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Meningococcal Chest Infections in a General Hospital

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In the course of one calendar year (1989–1990), 46 specimens of respiratory secretions (from 44 patients) cultured in the microbiology department of a large district general hospital in The Netherlands were found to yield *Neisseria meningitidis*. Twenty-eight of the 46 samples yielded pure cultures of meningococci and 18 yielded other recognised respiratory pathogens as well. Only one patient had pneumonia, whereas 19 had acute respiratory infections and 18 acute purulent exacerbations of chronic bronchitis. The remaining patients, who had a variety of symptoms, all had purulent sputum. Only 8 of the 44 patients were under 40 years of age; 21 were aged more than 60 years. Serological grouping and subtyping showed a predominance of group B strains (in 24 of 44 patients) and 13 strains were non-groupable. The importance of recognising or overlooking meningococci in cultures of respiratory secretions is discussed.

Although meningococcal meningitis occurs regularly in many countries, it is not generally considered to reach epidemic levels in The Netherlands where there are, on average, 1.5 to 2.5 cases per 100,000 head of population annually. However, occasional periods may occur when there is an undoubted increase in the prevalence of meningococcal infections nationwide. This was the case in 1966 and again in 1988–1989, as recently reported by Postema et al. (1). Ever since 1970, strains of group B have predominated, followed by those of group C (2).

Although meningococcal respiratory infections (especially pneumonia) have been well documented, we have recently noted an increase in the numbers of patients attending hospital, either as outpatients or inpatients, because of acute non-pneumonic respiratory infections. The sputum cultures of these patients have yielded *Neisseria meningitidis*. In view of this observation, a special watch was kept for sputum isolates suggestive of *Neisseria meningitidis*. After their morphology had been verified and their oxidase-reactivity and biochemical reactions confirmed by standard methods, any such isolates were sent to the Netherlands Reference Laboratory for Bacterial Meningitis at the University of Amsterdam, for confirmation of the identification and serological typing. This article presents the results in patients seen between mid-January 1989 and mid-January 1990 at the De Wever Ziekenhuis, which is an 875-bed district general hospital in Heerlen in the extreme south of The Netherlands, adjacent to the borders with Germany and Belgium.

Materials and Methods

Collection and Processing of Sputum. Specimens of expectorated sputum were collected in sterile glass Petri dishes from all patients attending hospital, and were brought immediately to the Department of Medical Microbiology for examination. Specimens submitted by general practitioners outside the hospital were generally brought in by the doctors themselves in wide-mouthed sterile containers designed for faeces or urine. Simultaneous nasal or pernasal swabs were not taken. On arrival in the laboratory, the sputum was inspected with the naked eye, and the degree of purulence assessed. Grossly unsuitable specimens were rejected immediately. The sputum was then washed in three changes of sterile saline by the standard Dutch method (3, 4). Purulent material, washed free of extraneous throat commensals by this procedure, was then used to inoculate blood agar and chocolate agar plates and to make a smear for staining by Gram's method. During the microscopical examination, leucocytes and squamous epithelial cells were assessed and a further impression of the quality of the sputum specimens was recorded. Once the specimen had been shown to be satisfactory, the numbers of leucocytes per oil-immersion field were counted and the counts scored (sporadic = less than 1 per field, + = 1–3 per field,

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++ = 4–12 per field and +++ = > 12 per oil-immersion field).

Sputum cultures were made on blood agar plates containing 5 % sheep blood, and on chocolated blood agar. All culture plates were incubated in 10 % CO_2 in a special incubator and were read by experienced technicians 18 and 42 hours later. Conventional respiratory pathogens such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Branhamella catarrhalis* were identified by standard methods (5) and the culture densities were graded from +++ (profuse) to ± (very light).

