, and establishes the minimum required maintenance dose of medication. On the basis of the histamine threshold, he evaluates whether the inhaled steroid dose can be tapered off. In the majority of cases, it is possible to refer the patient back

to the GP with clear treatment instructions and recommendations for frequency-of-monitoring visits. Adaptation of a medication regime by the pulmonologist should always include a period of intensive spirometry or peak flow measurements which, in principle, the GP can undertake. When a patient in the care of a pulmonologist has become clinically stable on an 800 to 1000 μg daily dose of inhaled steroids, he can normally be referred back to his GP. Even at higher doses, back-referral does not need to be a problem if the patient has been stable for some time. In only one of the discussion groups was the term 'stable' further specified as: normal lung function and very few respiratory symptoms, while the steroid dose is clearly based on the minimum required dose. The main reasons mentioned by the pulmonologists for not referring asthma patients back to the GP are given in *table 4*. If a patient is using an inhaled steroid dose of more than 800 to 1000 μg a day (with or without addition of a long-acting β_2 -agonist) the pulmonologist can decide to monitor the patient himself. However, cooperation with the GP in the form of a shared-care construction is also possible, although structured communication between the pulmonologist and GP is essential in this situation.

Diagnosis and monitoring

Referral by GP to pulmonologist: In the majority of cases, the GP can make the diagnosis of asthma himself using peak flow measurements. Spirometry in patients with suspected asthma only has additional value when previously conducted peak flow measurements have shown that the patient has reversible airway obstruction or day-night variability. In asthma patients who have very few respiratory symptoms but show persistent airway obstruction, despite adequate treatment with inhaled steroids, there seems to be an indication for referral. Stipulations for referral are that the obstruction must in principle be fully reversible and there must be an obvious discrepancy between lung function and respiratory symptoms. Relatively young patients with persistent airway obstruction that does not subside after a 'diagnostic' course of oral steroids should be referred to the pulmonologist for further testing. Other reasons mentioned for referral are given in *table 4*.

Back-referral by pulmonologist to GP: The discussions showed that pulmonologists do not tend to refer patients back to general practice on the basis of hard evidence alone. The feeling that the pulmonary condition is stable plays a more important role. When the pulmonologist refers the patient back, he expects the patient to be monitored by his GP in accordance with the current asthma guidelines for GPs. It therefore depends on the GP in question whether the pulmonologist refers the patient back or not, especially in patients whose monitoring is of an urgent nature.

Table 4

Summary of statements concerning referral and once-only consultation in asthma, derived from four discussion sessions with non-university pulmonologists (n=29)

	DESCRIPTION OF STATEMENT	NO. MEETINGS IN WHICH ITEM CAME UP ⁵	PRO/CON [*]
Situations in which GPs should consider (once-only) consultation with a pulmonologist			
Consider referral if:	Attempts to taper off a high dose of inhaled steroids (>800-1000 µg budesonide or beclomethasone, >500 µg fluticasone) are unsuccessful after two years	4	(4/0)
	(Partial) substitution of inhaled steroids by a long-acting β ₂ -agonist is considered	4	(1/3)
	Poor medication compliance, ill-advised lifestyle or other patient-centred causes for recurrent exacerbations despite sufficient attention from the GP	4	(4/0)
	Persistent asthma symptoms coinciding with normal lung function, despite otherwise adequate treatment with inhaled steroids	3	(3/0)
	≥3 asthma exacerbations a year, each requiring treatment with oral prednisolone, without an identified trigger for the high exacerbation rate	3	(3/0)
	No clinical improvement is observed six months after adjustment of the asthma medication regime	2	(2/0)
Consider once-only consultation if:	Persistent diagnostic uncertainty, even after repeating medical history taking, elimination of all possible trigger factors and additional peak flow monitoring	4	(4/0)
	Doubt about the feasibility of tapering off inhaled steroids	4	(4/0)
	Persistent airway obstruction after a diagnostic prednisolone course at relatively young age	3	(3/0)
	Drastic allergen avoidance measures are inevitable	2	(2/0)
Situations in which pulmonologists should consider back-referral to a GP			
Consider referring back if:	A patient has been clinically stable [#] for 1.5 to 2 years on a low to moderately high dose of inhaled steroids (≤800-1000 µg budesonide/beclomethasone, ≤500 µg fluticasone)	3	3/0
	A patient has been clinically stable [#] for 1.5 to 2 years on a high dose of inhaled steroids (>800-1000 µg budesonide/beclomethasone, >500 µg fluticasone), with or without a long-acting β ₂ -agonist, provided that the GP supervises the monitoring schedule, or a solid shared-care construction is available	3	3/0
	None of the following are applicable: Persistent necessity for the combination high-dose inhaled steroid + long-acting β ₂ -agonist Persistent airway obstruction Asthma-related hospital admission <1.5 to 2 years ago	1	1/0

Statements are ranked by the number of meetings in which each particular issue was discussed. ⁵ Minimum 1, maximum 4; ^{*} PRO=prevailing view during session in favour of statement; CON=prevailing view during session against statement; [#] in one session specified as 'normal lung function, few respiratory symptoms and inhaled steroids adjusted to the lowest possible effective dose'.

Asthma exacerbations

Referral by GP to pulmonologist: If an asthma patient is undergoing optimal monitoring by the GP but suffers three or more exacerbations a year that require prednisolone, then referral to a pulmonologist is indicated. In cases with a clear explanation for the recurrent exacerbations, referral does not seem to be so worthwhile. If the GP is unable to identify the triggering factor in a patient with recurrent exacerbations, then referral is indicated. Two of the discussion sessions revealed that some of the pulmonologists felt that particularly patients with persistent symptoms were referred to them relatively quickly, whereas patients

who needed several courses of prednisolone a year but expressed very few respiratory symptoms were not referred until the prednisolone became less effective. Several pulmonologists suggested that GPs are sometimes too premature with administering courses of prednisolone, without first attempting to identify the underlying cause of the exacerbation. If there is no relevant improvement or persistent deterioration occurs while a patient is receiving optimally regulated maintenance treatment, then the GP should not wait too long before referring the patient to a pulmonologist.

Although the current GP guidelines recommend that an asthma patient should be referred to a pulmonologist in the case of two or more exacerbations a year, it seems to be difficult – if not impossible – in practice to establish a general absolute cut-off point. The specific circumstances of the patient and the existence of a possible explanation for a high exacerbation rate are strong determinants. In addition, the degree to which the asthma patient himself is responsible for ‘aggravating’ his asthma can play a role in the GP’s decision whether or not to refer the patient.

Back-referral by pulmonologist to GP: If a patient has recently suffered an acute severe asthma attack, it is advisable for him to remain under the care of the pulmonologist for a fairly long time. An evaluation period of 18 to 24 months was mentioned as a rule of thumb in several of the discussion groups, irrespective of whether the patient has become clinically stable on a maintenance dose of inhaled steroids. After the evaluation period the pulmonologist can consider referring the patient back to the GP. If he decides to refer the patient back, he should preferably give the most concrete possible advice about the further management policy.

Conclusions regarding referral and consultation in asthma are summarised in *table 4*.

Issues on referral and consultation in COPD

Lung function, exacerbations and treatment options

Referral by GP to pulmonologist: In all discussion groups the pulmonologists made it clear that when making a referral decision, GPs should not only take the Dutch GP guidelines (*table 5*) into consideration, but also the respiratory symptoms and possible discrepancies between these symptoms and clinical presentation. In the GP guidelines, the lung function criteria for referral are an FEV₁ <50% of the predicted value and/or an FEV₁ <1.5 litres. An

important point of discussion in relation to these criteria was that a COPD patient who has not (yet) dropped under these cut-off levels will develop problems at some stage, which will persist for the rest of his life. If the GP does not establish any relevant baseline values for lung function, then the pulmonologist should be given the opportunity to do that for him.

The pulmonologists held the view that COPD patients with moderate to severe airway obstruction, but a discrepancy between respiratory symptoms and clinical presentation, should always be referred. Although there is evidence in the literature that the prognosis deteriorates when lung function falls below the above-mentioned FEV₁ cut-off levels, it is not clear whether earlier referral has any additional value. However, owing to the fact that, depending on the specific circumstances, multiple problems can be expected in patients with moderate to severe airway obstruction in a relatively early stage of the disease, earlier referral is desirable, for instance at FEV₁ <60% of the predicted value. In any case, GPs must be encouraged not to wait until the FEV₁ has fallen below 50% before they refer a COPD patient. A possible disadvantage of lowering the referral limit is the considerable increase in burden on specialist care. Furthermore, the pulmonologists agreed that GPs should not base their referral decision only on FEV₁ values. FEV₁ alone is not sufficient to characterise a COPD patient, although in practice, this is all the GPs have to go on. Discussions on the role of exacerbations revealed that in the case of frequent exacerbations (i.e. two or more exacerbations a year), there are two arguments in favour of referral by the GP: evaluation of the causal factors and the risk of side effects from frequent prednisolone courses.

Bronchial hyperresponsiveness in COPD patients not only forms a prognostic factor, it can also be used to identify the (relatively small) group of COPD patients that also have

Table 5

Treatment targets and indications in patients with COPD for (once-only) consultation with a pulmonologist, according to the national guidelines of the Dutch College of General Practitioners⁹

TREATMENT TARGETS IN PATIENTS WITH COPD

Short term: reduce respiratory symptoms, improve exercise tolerance, improve lung function and prevent exacerbations

Long term: decelerate progressive lung function decline and postpone or prevent complications and disability

INDICATIONS FOR CONSULTATION WITH A PULMONOLOGIST

Severe COPD (FEV₁ <50% of predicted value or <1.5 l) despite optimal treatment

Persistent uncertainty about whether COPD is complicated by chronic heart failure

COPD at a relatively young age (<50 years)

Severe progressive FEV₁ decline (>100 ml/year) despite treatment with inhaled steroids

Frequent exacerbations despite treatment with N-acetylcysteine

Possible indication for oxygen treatment, maintenance treatment with antibiotics or theophylline, pulmonary rehabilitation

features of asthma. With changing insights into the role of inhaled steroids in COPD it remains to be seen whether in the future, GPs should also consider the degree of bronchial hyperresponsiveness in their decision to prescribe inhaled steroids. As pulmonologists are better able to distinguish between subgroups than the GP, some patients might not receive maximum benefit from the existing treatment options during the years that are lost prior to referral. In two of the sessions, discussion arose about whether pulmonologists have more means at their disposal than GPs to help COPD patients quit smoking. Perhaps pulmonologists in their capacity as medical specialists have greater authority in the patient's view, but in principle, the GP should be able to achieve the same results.

Back-referral by pulmonologist to GP: Pulmonologists should include the factor (advanced) age in their decision about whether or not to refer COPD patients back to general practice. Otherwise there is the risk that the outpatient clinic will 'fill up' with elderly COPD patients. If these elderly patients can manage on their regular maintenance treatment supplemented with a course of prednisolone now and again, then the pulmonologist has little more to offer than the GP. However, it is better for patients with gas transfer abnormalities to remain under the care of the pulmonologist, although a shared-care construction can also be considered, in which the GP monitors the patient and specially trained COPD nurses provide assistance. If the pulmonologist refers a patient on oral theophylline back to his GP, then it is important that he realises that the GP guidelines do not contain any recommendations about this treatment. Therefore his advice should include clear instructions. If the pulmonologist has tried in vain to stop the theophylline, this should also be mentioned explicitly in the back-referral letter.

Diagnosis

Referral by GP to pulmonologist: Although the GP himself can refer a patient for supplementary tests (e.g. chest X-ray), referral to a pulmonologist might be worthwhile to exclude malignancy or to 'map' the patient's status on the basis of carbon monoxide diffusion capacity, blood gasses, respiratory mechanics and ergometry. In every COPD patient with moderately severe airway obstruction (FEV_1 50 to 70% of the predicted value) the GP should consider referral for a once-only (diagnostic) consultation. The pulmonologist can map the patient's lung function more extensively and evaluate unfavourable prognostic factors. When they refer a patient just for spirometry and the accompanying interpretation of the pulmonologist, GPs also expect to receive concrete information about the diagnosis and advice about treatment. As the pulmonologist only sees the spirometry test results and not the patient himself, this is not an ideal

situation. Within the discussion groups the participants clearly expressed preference for 'evaluation mapping' by the pulmonologist in such circumstances, in which he personally sees the patient (at least) once.

Back-referral by pulmonologist to GP: A COPD patient cannot be referred back to the GP on the basis of lung function criteria alone. It is important for the pulmonologist to gain insight into the impact of COPD on the patient's daily functioning so that he can give the GP more detailed advice about treatment. In the case of moderately to severely disturbed diffusion capacity, continuation of regular monitoring by the pulmonologist takes preference over referral back to the GP. Although the spirometry and ventilatory parameters might be borderline normal, these patients are approaching the level of permanent invalidity. In patients with ventilatory limitations, hypoxaemia and/or hypercapnia on exertion, it is preferable for the pulmonologist to continue seeing the patient for checkups. If the patient is subjectively and objectively stable and the pulmonologist considers it possible to transfer the checkups to the GP, then he can refer the patient back. The pulmonologist can, for example, advise the GP to refer the patient to a lung function laboratory for periodical supplementary testing.

Conclusions regarding referral and consultation in COPD are summarised in *table 6*, see page 78.

DISCUSSION

The results of this explorative study sketch a useful profile of the views of Dutch pulmonologists regarding the wide-sweeping theme: referral and consultation in asthma and COPD. Although previous research has shown that questionnaires can be used to make such inventories,^{14,15} it has also become clear that they are unable to map nuances. The present qualitative study design offered the opportunity to explore the major issues and discussion points surrounding this complex theme in fairly great detail. However, it is possible that the selection of regions influenced the findings: our survey did not include all the separate regions of the Netherlands. If regionally determined variations exist in referral and back-referral policies and views, then this may have affected the direction of the results. In addition, the discussions, despite uniform structuring by means of the standardised case descriptions on an overhead sheet, were kept fairly open. It is therefore possible that not all prevailing views were expressed, as certain topics received less attention.

One of the most important findings in this study was that broadly speaking, Dutch pulmonologists approved

Table 6

Summary of statements concerning referral and once-only consultation in COPD, derived from four discussion sessions with non-university pulmonologists (n=29)

	DESCRIPTION OF STATEMENT	NO. MEETINGS IN WHICH ITEM CAME UP ⁵	PRO/CON* PRO/CON*
Situations in which GPs should consider (once-only) consultation with a pulmonologist			
Consider referral if:	FEV ₁ <50% of predicted value or FEV ₁ <1.5 l	4	3/1 [§]
	FEV ₁ value ≥50% of predicted value or FEV ₁ ≥1.5 l, but persistent respiratory symptoms or a discrepancy between symptoms and the clinical profile	4	4/0
	≥2 exacerbations a year, in order to evaluate causal factors and assess the risk of side effects due to frequent prescription of prednisolone courses	3	1/2 [#]
Consider once-only consultation if:	FEV ₁ is 50 to 70% of predicted value, in order to enable the pulmonologist to map relevant baseline parameters (e.g. TL _{CO} , blood gasses)	3	3/0
	The GP anticipates that the probability of successful smoking cessation may be higher when supervised by a pulmonologist	2	2/0
	Determine whether treatment with inhaled steroids is appropriate, based on measurement of bronchial hyperresponsiveness	2	2/0
Situations in which pulmonologists should consider back-referral to a GP			
Consider referring back if:	None of the following are applicable: Presence of moderate to severe gas transfer abnormalities (except when a high-quality shared-care construction is guaranteed) Presence of ventilatory limitations Presence of hypoxaemia and/or hypercapnia	2	2/0
	An elderly patient is managing sufficiently well on the established maintenance treatment and an occasional oral prednisolone course	1	1/0

Statements are ranked by the number of meetings in which each particular issue was discussed. ⁵ Minimum 1, maximum 4; * PRO=prevailing view during session in favour of statement; CON=prevailing view during session against statement; # in two sessions, the participants were in doubt whether it is appropriate to assert one cut-off point concerning annual exacerbation rate in all patients with COPD; § in one session a cut-off point of 60% of the predicted FEV₁ value was proposed; TL_{CO} = diffusing capacity for carbon monoxide.

the contents of the GP guidelines⁷⁻⁹ and the transmural agreements published by their own, and the GPs' professional organisations.^{11,12} However, they clearly had their own professional views about referral by GPs and subsequent back-referral. Another important conclusion is that it is reasonably easy to formulate univocal referral criteria for asthma; the literature and empiricism offer sufficient points of application for this. In contrast, this task is much more complex for COPD. According to the pulmonologists, there are so many individual, patient-related factors that can play a role in the GP's decision to refer a patient with COPD that it is very difficult to devise strict criteria. On the one hand, this situation is inconsistent with the referral limit of an FEV₁ <50% of the predicted value or <1.5 litre currently recommended,^{9,12} because this cut-off point still leads to many discussions between GPs and pulmonologists. On the other hand, it is not clear whether the pulmonologists justifiably expressed concern that GPs wait until the FEV₁ has deteriorated to the recommended cut-off point. A possible solution was the proposal to refer all COPD patients with

an FEV₁ of 50 to 70% of the predicted value ('moderate obstruction') to a pulmonologist for once-only evaluation mapping of diffusion capacity, blood gasses, etc. This policy is in line with the position held by Dutch pulmonologists regarding detection of the group of COPD patients with moderate to severe bronchial hyperresponsiveness. In this way, pulmonologists can evaluate the presence of an asthma component in the cause of airway obstruction and the indication for inhaled steroid treatment.

Comparison with published Dutch transmural agreements

Nine months after the last discussion session was held, the Dutch professional organisations of GPs and pulmonologists published their joint transmural agreements for asthma and COPD,^{11,12} which include detailed recommendations on referral and back-referral for GPs as well as pulmonologists. In many respects, the contents of the transmural agreements are in line with the existing asthma and COPD guidelines for GPs.⁷⁻⁹ The outcomes of our discussion sessions and the transmural agreements showed considerable

similarity, but also some marked discrepancies. For asthma, the most notable discrepancies were:

- the issue of tapering off inhaled steroids does not come up at all in the agreement,¹¹ whereas it was a major issue in all discussion sessions;
- GPs should wait longer (i.e. six instead of three months)¹¹ after adjustment of an asthma medication regime before concluding that no clinical improvement has been achieved;
- GPs should first try to identify underlying triggers for (recurrent) asthma exacerbations before referring a patient to a pulmonologist;
- GPs should refer an asthma patient for once-only consultation in case drastic allergen avoidance measures are planned;
- pulmonologists should take longer (i.e. 18 to 24 months instead of 3 to 12 months)¹¹ before referring clinically stable asthma patients back to their GP, regardless of the maintenance dose of inhaled steroids.

The transmural COPD agreement¹² comprises more (and far more detailed) recommendations regarding referral and back-referral compared with the pulmonologists' views expressed during the discussion sessions. As indicated above, some notable additions were suggested: referral of patients with a predicted FEV₁ of 50 to 70% for once-only (diagnostic) consultation to map relevant baseline characteristics; once-only consultation of a pulmonologist to evaluate the indication for inhaled steroid treatment on the basis of bronchial hyperresponsiveness.