Identification and Typing of Neisseria meningitidis. Any colonies suspected of being *Neisseria meningitidis* were investigated by Gram staining and the oxidase reaction. Oxidase-positive gram-negative cocci were further tested for carbohydrate fermentation on three-compartment plates of ascites agar containing 1 % of glucose, maltose or saccharose with phenol red as indicator. These plates were incubated in a candle jar rather than in the CO_2 incubator. As an extra control, two blood agar plates were also streaked out: one for incubation in air and one in 10 % CO_2 in the special incubator. When an organism morphologically and culturally resembling *Neisseria meningitidis* was noted, it was subcultured on to a special transport medium and posted to the National Reference Laboratory for Bacterial Meningitis at the University of Amsterdam. There, the identification of the isolate was confirmed by Gram staining, oxidase reaction, fermentation of glucose, maltose, lactose, saccharose and fructose and by testing for the production of γ-glutamyl aminopeptidase (6). For this test, a few colonies were suspended in a solution of L-γ-glutamyl-p-nitro anilide (0.14 g/l); the result was regarded as positive if the red colour changed to yellow.

Serogrouping was performed by double immunodiffusion using rabbit antisera that were made group-specific by absorption. Serotyping was done with a whole-cell EIA using monoclonal antibodies against serotype and subtype-specific outer membrane proteins (7).

Results

During the period between 18 January 1989 and 18 January 1990, cultures of 46 respiratory specimens from 44 different patients were found to yield *Neisseria meningitidis.* Forty-four of the 46 specimens consisted of expectorated sputum, and there was one nose swab and one specimen of bronchial washing.

Nearly all the patients presented with the typical signs of acute respiratory tract infection consisting of cough and production of green purulent sputum. Almost half of these infections (20 of 44) occurred in patients who were not known to have any form of chronic respiratory disease, whereas there were 18 patients who had acute purulent exacerbations of pre-existing chronic bronchitis.

A wide variety of respiratory and non-respiratory symptoms were also reported, and these are summarised in Table 1. Only one patient was diagnosed clinically and radiologically as having pneumonia superimposed on his chronic bronchitis. The majority of the patients (27 of the 44) were under the care of the Department of Respiratory Diseases (13 as inpatients and 14 as outpatients) but there were five patients from the Department of Internal Medicine (four of whom were inpatients) and four under the care of general practitioners outside the hospital. The Departments of Neurology, Paediatrics and Surgery each contributed two patients, the Department of Ear, Nose and Throat diseases only one. The majority of the patients were relatively elderly. There were 35 male patients whose mean age was 58.6 years (range 4–85 years) and 9 females, with an average age of 49.2 years (range 16–78 years). The ages of the patients in the individual groups are given in Table 2.

Table 1: Mode of presentation of meningococcal respiratory infections in 44 patients.

Acute purulent respiratory tract infection without signs of pneumonia	19
Acute purulent exacerbation of chronic bronchitis	18
Spontaneous pneumothorax, purulent sputum	2
Acute productive pneumonia (community-acquired)	1
Pulmonary embolism, purulent sputum	1
Pleurisy, purulent sputum	1
Status asthmaticus, purulent sputum	1
Herpes encephalitis, purulent sputum	1

Thirty-eight of the 44 sputum specimens were highly purulent and contained more than 12 leucocytes per oil-immersion field (OIF). Five specimens contained 4–12 leucocytes per OIF and one 1–3 leucocytes per OIF. The gram-negative diplococci were sometimes noted to lie intracellularly, but were sometimes all extracellular. In most smears, there was a mixture of intra- and extra-cellular organisms. *Neisseria meningitidis* was present in pure culture in 28 of the 46 specimens, and in combination with recognised respiratory tract pathogens such as *Streptococcus pneumoniae, Haemophilus influenzae* or *Branhamella catarrhalis* in 18 others (Table 3). Two of the patients with pure cultures had postoperative chest infections. Analysis of the density of the

Table 2: Age distribution of 44 patients with meningococcal respiratory infections.

	Age distribution (years)					Mean
	0–19	20–39	40–59	60–79	80–89	
Acute respiratory tract infection	2	3	8	7	–	46.1
Exacerbations of chronic bronchitis	1	–	5	9	3	63.7
Other respiratory symptoms	1	1	2	2	–	57.1
Total	4	4	15	18	3	

Table 3: Culture results for 46 respiratory specimens.