Referral and efficiency of care

Although there is only one indication in the literature that a structured referral policy can result in more efficient asthma care,¹⁶ we do not know which set of referral criteria leads to the most efficient care for asthma patients. No studies have been performed on COPD in this area. Therefore for the time being, guidelines for referral and consultation in asthma and COPD can be based solely on common sense and consensus. It is particularly for this reason that the findings in this study may offer useful leads for authors who are formulating or revising referral guidelines. The fact that the pulmonologists from the study regions could apparently hold different views about who should be responsible for substituting inhaled steroids for a long-acting β_2 -agonist can in practice form a barrier against accepting asthma guidelines. Most pulmonologists agreed that an 800-1000 μg dose of inhaled steroids was a useful referral criterion, which provides support for the current GP guidelines and transmural agreement. The additional referral criteria for GPs proposed in the discussions about asthma (see *table 4*) can be taken into consideration when devising or revising guidelines. It is possible that clear formulation of the reason for referral and clear presentation

of the question – something that was often missing according to our study participants – would contribute to more efficient care. In the literature, it is stated that in at least 15% of all referrals, the nature of the problem remains obscure.¹⁷

GPs' diagnostic uncertainty and the value of spirometry

In one of the discussion groups it was stated that when asthma is suspected, spirometry only has supplementary value if the GP finds reversible airway obstruction or day-night variability using peak flow measurements. Because airway obstruction – or its reversibility – can be detected more effectively with spirometry than with peak flow measurements, this is doubtful. As a steadily increasing number of GPs are setting up their own spirometry facilities, the value of peak flow measurements is decreasing. However, negative findings on supplementary tests (i.e. normal peak flow, absent peak flow variability, normal spirometry), while the GP nevertheless has clinical suspicions of asthma, can form a relevant referral indication. In such a case, supplementary tests by the pulmonologist have clear additional value: if the histamine threshold is normal, then clinical asthma is almost certainly excluded and the GP can continue his search within the differential diagnosis. During the discussions, the pulmonologists laid great emphasis on the 'degree of certainty' about the diagnosis asthma. Recent studies have also shown that this should be an important point of attention for GPs. For instance, Marklund *et al.* found that GPs' diagnoses of asthma could not be confirmed by an allergologist in 34% of the patients.¹⁸ In addition, 7% of the patients were found to have a combined diagnosis of asthma and COPD, which the GP had not recognised. Primary care research by Pinnock *et al.* showed that spirometric re-evaluation of COPD patients led to a different (spirometric) diagnosis in 35% of the cases.¹⁹

Back-referral to general practice and 'shared-care'

The suggestion made to stimulate pulmonologists to refer asthma patients back to general practice once their lung function has normalised, they have few respiratory symptoms and inhaled steroids have been reduced to the lowest possible maintenance dose is of particular interest. This also applies to the exclusion criteria mentioned in the discussions, an asthma-related hospital admission less than two years previously and the persistent need for combined treatment with high-dose inhaled steroids and a long-acting β_2 -agonist. The support that seems to exist among pulmonologists for cooperation with GPs in the form of shared-care is an extra reason to stimulate such constructions for the group of more complex asthma and COPD patients. However, the term 'more complex' should be clearly defined, because research has shown that shared-care in a large group of asthma patients as a whole did not prove to be more effective than full specialist treatment, even though the financial cost was considerably lower.²⁰

In the discussion about when pulmonologists should refer COPD patients back to general practice, it was concluded that guidelines can only offer a certain amount of footing, because the pulmonologist's own 'feeling' must continue to play a major role. Although it is difficult to lay down hard criteria, the view that patients with moderately to severely disturbed diffusion capacity, ventilatory limitations, hypoxaemia and/or hypercapnia on exertion should remain under the care of the pulmonologist, is relevant within this framework.

Communication and mutual expectations by GPs and pulmonologists

Research into referral and consultation in patients with chronic respiratory diseases has received little attention in the literature. Recently, Li *et al.* performed a survey in the USA on 37 GPs to gather information on the prevailing customs, preferences and expectations when referring asthma patients.¹⁵ Although the GPs who participated were not at all representative for the 'average' GP (all the respondents had affiliations with the university that conducted the survey), a striking finding in the study was that the majority of referrals to pulmonologists were written at the patient's own request. A satisfied patient and clear, applicable recommendations from the pulmonologist appeared to be the prevailing expectations of the GPs. Research in Canada by Langley *et al.* showed that the geographic distance to specialist care and the relationship between GP and specialist were important factors in the GP's decision whether or not to refer a patient.²¹ The study concerned not only asthma and COPD patients, but referrals by GPs in general. The view expressed in the current study that pulmonologists should give clear advice about the treatment policy when referring patients back to the GP is in line with the findings in other studies. Williams *et al.* reported that pulmonologists and GPs in the USA are of the opinion that the information supplied when a patient is referred is too often inadequate or unclear.²² Primary care research has shown that GPs follow referral guidelines for asthma and COPD only to a limited extent. Jans *et al.* reported that the guidelines for referral to the pulmonologist were followed by the GP in only 17% of the cases with an indication.²³ Doubt about the value of referral in individual cases was the most important reason for this. Studies have also shown that referral behaviour of GPs can be influenced positively, although it is not yet clear which intervention method is the most effective.²⁴

CONCLUSION

This explorative study provided insight into how non-academic pulmonologists visualise a rational referral policy for asthma and COPD patients. Although the outcome of

the discussions and the recently published GP guidelines and transmural agreements showed considerable similarity, we also observed some marked discrepancies. To achieve optimal integration of published referral guidelines into daily practice the insights of this study should be taken into consideration during future revisions of referral guidelines for patients with asthma or COPD.

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Perianal ulcer and rash

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CASE REPORT

A 45-year-old, HIV-seropositive male presented with an extremely painful perianal ulcer and an enlarged, tender, inguinal lymph node. He had had sexual intercourse with several male partners lately, but said he had used condoms. Besides HIV, he denied any sexually transmitted diseases in the past. After highly active antiretroviral therapy was administered in 2001, HIV-RNA copies were undetectable and CD4 lymphocyte count was stable at about $700 \times 10^6/l$. This last parameter decreased to $420 \times 10^6/l$ a few weeks before presentation. His general practitioner had performed testing for sexually transmitted diseases. Serology for syphilis showed a negative VDRL and a positive TPHA, interpreted as a contracted syphilis in the past. Physical examination revealed a one centimetre, tender, clear-based, perianal ulcer with a raised, indurated margin. In his left groin a four centimetre, painful, left-sided inguinal lymph node was palpated. No further abnormalities were present.

Because of the tenderness of the ulcer, genital herpes simplex virus (HSV) infection was considered and the patient was treated empirically with valaciclovir. However, cultures for HSV were negative and the symptoms did not improve. Ciprofloxacin was added to treat a possible co-infection with *Chlamydia trachomatis*. Again, there was no change in the symptoms. A few days later, a symmetric maculopapular rash on the trunk and extremities, including palms and soles, appeared (figures 1 and 2).

WHAT IS YOUR DIAGNOSIS?

See page 98 for answer to this photo quiz.



Figure 1



Figure 2

Geriatric syndromes: medical misnomer or progress in geriatrics?

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ABSTRACT

Both in geriatric and internal medicine journals, and in medical textbooks certain (aggregates of) symptoms are labelled as 'geriatric syndromes'. In frail elderly patients a large number of diseases present with well-known and highly prevalent atypical symptoms (e.g. immobility, instability, impaired cognition and incontinence), which are referred to as geriatric syndromes. While classically the term syndrome is used for grouping together multiple symptoms with a single pathogenetic pathway, geriatric syndrome primarily refers to one symptom or a complex of symptoms with high prevalence in geriatrics, resulting from multiple diseases and multiple risk factors. The geriatric workup should therefore consist of both a search for and treatment of the aetiologically related diseases and a risk factor assessment and reduction. Effectiveness and efficiency of this specific geriatric syndrome workup has been demonstrated predominantly for combinations of geriatric syndromes that often serve as targeting criteria for geriatric interventions, and for some specific geriatric syndromes. Therefore, we argue that the concept of geriatric syndromes is valuable as a theoretical frame, a directive for diagnostic analysis and as an educational tool in teaching geriatrics to medical students and trainees. Added to this, explaining the heterogeneous way 'syndrome' is used in current clinical practice, as opposed to 'disease', will also substantially improve clinical reasoning both in geriatrics and general internal medicine.

INTRODUCTION

The collective 'geriatric syndrome' is frequently used in Northern American geriatric and internal medicine literature. Here we plead for the use of geriatric syndrome as a useful term, especially in teaching geriatrics, as it emphasises important principles in geriatric medicine. The primary principle of geriatrics is the decline of homeostatic reserve capacity of all organ systems with increasing age, generally called homeostenosis. This highly individual decline in organ function results from exposure to multiple individual risk factors and is further attenuated by chronic diseases. It leads to atypical disease presentations, which are typical for geriatric medicine and currently referred to as geriatric syndromes. These atypical presentations are found in the organ system most affected in homeostatic reserve function ('the weakest link'), and are precipitated by diseases that are often unrelated to the presenting symptom (e.g. urinary incontinence precipitated by pneumonia). The differential diagnoses of these geriatric syndromes are often highly similar. Generally, more than one risk factor and disease of this differential diagnosis is aetiologically related to the presenting symptom or geriatric syndrome. However, to serve a clear educational goal, the term geriatric syndrome first needs clarification and has to be contrasted to the way syndrome is primarily used in medical literature. In this article, we will subsequently describe how geriatric syndrome is used in practice and in the literature, clarify the historical, semantic, and medical roots of the terms syndrome and geriatric syndrome, and discuss the evidence base for geriatric syndromes.