	No. of specimens
Neisseria meningitidis	28
Neisseria meningitidis + *Streptococcus pneumoniae*	9 [a]
Neisseria meningitidis + *Haemophilus influenzae*	4
Neisseria meningitidis + *Haemophilus influenzae* + *Streptococcus pneumoniae*	2
Neisseria meningitidis + *Branhamella catarrhalis*	1 [b]
Neisseria meningitidis + *Moraxella phenylpyruvica*	1
Neisseria meningitidis + *Klebsiella pneumoniae*	1
Total	46

[a] One specimen of bronchial washings.
[b] One nose swab.

meningococcal cultures showed that 22 specimens yielded profuse (+++) growth and 14 moderately heavy (++) growth. There were only seven specimens in which the growth of meningococci was light (+) and three in which it was scanty. The patient who had been admitted to hospital for acute community-acquired pneumonia yielded profuse growth of *Haemophilus influenzae, Streptococcus pneumoniae* and *Neisseria meningitidis* in his sputum culture.

The meningococcal typing results were identical in duplicate cultures from two patients. The results of the serogroup studies are shown in Table 4, from which it is clear that the 24 strains of serogroup B and the 13 non-groupable strains made up the majority. Only one strain each of serogroups 29E, X, Y, and Z and three of group C were seen during the whole year. Most of the meningococcal respiratory infections occurred in the autumn and winter period, i.e. between September and March, and only five infections were recorded in the period from April to July 1989. Further analysis of the serotyping results showed that no single serotype or subtype had an absolute predominance. However, seven strains of serogroup B were non-typable in the serotyping and also in the subtyping.

All patients whose antimicrobial therapy was documented and the records available to us responded extremely well either to temafloxacin (one of the newer quinolones which was being studied at the time) or to third generation cephalosporins such as cefepime, cefodizime, cefotaxime or ceftazidime, which were also being studied in the Department of Respiratory Diseases. In all patients, disappearance of the meningococci from the sputum was accompanied by disappearance of the purulence and of the clinical symptoms. Not one of the 46 isolates was found to produce β-lactamase. All except one strain (which had an ampicillin MIC value of 1 mg/l) were highly susceptible to penicillin and ampicillin with MICs of 0.125 mg/l or less. All the 44 strains were highly susceptible to cefotaxime but seven strains (15.9 %) were resistant to cotrimoxazole. None of the patients died as a result of the meningococcal infection, nor did any subsequently develop septicaemia or meningitis.

Discussion

In the latest (1990) edition of Mandell's "Principles and Practice of Infectious Diseases",

Table 4: Serological subtyping of non-groupable and group B strains of *Neisseria meningitidis* from 44 patients with respiratory infections. Other serogroups were C (3 strains), and 29E, X, Y, and Z (one strain each).

	Serotype	No. of strains	Subtype	No. of strains
Serogroup B (24 strains)	NT	15	NT	7
			P1.15	3
			P1.7	2
			P1.1	1
			P1.2	1
			P1.6	1
	type 4	8	NT	1
			P1.1/P 1.7	2
			P1.4	2
			P1.7/P 1.16	1
			P1.10	1
			P1.14	1
	type 1	1	P1.6	1
Non-groupable (13 strains)	NT	6	P1.6	2
			P1.15	2
			P1.1	1
			P1.16	1
	type 4	5	NT	2
			P1.2	1
			P1.4	1
			P1.15	1
	type 2a	1	P1.4	1
	type 15	1	P1.9	1