HETEROGENEITY IN GERIATRIC PATIENTS

Geriatric syndromes are used as nosological entities in clinical guidelines, health services research and teaching. An example of the application of geriatric syndromes in clinical guidelines is the decision rule, in which the number of geriatric syndromes in elderly patients are counted as a selection criterion whether to give life-prolonging oncological treatment or not.¹ Balduci and Santa consider patients who are suffering from one or more geriatric syndromes as too frail to have an acceptable risk-benefit ratio for life-prolonging therapy. An appropriate prognostic validation study of this oncological decision rule is lacking. Moreover, Balduci's list of geriatric syndromes slightly differs from other lists presented in important geriatric textbooks, such as the Geriatric Review Syllabus and the textbook edited by Hazzard *et al.*^{2,3}

Other applications of geriatric syndromes can be seen in health services research in geriatrics. Winograd *et al.* investigated the possibility of using geriatric syndromes as targeting criteria to select case-mix groups that might benefit from hospitalisation.⁴ They used 15 criteria (a mixture of medical diagnoses and geriatric syndromes) as targeting criteria. The authors point out, based on the finding of their large prospective clinical trial in 985 patients, that the persons who benefit most from a geriatric intervention are probably better identified with geriatric syndromes than with diagnoses. In contrast, Berlowitz *et al.* found that a short list of geriatric syndromes (i.e. urinary incontinence, pressure ulcers, falls and functional decline) cannot serve as a valid endpoint for quantifying quality of hospital care.⁵ In teaching geriatrics, the Education Committee Writing Group (ECWG) of the American Geriatrics Society recommends that undergraduate students should be trained profoundly in the 13 most common geriatric syndromes (dementia, inappropriate prescribing of medications, incontinence, depression, delirium, iatrogenic problems, falls, osteoporosis, sensory alterations including hearing and visual impairment, failure to thrive, immobility and gait disturbances, pressure ulcers, and sleep disorders).⁶ Resnick also stresses the importance of geriatric syndromes in his introduction on geriatric principles in Harrison's Principles of Internal Medicine.⁷

One may conclude that in the most important fields of geriatric medicine (clinical practice, teaching, research and management) geriatric syndromes play an important role, despite the fact that the definition of geriatric syndrome is heterogeneous. The term is probably still unclear for most clinicians, as the term syndrome itself is interpreted in many ways. All this asks for a careful reconsideration of the terms syndrome and geriatric syndrome, because as clinicians we are expected to eliminate misunderstandings associated with our concepts.

DEFINITIONS

Syndrome is derived from the Greek συνδρομος, which means: to walk, run or group together. Probably the concept syndrome was first used by the empirists, who lived and worked in Greece, a century after Hippocrates.⁸ Currently, the word syndrome is generally defined in medical dictionaries as the aggregate of signs, symptoms or manifestations, which together are considered to constitute the characteristics of a nosological entity. Often, without clearly defining it, syndrome and disease are regarded as poles that end the continuum of unclear (syndrome) and clear (disease) pathological conditions. Wulff and Gøtzsche started clarification of the position of syndromes in medical taxonomy by stating that a disease is a clinical entity that can be unequivocally defined by its pathogenesis and aetiology and is presented as a single symptom or clinical sign or a well-known combination of clinical signs.⁹ This disease construct may be developed on an anatomic base (e.g. small-cell lung carcinoma), on a physiological or metabolic base (e.g. hypogonadism, hypothyroidism) or an aetiological base (e.g. pneumococcal pneumonia), or a combination of these bases (e.g. lung TBC, multinodular hyperthyroidism). In essence, according to this clinical nosology, a disease has a more or less known aetiology, pathogenesis, symptomatology and prognosis. In contrast to a disease, a syndrome is often unknown in its aetiology and/or pathogenesis and is mostly defined by a complex and often non-fixed combination of clinical signs and symptoms. Leiber *et al.* describe three types of clinical syndromes in which combinations of symptoms are grouped together without evidence of aetiology or pathogenesis (e.g. chronic fatigue syndrome), with evidence of aetiology but without clear pathogenesis (e.g. Marfan's syndrome), or with evidence of pathogenesis, but without evidence for aetiology (Cushing's syndrome) (*figure 1*).⁸

A syndrome in one of these meanings may evolve to the disease stage as clinical research succeeds in disentangling the cause or, in the absence of a single cause, in identifying the most important aetiological factors and/or the pathogenesis. An example is what used to be known as the Merseburg triad, which consisted of exophthalmus, goitre and tachycardia. In fact, this was the prototype of a (hyperthyroid) syndrome. As the pathogenetic pathway and the metabolic and endocrine causes of this triad of hyperthyroidism have been elucidated, this syndrome diagnosis has been replaced by a disease diagnosis (i.e. Graves' disease). As exceptions to this evolution of syndromes towards diseases, some rare diseases in which the aetiology and pathogenetic pathway has been elucidated, such as in the so-called Brugada's syndrome (a cardiac arrhythmia), are still being called a syndrome.

Clarification of a syndrome may also take place in individual patients. Without a careful diagnostic workup a patient with

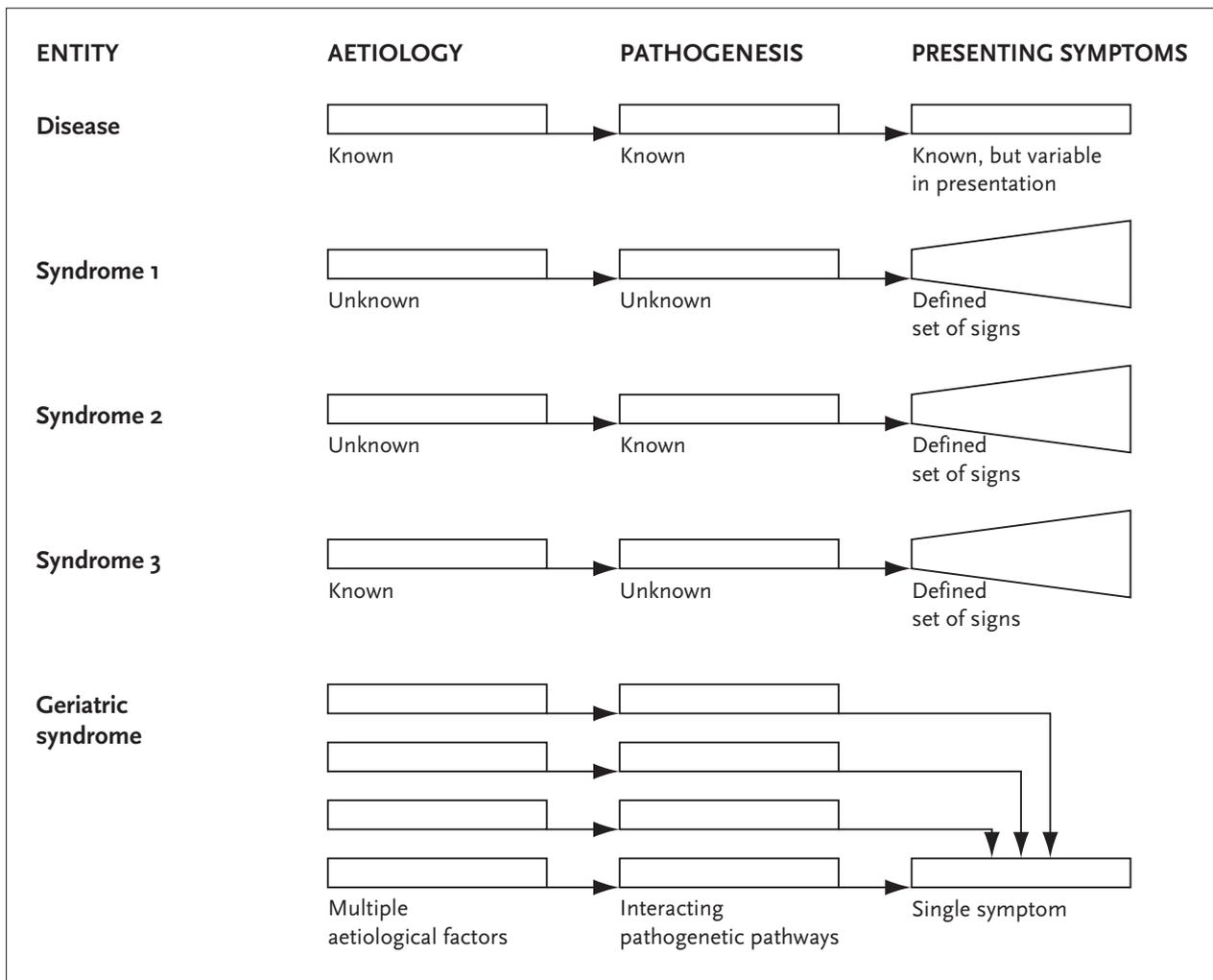


Figure 1

Symbolic presentation of 'disease', 'syndrome' and 'geriatric syndrome', in which the number of aetiological and pathogenetic factors and the complexity of outcome symptoms is reflected⁸

tremor, rigidity and balance problems may be diagnosed as suffering from a hypokinetic rigid syndrome or a Parkinsonian syndrome. As diagnostic tests are performed this syndrome may evolve in the disease diagnosis (e.g. Parkinson's disease) of which aetiology is clarified to a certain extent.

Added to the multiple interpretations of the term syndrome, a geriatric syndrome is a specification of the syndrome for a number of highly prevalent, often so-called atypical, clinical presentations in geriatrics. The term geriatric syndrome can be clarified further by contrasting it to the general meaning of syndrome in younger non-geriatric patients:

- A geriatric syndrome refers to highly prevalent, mostly single symptom states, whereas a syndrome is defined by a group of symptoms that do not need to be highly prevalent. In fact many syndromes are rare in younger patients.

- In geriatric syndromes the leading symptom is linked to a number of aetiological factors or diseases in other organs. Generally, in a syndrome it is most likely that a single pathogenetic pathway, known or unknown, causes the symptoms.
- In geriatric syndromes there is a large overlap between the aetiological factors of different geriatric syndromes. In contrast, syndromes in younger patients are separate entities, and there is no overlap between aetiological factors of different syndromes.
- A geriatric patient often suffers from more than one geriatric syndrome, while in younger patients one usually finds a single syndrome in one patient.

Falls, incontinence and dizziness, although consisting only of one presenting symptom, and heart failure, delirium and dementia, consisting of a complex of symptoms, are frequently called geriatric syndromes,²⁻⁵ and they fulfil the

above-mentioned criteria. The diagnostic workup of geriatric syndromes should consist of a search for both a possible single disease that may have precipitated the symptom(s), and of a multiple risk factor assessment.¹⁰ One may say that using geriatric syndrome for these medical problems is just a misuse of the term syndrome.¹¹ However, 'syndrome' in geriatric syndrome does not violate the Greek origin of the word, in the way that risk factors and precipitating (chronic) diseases are now grouped together with a single symptom or multiple presenting symptoms. Similarly, multiple risk factor assessment and reduction per disease is becoming more and more common in internal medicine.¹² However, this is more often linked to diseases and not to single clinical signs or symptoms. Some examples may clarify the differences between geriatric syndrome analysis in the frail elderly and the correct and most efficient syndrome analysis in middle-aged persons. Acute confusion as geriatric syndrome is less often caused by a new brain lesion than in younger patients. Depression as a geriatric syndrome is usually not just a result of a psychiatric disorder; somatic causes play a major role in the pathogenesis of depression in old age. Similarly, incontinence as a geriatric syndrome is not only due to bladder dysfunction, falling results from more than neuropathy alone, and syncope is often not explained just by a single heart disease.⁷ Therefore, the most efficient workup of young and middle-aged individuals differs from the workup needed in frail elderly subjects, although presenting with similar symptoms.

EVIDENCE

The best evidence for the meaningful use of geriatric syndromes comes from the large series of randomised trials that evidenced efficacy, effectiveness and efficiency of geriatric inpatient and outpatient services when compared with regular practice on general medical wards. From the early trial by Rubinstein *et al.* until the recent study by Cohen *et al.* mostly patients with problems, currently classified as geriatric syndromes, were enrolled and both the diagnostic and the risk factor assessment and intervention were carried out by the interdisciplinary geriatric intervention team.^{13,14} In the control groups on the medical wards, the medical model of a monodisciplinary search for single causes is more likely to have been the guiding principle. However, regular care is not often described carefully in those trials, so one can still argue about the precise differences between the clinical approaches. In the earliest trials the differences between geriatric syndrome analysis and regular care resulted in a significant decline in mortality and improvement in functional performance.¹³ The differences in functional performance have been clearly present until now. However, the differences between geriatric and medical wards are declining, possibly by broadening the

general medical assessment for geriatric syndromes in internal medicine as well.¹³

Fairweather *et al.* and Fried *et al.* argued that diagnostic procedures in geriatric patients should also take into account the time sequence and the interaction of comorbidity.^{15,16} Fried even presented different models of illness presentation, which are widely accepted although scarcely evidenced. Based on their own data, both authors state that simple, single diagnoses only explain geriatric health problems in less than 50% of the patients. The medical model, with its primary law of parsimony, does not suffice in geriatrics. The concept of geriatric syndromes may bridge this gap between classical medical diagnostics and the highly prevalent interaction of age, comorbidity and risk factors in geriatrics.

In a systematic search of the literature, the term geriatric syndrome appears to be primarily associated with delirium, falls, urinary incontinence and dizziness. Silent angina pectoris and emesis were also proposed as geriatric syndromes,^{17,18} but this was not followed by other authors. Only Tinetti and Inouye *et al.* explain the term geriatric syndromes in their studies on dizziness, falls and incontinence and provide evidence for the multiple risk factor analysis.¹⁹⁻²¹ Tinetti *et al.* found five to seven significant risk factors for the development of dizziness in the elderly. When the number of risk factors that is present in a patient increases, the total risk will increase proportionally. There is also sufficient evidence that falls, delirium and urinary continence are related to multifactorial aetiology in most patients, with multiple risk factor reduction being more effective than the regular medical model approach.^{22,23} However, for most of the medical problems labelled as geriatric syndrome there is not yet sufficient evidence of the improved effectiveness by geriatric syndrome-driven combined diagnostics and multiple risk factor assessment and intervention. For example, to the best of our knowledge only Lipsitz *et al.* have performed a study on multiple risk factor aetiology in syncope. Among 97 geriatric syncope patients they found that in only 30% (n=34) syncope could be explained by one diagnosis, while in 58% (n=63) multiple factors were responsible.²⁴

CONCLUSION

In this article we have critically reviewed how symptoms and medical problems are labelled as geriatric syndromes, which currently implies a great similarity in aetiology, multiple risk factor involvement and atypical clinical/disease presentation. Similar to Tinetti *et al.* and Phelan, we advocate defining a geriatric syndrome as a symptom, or a fixed combination of symptoms, with a high prevalence in the elderly, in which the diagnostic process should consist of both a search for a single or for more diseases that

precipitated the symptom(s), and of a multiple risk factor assessment.^{10,19,20} However, according to the principles of evidence-based medicine, the use of geriatric syndrome as tool in clinical practice, teaching and research in geriatrics is still preliminary and requires:

- unequivocal definition of diagnostic criteria for geriatric syndromes;
- proof of multiple risk factor causality for all geriatric syndromes;
- evaluation of cost-effectiveness of the use of the proposed geriatric syndrome workup in future trials.

The concept of geriatric syndromes can be used as an evidence base for dizziness, falls, delirium and incontinence in frail elderly patients. For other complex medical problems in the elderly, it may also improve effectiveness and efficiency of medical care and teaching on geriatric and internal medicine wards. Therefore, we argue that the concept of geriatric syndromes is valuable as a theoretical frame, a directive for diagnostic analysis and as an educational tool in teaching geriatrics to medical students and trainees. Added to this, explaining the heterogeneous way in which 'syndrome' is used in current clinical practice, as opposed to 'disease', will also substantially improve clinical reasoning both in geriatrics and general internal medicine.

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Fatal combination of moclobemide overdose and whisky

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ABSTRACT

The antidepressant moclobemide (Aurorix) is a reversible inhibitor of monoamine oxidase-A. Pure moclobemide overdose is considered to be relatively safe. Mixed drug overdoses including moclobemide are potentially lethal, especially when serotonergic drugs are involved. So far, only one fatality due to moclobemide mono-overdose has been reported. We report here on a fatality following the ingestion of a moclobemide overdose in combination with half a bottle of whisky. Although dietary restrictions during moclobemide therapy are not considered necessary, the combination of large quantities of moclobemide and tyramine-containing products seems to be lethal, probably because monoamine oxidase-A selectivity is overwhelmed after massive overdoses. Since there is no specific antidote and treatment is only symptomatic, the severity of an overdose with moclobemide must not be underestimated.

INTRODUCTION

The antidepressant moclobemide (Aurorix) is a specific reversible inhibitor of monoamine oxidase-A (MAO-A), which is responsible for the metabolic degradation of monoamines such as noradrenaline and serotonin in nerve terminals. The MAO-B of the gut and liver remains active for the metabolic degradation of tyramine absorbed from food.¹ The recommended dosage range is 300 to 600 mg a day.² Moclobemide does not appear to be associated with many of the adverse effects produced by the older MAO inhibitors. Most commonly reported adverse effects

are headache, nausea, dry mouth, insomnia, dizziness and epigastric discomfort. Serotonin syndrome may occur.³ Moclobemide potentiates the effects of orally administered tyramine approximately three to fourfold, which is considered not to be clinically significant. Dietary restrictions are therefore not thought to be necessary during moclobemide therapy.² Previous reports suggest that moclobemide is a safe drug even when taken in large quantities.^{4,5} The few reported fatalities have all been ascribed to serotonin syndrome, due to an interaction between moclobemide and other serotonergic agents.³ However, one case report has been published, where death was attributed to the toxic effects of moclobemide alone.⁶ We report here on a fatality due to the ingestion of a moclobemide overdose in combination with half a bottle of whisky.

CASE REPORT

A 38-year-old man was admitted at 8.30 am after ingesting approximately 12 tablets of moclobemide (150 and 300 mg) the night before. Apart from the ingestion of moclobemide he had drunk over half a bottle of whisky (>350 ml). His wife had found him in the morning in a confused and agitated state and brought him to hospital. Within minutes of entering the hospital, the patient suddenly collapsed. He was tachypnoeic, tachycardic and suffered from spontaneous muscle spasms. His Glasgow Coma Score was E2M4V1 and body temperature was 37°C. The electrocardiogram showed a supraventricular tachycardia of 174 beats/min and a right bundle branch block. He received 40 mg diazepam in

three injections intramuscularly within 35 minutes, which was followed by a decrease in his heart rate to 80 beats/min. Because of absent pupillary light responses he then received a total of 5 mg flumazenil, which was followed by cardiac arrest. Resuscitation was unsuccessful and our patient died at 9.50 am. Laboratory tests of blood drawn on admission showed leucocytes $22.3 \times 10^9 / l$ (N $4.0-10.0 \times 10^9$), creatinine $212 \mu\text{mol}/l$ (N $60-100 \mu\text{mol}/l$), urea $10.8 \text{ mmol}/l$ (N $2.5-7.5 \text{ mmol}/l$), sodium $149 \text{ mmol}/l$ (N $135-146 \text{ mmol}/l$), potassium $5.4 \text{ mmol}/l$ (N $3.5-5.0 \text{ mmol}/l$), and creatinine kinase 284 (N <105). There was a slight metabolic acidosis (pH 7.34 , pCO_2 34.3 mmHg , bicarbonate $18.2 \text{ mmol}/l$, pO_2 65 mmHg). Serum moclobemide was $55 \text{ mg}/l$ (N $1.5-2.5 \text{ mg}/l$). Ethanol and cocaine, assessed five months after his death, were not detectable in the serum. No urine was available for analysis. A post-mortem was not conducted. The patient had complained of suffering from depression during the last few weeks. Because of a past history of abuse and overdose of sedatives, however, his general practitioner did not prescribe any antidepressants. Being an irregular user of cocaine he had managed to obtain Aurorix tablets on the illegal circuit. He had never used moclobemide before. It is unclear if our patient had used cocaine the night before admission. He had no history of cardiac or neurological diseases.