NT = Not typable

Apicella (8) discusses the available literature on meningococcal respiratory infections and refers to the fact that explosions of meningococcal pneumonia have been described, both in Air Force recruits (9) as well as in otherwise normal patients with community-acquired pneumonia (10, 11), especially during an influenza epidemic (12). In the latter instance the nasopharyngeal carriage rate for meningococci in asymptomatic outpatients varied between 7 % and 13 %. *Neisseria meningitidis* was cultured from the sputum of 14 of 47 pneumonia patients (in 4 in pure culture) and in 7 of 23 patients with respiratory infections other than pneumonia, 3 of them also yielding pure cultures. After the great influenza pandemic in 1918, various studies which were reviewed by Irwin et al. (10) showed that meningococcal pneumonia was a fairly frequent complication, but we have not been able to find much information in the literature concerning meningococci as infecting agents in acute purulent exacerbations of chronic bronchitis or in acute purulent non-pneumonic chest infections. Only in the single pneumonia patient in the present study were serological investigations for viruses carried out, but they were completely negative. We do not believe that sporadic viral infections (e.g. influenza) had any association with the meningococcal chest infections. The 44 cultures yielding *Neisseria meningitidis* formed only a tiny proportion (2.2 %) of the 2005 positive sputum cultures obtained in the laboratory at Heerlen during 1989. In 1988, before we had realised how common meningococci were, we recorded 54 isolates of "*Neisseria* species" out of 1696 positive sputum cultures (3.2 %), but we cannot say how many of them were meningococci. Weinberg (13) also noted the association of *Neisseria meningitidis* with pneumonia but was not sure whether there had been a real increase in recent years, or whether increased awareness was responsible. In The Netherlands, most experienced medical microbiologists can recall having seen very occasional cases of pneumonia associated with *Neisseria meningitidis*, but we were extremely surprised to find 43 non-pneumonic patients and one with pneumonia in a single hospi-

tal in the course of one calendar year. It has however been shown that a considerable rise in the incidence of meningococcal meningitis occurred in 1989 in The Netherlands (1), and this may be the result (or even the cause) of a considerable increase in the meningococcal carriage rate, possibly resulting in an increased incidence of purulent respiratory infections associated with these organisms. However, in the absence of nasopharyngeal cultures we cannot say whether meningococcal colonisation of the upper respiratory tract was present, or whether colonisation preceded the lower respiratory tract infection. It did not appear from the study of Koppes et al. (9) that patients with meningococcal infections of the lower respiratory tract were at any increased risk of developing septicaemia or meningitis, a point confirmed in the present study. It is interesting to note that, whereas meningococcal carriage rates fall with increasing age, there is a tendency for the non-pneumonic meningococcal respiratory infections to occur in the more elderly age groups. Perhaps there is an increasing immunity to meningococci with increasing age which tends to limit the occurrence of invasive forms of meningococcal infection in older patients. However, this did not seem to prevent acute symptomatic purulent respiratory infections occurring. No studies on the immune responses to the meningococcal chest infections were carried out, so that the role of immunity in the older patients must remain conjectural.

Most of the literature sources studied make the point that *Neisseria meningitidis* present in a culture of sputum or other respiratory material may easily be overlooked. Unless a culture is specifically requested to detect meningococcal carriage (e.g. in a pernasal swab) no special laboratory procedure for detection of meningococci will usually be carried out. Furthermore, in areas where respiratory infections with *Branhamella catarrhalis* are common (14), the microscopical findings will not allow distinction of meningococci from branhamellae. Perhaps a suitable selective culture medium ought to be inoculated whenever gram-negative diplococci are seen in the stained smear. Although we did not use any selective media in the present study, incubation of the chocolate agar and sheep blood agar plates in the CO_2 incubator resulted generous growth of meningococci. However, the skill of the microbiology technician is needed in order to assess the colonies present, and to decide on further tests for their identification.

The question arises as to how important it is that meningococcal respiratory infections are not overlooked. Because meningococci are usually still susceptible to most of the antimicrobial agents commonly employed for treating respiratory infections (penicillins, cephalosporins, erythromycin, tetracyclines, etc.), they will generally be eradicated by such therapy. This contrasts with the difficulty encountered with penicillins in eliminating meningococci from the upper respiratory tracts of chronic carriers (12). However, trimethoprim alone is not likely to be successful because of the inherent resistance of neisseriae and branhamellae. Although the consequences are probably not serious if a meningococcal respiratory infection is overlooked in the microbiology department, we hope with this communication to remind all laboratory workers that these infections do occur, and that they can be identified without recourse to extra (and expensive) procedures.

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