DISCUSSION

This patient died as a result of cardiovascular collapse due to moclobemide intoxication. He had no history of cardiovascular disease and had not used any other drugs in the days before admission to the emergency room. Although we can not exclude that the administration of flumazenil contributed to the patient's death,⁷ it is unlikely that this explained the clinical course in this patient. Although he was known to use cocaine irregularly it is unclear if he had used cocaine the night before his death. The fact that cocaine was not detectable in his serum cannot completely rule out the possibility of cocaine abuse, but there were no indications for this in the night before admission. Although ethanol was not detectable in the patient's serum, his wife had said that he had drunk over half a bottle of whisky together with the ingestion of moclobemide. This could have potentiated the sympathicomimetic overactivity due to moclobemide overdose, because of the potential presence of tyramine in whisky.⁸ The fact that ethanol is lost from fluoride-free specimens with prolonged storage may explain why no ethanol was found in the serum.⁹ Unfortunately, due to the sudden collapse of the patient and the rapid deterioration despite resuscitation, his blood pressure was not recorded. Reported symptoms of moclobemide overdose range from no symptoms or mild gastrointestinal symptoms at doses

up to 2 g, to fatigue, agitation, tachycardia, increased blood pressure and dilated, slowly-reacting pupils at doses of 7 to 8 g. The MAO-A selectivity seems to be overwhelmed after massive overdoses of moclobemide.¹⁰ Intoxication with non-selective MAO inhibitors can be divided into four phases. First there is a period with no symptoms, followed by a hypermetabolic phase with agitation, neuromuscular excitation, hypertension and tachycardia. Then there is a phase of cardiovascular collapse, probably as a result of a decrease in catecholaminergic activity followed by the last phase with multiorgan failure with pulmonary oedema and renal insufficiency. There is no specific antidote. Treatment is symptomatic and aimed at maintaining vital functions.¹¹

Pure moclobemide overdose is considered to be relatively safe. At doses as high as 20.55 g and plasma concentrations as high as $84 \text{ mg}/l$,¹ no fatalities have been reported. Mixed drug overdoses including moclobemide are considered to be potentially lethal, especially when serotonergic drugs are involved. So far, only one fatality due to moclobemide mono-overdose has been reported. A 48-year-old woman was found dead at home. Her plasma concentration of moclobemide was $137 \text{ mg}/l$.⁶ As our patient died with a relatively low plasma concentration of $55 \text{ mg}/l$, we hypothesise that the potential combination with tyramine in the whisky may have aggravated the clinical picture. In conclusion, moclobemide (mono-)overdose is potentially fatal. Although dietary restrictions during moclobemide therapy are not considered necessary, the combination of large quantities of moclobemide and tyramine-containing products seems to be lethal, probably because MAO-A selectivity is overruled after massive overdoses. Since there is no specific antidote and treatment is only symptomatic, the severity of an overdose with moclobemide must not be underestimated.

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Severe diffuse interstitial pneumonia due to *Mycoplasma pneumoniae* in a patient with respiratory insufficiency

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ABSTRACT

We report a 25-year-old man presenting with high fever, dyspnoea and somnolence. The presence of severe diffuse interstitial pneumonia with extrapulmonary symptoms, such as myositis and subclinical haemolysis, strongly suggested an infection by *Mycoplasma pneumoniae*. This diagnosis was supported by high titres of cold agglutinins and a positive Coombs test, and directly confirmed by specific IgM serological tests. After initiation of the appropriate antimicrobial treatment mechanical ventilation could be avoided and the patient showed a slow but complete clinical recovery. This diagnosis should be considered in any febrile patient with hypoxaemia and diffuse interstitial pneumonia, and rapid initiation of appropriate antibiotic treatment seems to be crucial for a favourable outcome.

INTRODUCTION

Mycoplasma pneumoniae is one of the most important causes of an atypical (non-pneumococcal) community-acquired pneumonia. Although *M. pneumoniae* usually causes mild and subclinical disease, this infection is capable of causing severe disease. It is important to be aware of the incidence, pathogenesis and particularly the respiratory and extrapulmonary symptomatology of an infection due to this micro-organism so that the diagnosis *M. pneumoniae* infection can be considered at an early stage. We describe a patient with severe diffuse interstitial pneumonia due to *M. pneumoniae* and imminent respiratory insufficiency. The combination of severe diffuse interstitial infiltrates together with extrapulmonary involvement led to the correct

diagnosis; adequate antimicrobial treatment could be given and mechanical ventilation could be avoided.

CASE REPORT

A 25-year-old male with high fever, shortness of breath and somnolence was admitted to the emergency room of our hospital. His past medical history included physical and mental retardation due to asphyxia at birth, pneumonia of the right lower lobe in 1983 and laryngitis subglottica in 1985. Further history revealed weakness for one week and possible fever. He had developed a cough and started expectorating white sputum during the last few days. In the last 24 hours his rectal temperature rose to 40°C and he became somnolent. Suspecting acute bacterial bronchitis, the general practitioner started treatment with co-amoxiclav. The patient had not been abroad and had not been in contact with (swimming) water or birds. No infectious diseases were prevalent in his environment. On examination, we saw a very ill somnolent man. His temperature was 40.5°C, blood pressure 140/80 mmHg and pulse rate 125 beats/min. Pulmonary examination was normal. Nuchal rigidity could not be ruled out. Cerebrospinal fluid showed a glucose level of 4.1 mmol/l, a protein content of 0.17 g/l and no white cells. The ESR was 67 mm, with a C-reactive protein of 115 mg/l and a white-cell count of $9.4 \times 10^9/l$ with a normal differential. Haemoglobin was 7.3 mmol/l (MCV 85 fl). Values for serum aspartate aminotransferase and alanine aminotransferase were slightly elevated, the lactate dehydrogenase level was 906 U/l, bilirubin 17 µmol/l and haptoglobin 4.41 g/l. Creatine kinase was 2141 U/l

without elevation of CK-MB. The arterial pO_2 was 7.8 kPa, pCO_2 4.7 kPa and oxygenation 92%, while the patient was given nine litres of oxygen a minute via a rebreathing mask. The chest X-ray showed a diffuse slightly intensified reticulonodular pattern without evidence of alveolar consolidation. The differential diagnosis consisted of the early phase of pneumonia or another infection possibly with incipient adult respiratory distress syndrome. After blood, sputum, cerebrospinal fluid and urine had been taken for culture, empirical treatment was started with co-amoxiclav 1200 mg four times a day intravenously and gentamycin once daily.

In spite of this treatment, the patient deteriorated during the next three days. His temperature remained elevated and a tachypnoea with a frequency of 40/min developed with a decline in the oxygenation of the blood. In arterial blood the pO_2 was 7.0 kPa, pCO_2 3.4 kPa and oxygenation 89%, with an inspired oxygen fraction (FiO_2) of 40%. Chest X-ray showed a diffuse reticulonodular pattern, without evidence of alveolar consolidation (figure 1). High resolution CT scan of the chest showed, much more clearly than the X-ray, a very serious diffuse reticulonodular pattern with bilateral small consolidations (figure 2). The clinical picture consisting of an interstitial pneumonia, myositis and a high ESR with possible haemolysis (which raised the suspicion of cold agglutinins) made us think of a severe *M. pneumoniae* infection. Because of the threatening respiratory insufficiency and possible necessity for mechanical ventilation, the patient was admitted to the intensive care unit and received a rebreathing mask with a FiO_2 of 60% plus six litres O_2 /minute by way of a nasal tube. Co-amoxiclav was discontinued and intravenous erythromycin 500 mg four times a day was started. The same day the diagnosis *M. pneumoniae* pneumonia was confirmed by a strongly positive complement fixation test

for IgM antibodies directed against *M. pneumoniae* (titre 1:320), while the IgG was negative (titre <8), which confirmed an acute infection. The diagnosis was also supported by positive cold agglutinins (titre 1:128). This was an explanation for the high ESR, positive direct Coombs and subclinical signs of haemolysis. The microbiological investigations yielded no pathogens.

Our patient stayed in the intensive care unit for seven days. Mechanical ventilation could be avoided by means of a rebreathing mask and supplementary oxygen delivery. After three days erythromycin i.v. was converted to clarithromycin 500 mg orally twice a day for nine days. During his stay in the ICU he slowly recovered and his oxygen demand declined. He became more responsive and less somnolent. The laboratory abnormalities normalised. The patient was discharged in a good clinical condition one week later.

DISCUSSION

In this critically ill patient with a severe diffuse interstitial pneumonia, myositis and subclinical haemolysis, *Mycoplasma pneumoniae* infection was diagnosed.

M. pneumoniae is one of the most common causes of non-pneumococcal community-acquired pneumonia. The frequency of this infection reported in ambulatory patients and hospitalised patients varies, probably due to the use of different diagnostic tests, lack of consensus with regard to diagnostic criteria, geographical differences and the existence of world-wide outbreaks with a four- to eight-year periodicity. The incidence of *M. pneumoniae* in severe 'community-acquired pneumonia' (CAP), requiring hospitalisation or even admission to an ICU, is approximately between 1 to 7%.¹⁻⁸ However, the incidence of mycoplasma may be much higher in patients with milder disease that



Figure 1
Chest X-ray: bilateral reticulonodular pattern, without evidence of alveolar consolidation in a patient with *Mycoplasma pneumoniae* infection



Figure 2
High-resolution computer tomography of the chest: diffuse interstitial pneumonia with bilateral small consolidations in a patient with *Mycoplasma pneumoniae* infection

can be managed without hospitalisation. A recent study showed *M. pneumoniae* was the causative pathogen in 22.8% of the patients with mild CAP, which is much higher than the incidence of other atypical pathogens such as *Chlamydia pneumoniae* and Legionella species (10.7 and 0.7% respectively).⁹

Infection by *M. pneumoniae* is seen at all ages, but most often in the first two decades of life. This infection occurs in any season, with a four- to eight-year periodicity for worldwide epidemics. Outbreaks are especially seen in places where many (young) people are brought together, like in schools, homes, military academies and universities. In our patient, his stay in a facility for the mentally retarded may have been important in this respect.

Transmission from person-to-person takes place via droplet nuclei after close and prolonged contact. The incubation period averages three weeks.

Clinical features caused by *M. pneumoniae* infection may be divided into those due to respiratory tract disease and those due to extrapulmonary disease. However, approximately 20% of *M. pneumoniae* infections are asymptomatic. The most common respiratory symptoms are a tracheobronchitis with a non-productive or mild productive cough (\pm 75% of patients), pharyngitis, rhinorrhoea and earache. Up to 5% of patients have severe earache resulting from bullous myringitis. Only 5% of patients will develop pneumonia. The most common radiographic finding on chest X-ray is a bilateral peribronchial pneumonia pattern, which consists of thickened bronchial shadows, patchy alveolar consolidations with areas of plate-like atelectasis, and streaks of interstitial infiltration. It has been shown that the interstitial abnormalities in *M. pneumoniae* pneumonia are often difficult to recognise on plain X-rays of the chest but can usually be detected by high-resolution CT scan,¹⁰ as in our patient. The interstitial abnormalities can be localised, but diffuse involvement of both lungs has been described, even requiring mechanical ventilation. In those severe cases *M. pneumoniae* pneumonia can result in interstitial fibrosis and even bronchiolitis obliterans-organising pneumonia (BOOP) with long-term sequelae.¹¹ The differential diagnosis of an interstitial pattern on chest X-ray is very extensive.

Extrapulmonary abnormalities are common in infections by *M. pneumoniae* and are usually superimposed on pulmonary disease so that mycoplasmal aetiology can be suspected. These include dermatological manifestations, central nervous system involvement, gastrointestinal symptoms and cardiac complications. Mild myositis is also frequently seen, as in our patient, and even rhabdomyolysis has occasionally been described.¹² The most prominent extrapulmonary symptom is the presence of cold agglutinins. These are IgM antibodies directed against the glycolipid antigens of *M. pneumoniae* and cross-reacting with the I antigen of the red blood cell. Elevated cold agglutinin titres are seen in a variety of infections, including influenza, mononucleosis, psittacosis,

rubella, adeno virus and measles, but usually occur at a higher titre in mycoplasmal infection. They are seen in up to 60% of patients with mycoplasmal infection. Cold agglutinins appear in the second week of illness, they peak at four weeks and disappear by two months. As in our case, they usually cause an elevated ESR and evidence of haemolysis, such as a positive direct Coombs' test and an elevated reticulocyte count. The titre usually exceeds 1:128 in patients with *M. pneumoniae* pneumonia and overt haemolysis may arise. Although *M. pneumoniae* usually causes mild disease with a mortality rate of less than 1%, respiratory insufficiency, need for mechanical ventilation and death may occur. A severe course is strongly associated with comorbidity.¹³ Examples of pre-existing chronic diseases are chronic obstructive pulmonary disease, chronic cardiac insufficiency, diabetes mellitus and immunosuppressive diseases or therapies. Our patient did not have comorbidity but the disease definitely ran a severe course. Serious hypoxaemia, high oxygen demand and progressive somnolence necessitated admission to the ICU. Appropriate antibiotics, a high FiO₂ and breathing supporting measures (physical therapy, assistance with expectoration, half-sitting position in bed) could just prevent intubation and mechanical ventilation. In most cases, it is not possible to point to the causative pathogen of a pneumonia just from the symptomatology. Nevertheless this case report illustrates that in some cases it is possible. Mycoplasma-specific IgM test and measurement of cold agglutinins may help to make the diagnosis and install appropriate antimicrobial treatment.

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Coexistence of cystic intra-abdominal lymphangiomas and diffuse venous haemangiomas in adult life

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ABSTRACT

Diffuse haemangioma and intra-abdominal lymphangioma are rare in adults. In this case report, we present a 33-year-old female with coexisting multiple cutaneous and visceral cavernous haemangiomas and two huge intra-abdominal lymphangiomas of 25 and 35 cm in diameter. The organs involved were the liver, pericardium, renal hilus and bladder. She died due to disseminated intravascular coagulation and multiorgan failure, which resembled Kasabach-Merritt syndrome. The coexistence of generalised haemangiomas and intra-abdominal lymphangiomas and the lack of complaints until the age of 33 years makes her an unusual case in the literature. We also emphasise the other clinical conditions that should be considered in the differential diagnosis.

INTRODUCTION

Haemangioma is one of the most common soft tissue tumours, particularly in infancy and childhood, constituting 7% of benign tumours. The majority of haemangiomas are superficial lesions that have a predilection for head and neck, but may occur internally, notably in organs such as the liver. Lymphangiomas are the lymphatic analogue of the haemangiomas of blood vessels.^{1,2}

In this report, we present a case with coexisting cystic intra-abdominal lymphangiomas and diffuse venous haemangiomas in adult life.

CASE REPORT

A 33-year-old woman was admitted to the intensive care unit with renal failure and severe anaemia. She had widespread blue-coloured lesions, which she had first noticed on her neck at the age of 13. She did not seek medical help for these lesions. She had two uneventful births and her children were healthy. There was no family history of similar lesions. Physical examination revealed a body temperature of 36°C, pulse rate 120 beats/min and regular, respiration rate 24/min and blood pressure 80/50 mmHg, supine. Her general condition was poor; she was pale and had multiple blue-coloured, soft, nodular lesions, ranging from 3 to 80 mm in size throughout her body (*figure 1*). Two soft painless masses



Figure 1
Widespread blue-coloured, soft cutaneous lesions on the trunk and neck

were found during abdominal examination. Laboratory data showed a red blood cell count of 0.73 million/cu mm, haemoglobin 1.8 g/dl, haematocrit 5.6%, mean corpuscular volume 76 fl, mean corpuscular haemoglobin 25 pg/cell, mean corpuscular haemoglobin concentration 32 g/dl, WBC count $4.7 \times 10^9/l$, platelet count $24 \times 10^9/l$, blood urea nitrogen 28 mmol/l, creatinine 415 $\mu\text{mol/l}$, sodium 128 mmol/l, potassium 5.1 mmol/l, chloride 89 mmol/l, alanine amino transferase 129 IU/l, aspartate amino transferase 123 IU/l, lactic dehydrogenase 970 IU/l, total bilirubin 8.5 $\mu\text{mol/l}$, and direct bilirubin 3.4 $\mu\text{mol/l}$. Peripheral blood smear demonstrated polychromasia, anisocytosis, fragmented erythrocytes, normoblasts which were consistent with intravascular haemolysis, and thrombocytopenia. Bone marrow aspiration revealed erythroid hyperplasia. The prothrombin time was 28 sec (n=11-15 sec), partial thromboplastin time 40 sec (n=24-32 sec), fibrinogen 90 mg/dl (n=150-350 mg/dl), fibrin degradation products $>40 \mu\text{g/ml}$ (n $<10 \mu\text{g/ml}$), and disseminated intravascular coagulation (DIC) was considered. She was oliguric with a urinary output of 100 ml a day. Urine sediment revealed few red blood cells and leucocytes. Urine sodium was 17 mmol/l. Repeated occult blood tests of her stools were negative. She had no signs or findings that indicated either a site of occult haemorrhage or haemolytic and aplastic anaemia. Abdominal computerised tomography, which was performed on the first day of hospitalisation, revealed a sharply demarcated hypodense lesion measuring 4 cm in size in the right lobe of the liver, and two large, well-circumscribed rounded cystic masses that filled the abdominal cavity (figure 2).

She received a transfusion of 17 units of whole blood and the haemoglobin level increased to 7 g/dl. Dopamine and furosemide were administered for three days to treat acute renal failure, but she died on the fourth day of hospitalisation because of multiorgan failure due to DIC.

Necropsy was performed and macroscopic evaluation revealed extensive blue-coloured masses on her face, neck, chest, abdominal wall, major and minor labium, and limbs. Similar lesions were also observed on the pericardium, liver, renal hilus and bladder. Microscopically, these lesions were composed of large, blood-filled spaces with a thin endothelial lining and were consistent with cavernous haemangiomas. There were two cystic lesions measuring 25 and 35 cm in diameter in the abdomen, one filled with blood and the other with serous fluid (figure 3). Microscopic examination of these lesions, which were lined by attenuated endothelium, disclosed lymphangioma and there were small lymphoid aggregates in the stroma (figure 4). The gastrointestinal tract was examined carefully but no similar lesions were found. There were no pathological findings in any other organs such as brain, lungs, heart and spleen.



Figure 2
The abdominal CT of the patient, which was performed on the first day of hospitalisation, revealed two large cystic masses in the abdominal cavity

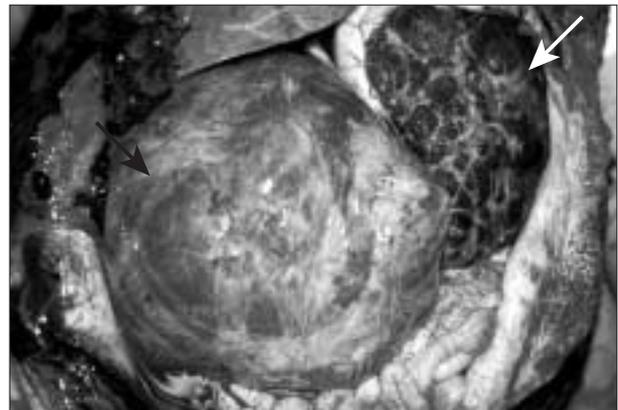


Figure 3
Two huge intra-abdominal lymphangiomas. One was filled with serous fluid (black arrow), the other with blood (white arrow).

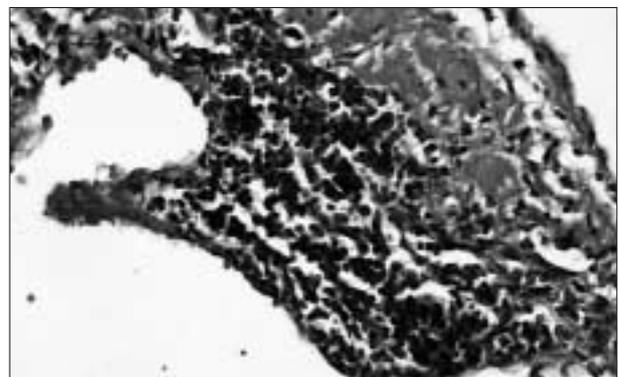


Figure 4
Lymphoid aggregates in the wall of lymphangioma (HE x 200)

DISCUSSION

Cavernous haemangioma is a benign vascular tumour usually found on skin and mucosal surfaces but it may involve any organ system.¹ Cavernous haemangiomas are found in two clinical conditions, namely Maffucci's syndrome and blue rubber bleb nevus syndrome (BRBNS). Maffucci's syndrome is characterised by bone fragility and multiple osteochondromas.³ BRBNS is an uncommon disorder which may demonstrate multiple, large, protruding cutaneous haemangiomas and gastrointestinal bleeding from vascular malformations. It is usually present at birth or early childhood but may also be seen in adulthood.^{3,4} Vascular anomalies are also described in other syndromes, such as Sturge-Weber syndrome (facial, ocular and intracranial vascular anomalies); Klippel-Trenaunay syndrome (capillary-lymphatic-venous malformations and limb gigantism); Parkes-Weber syndrome (capillary-lymphatic-arterial-venous malformations and limb gigantism); Bonnet-Dechaume-Blanc syndrome (visual system arteriovenous malformations); Cobb syndrome (arteriovenous malformations or fistula and spinal cord involvement); Solomon syndrome (capillary-lymphatic-venous malformations, limb gigantism, lipomas and epidermal nevi); and Proteus syndrome (capillary-lymphatic-venous malformations, macrodactyly, limb gigantism, macrocephaly, lipomas and epidermal nevi).⁵

One of the prominent findings in this case is the absence of gastrointestinal tract involvement in her necropsy while widespread haemangioma was observed throughout her body. At first glance the skin lesions together with the anaemia were suggestive of BRBNS in our patient, but lack of gastrointestinal tract involvement in her necropsy evaluation and no sign at all of gastrointestinal tract bleeding ante-mortem made the diagnosis of BRBNS unlikely. Other syndromes in which vascular malformations associated with various organ involvements could be excluded in this patient since she had no findings of accompanying manifestations.

At necropsy, she was found to have two intra-abdominal lymphangiomatous lesions. Coexistence of lymphangioma and haemangioma is another intriguing finding in the present case. It is often difficult to determine whether these lesions are true neoplasm, hamartoma or ectasia/malformation. At birth 50 to 65% of lymphangiomas are present, and nearly 90% of them may be manifest by the end of the second year of life.^{1,2} Intra-abdominal lymphangiomas are uncommon and generally occur in

childhood.⁶ Although most of the lymphangiomas are found in the head and neck area,⁷ intra-abdominal locations such as mesenteric area, omentum and retroperitoneum are also rarely observed.^{7,8} The lymphangiomas in the present case were mesenteric in origin and were diagnosed during post-mortem examination in spite of their huge sizes of 25 and 35 cm in diameter. This patient underestimated the minor signs, so the condition was not recognised early enough to enable surgical treatment of her abdominal cysts. Kasabach-Merritt syndrome may also be considered in this patient since she had multiple cavernous haemangiomas and the presentation of consumption thrombocytopenia and coagulopathy. Bleeding into cavernous haemangioma and lymphangioma probably caused the terminal event in this patient.

In conclusion, vascular malformations are sometimes not symptomatic until later in adulthood, even though they can reach huge sizes, and may lead to serious complications including sudden death. Any vascular malformation should therefore be considered for systemic evaluations at all stages in life. Our case seems to be unusual and rather rare because of its multiple features resembling different syndromes, and it can probably be placed somewhere in between the known syndromes, like an overlapping and as yet undescribed syndrome in the medical literature.

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ANSWER TO PHOTO QUIZ (ON PAGE 82)

PERIANAL ULCER AND RASH

The diagnosis was primary syphilis, followed by secondary syphilis. This was confirmed with repeated serological testing, showing a TPHA titre of 1:2560, VDRL titre of 1:64 and a positive FTA.

Primary syphilis is characterised by a painless, indurated, clear-based ulcer, accompanied by locoregional lymph node swelling. Establishing the diagnosis solely on the clinical picture is difficult, because the sensitivity and specificity for a characteristic syphilitic ulcer are 31 and 98%, respectively. Other diagnoses to be considered are genital herpes, chancroid and lymphogranuloma venereum.

The typical presentation of secondary syphilis is a symmetric papular rash on the entire trunk and extremities, including the palms and soles. The latter localisation is highly suggestive of secondary syphilis. Other possible symptoms include malaise, weight loss, fever, hair loss and generalised lymphadenopathy.

The clinical picture of syphilis in HIV-infected patients can differ from HIV-negative patients. HIV-infected patients with early syphilis appear to be more likely to present with secondary syphilis and those with secondary syphilis are more likely to have persistent chancres.

Although the diagnosis can be made by darkfield microscopy on direct preparations or PCR techniques on tissue biopsies, serology is usually used to establish the diagnosis. HIV-infected individuals more often have falsely reactive non-treponemal tests (VDRL). In advanced HIV infection, abnormal B cell function may lead to false-negative serological responses. In case of high spirochaetal load a false-negative result can occur due to the 'prozone' reaction, caused by a mismatch between concentrations of antigen and antibody. Many other non-HIV-related conditions can cause falsely reactive or non-reactive treponemal and non-treponemal tests. Moreover, in primary syphilis, serum samples for serology may be obtained before seroconversion has occurred. In general, FTA becomes positive first, followed by TPHA and finally VDRL. Therefore, repetitive testing is necessary to differentiate between early and late latent syphilis as was done in our patient.

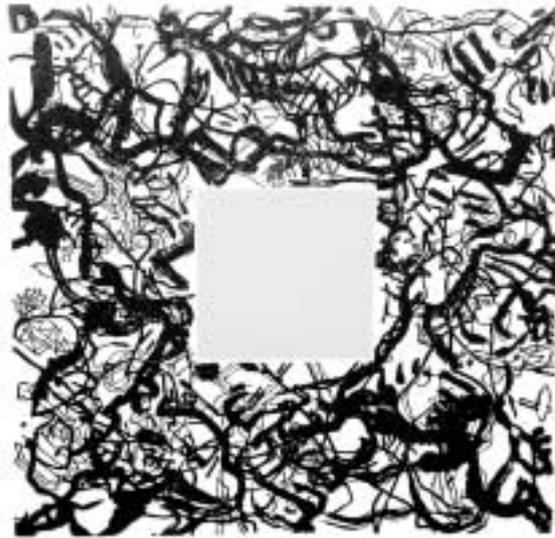
After the diagnosis was established, treatment was started with benzathine penicillin G, 2.4 million units intramuscularly. He developed a Jarish-Herxheimer reaction, which was treated in the emergency room. During follow-up, all symptoms vanished and VDRL became negative.

DIAGNOSIS

Secondary syphilis.

‘Normen en waarden’

Manuel Kurpershoek



This month's cover, entitled 'Normen en waarden', shows a linoleum-cutting made by Manuel Kurpershoek. Manuel was born in Amsterdam in 1952, where he attended the Gerrit Rietveld Academy and the School of Graphic Art. Nowadays he lives in Nijmegen and is professionally connected to the Academy of Art in Arnhem. His work is about watching and living to see, about discovering and reflecting about the human being and its surroundings,



and about music and travelling. He tries to express the daily miracles that you can see all over the place. It is about the game of coincidence, but above all his work involves freedom, honest freedom. A limited edition of original prints (size 49 x 49 cm) on Hanemulle paper 300 g/m (50 x 65 cm) is available at a price of € 145. You can order the print at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.

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