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RECENT ADVANCES IN THE MANAGEMENT OF ADULT RESPIRATORY TRACT INFECTIONS: OUT-PATIENT AND OFFICE PRACTICE

EDITED BY

CLAUDE CARBON

GUY HUMBERT

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Edited by
Claude Carbon
Guy Humbert

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Contributors

Editors

C. Carbon

Department of Internal Medicine, Bichat Hospital, Paris, France

G. Humbert

Infectious Diseases Department, Charles Nicolle Hospital, Rouen, France

Contributors

R. B. Brown

Infectious Disease Service, Baystate Medical Center, Springfield, MA, USA, and Tufts University School of Medicine, Boston, MA, USA

M. Cazzola

Occupational Pulmonary Disease Service, Department of Pulmonary Medicine, A Cardarelli Hospital, Naples, Italy

P. J. Cole

Host Defence Unit, Cardiothoracic Institute, Brompton Hospital, London, UK

H. Dabernat

Centre d' Etude des Haemophilus (GEEP), CHU Purpan, 31059 Toulouse, France

C. Ekedahl

ENT Clinic, Central Hospital, Vaxjö, Sweden

R. Ringelmann

Institute for Medical Microbiology and Immunology, Karlsruhe, Freiburg Medical School, West Germany

A. J. Weinstein

Lilly Research Laboratories, Indianapolis, USA

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Haemophilus influenzae: epidemiological problems of antibiotic resistance

H. DABERNAT

Centre d'Etude des Haemophilus (GEEP)
CHU Purpan, 31059 Toulouse, France

Introduction

Haemophilus influenzae (*Bacillus influenzae*) was first observed and isolated from the sputum of influenza patients by Pfeiffer during the influenza pandemic of 1889–1892.

Belonging to the genus *Haemophilus* ('which loves blood'), *H. influenzae* requires certain growth factors present in blood for culture. X factor (haemin) is needed for the synthesis of iron-containing respiratory enzymes. It is heat-stable and is present in erythrocytes. V factor (NAD or NADP) is present in blood and numerous tissues, and is synthesized by several bacterial species. NAD and NADP are co-enzymes for dehydrogenases (1).

In order to culture and identify haemophilus, appropriate media and conditions are needed in addition to factors X and/or V. The culture medium must contain growth factors. Chocolate agar, cooked blood agar, blood agar with a streak of *Staphylococcus aureus*, or nutrient agar supplemented with NAD and haemin are all suitable. Incubation must be carried out under a moist atmosphere. Various tests can show the requirement for factors X and V. The δ-aminolevulinic acid test (porphyrin test) allows evaluation of porphyrin synthesis from δ-aminolevulinic acid and consequently requirements for factor X (2,3,4).

Haemophilus species are normally present on the mucosa of the upper respiratory tract and mouth, and can also be isolated from the digestive tract and the vaginal mucosa. *H. influenzae* is present in the pharynx, particularly in children. The organisms are not encapsulated (fewer than 4% of children show colonization by type b strains) and there is wide variability in the frequency of pharyngeal colonization by the type b strains. This variability depends on living conditions (such as attendance at institutions or day care centres, and family contacts) and whether or not there are acute episodes of *H. influenzae* b infections (meningitis, epiglottitis) (5). In the presence of active colonization, chemoprophylaxis can be useful.

H. influenzae is pathogenic both in children and in adults. In children, the type b strains cause invasive infections including septicaemia, meningitis, arthritis,

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epiglottitis, pneumonia and cellulitis; both encapsulated and non-encapsulated strains can cause ENT infections. Acute infections (meningitis) are most common in children between the ages of 3 months and 3 years because at this age children do not possess anti-polysaccharide antibodies. In adults, predisposing factors are of primary importance in the development of *H. influenzae* infections; pulmonary and bronchopulmonary sites are most common (4).

Antibiotic susceptibility

Study of the antibiotic susceptibility of *H. influenzae* can be carried out with agar diffusion techniques (standard antibiotic susceptibility testing) or by determination of the minimal inhibitory concentration (agar dilution or microdilution in liquid medium). Media used must satisfy growth requirements for the species (X and V factors). Techniques will not be described in detail here. Dependant upon the antibiotic used, interpretation of diffusion tests can differ from that used for the rapidly growing bacterial species. The usual susceptibility profile of *H. influenzae* is shown in Table 1.

Table 1

Activity of various antibiotics against H. influenzae *(MIC in mg/l)*

	Susceptible strains	Resistant strains
Ampicillin	0.25	8–16
Cefalothin	2	–
Cefotaxime	0.015	–
Gentamicin	1	–
Kanamycin	2	128
Tetracyclin	1	32
Minocyclin	0.50	–
Chloramphenicol	0.50	8
Erythromycin	1–2	–
Lincomycin	–	32
Rifampicin	0.25	8
Trimethoprim	0.06	8
Pefloxacin	0.06	–

Development of antibiotic resistance

The problem of antibiotic resistance of *H. influenzae* was first evoked in the 1970s following isolation of the first ampicillin resistant and beta-lactamase producing strain in clinical meningitis (1973). Beta-lactamase producing strains are currently very widespread, and are found the world over. The other major antibiotics concerned with resistance are the tetracyclines and chloramphenicol; we would also note cases of resistance to kanamycin and trimethoprim.

Ampicillin resistance generally develops because of beta-lactamase production, but resistant strains due to modifications in penicillin-binding proteins (PBP) are also seen. In this case, activity of other antibiotics of the beta-lactam family are also modified (6,7). Production of beta-lactamase should be assessed systematically in all pathogenic strains; various techniques can be used including acidimetry,

cephalosporin chromogen and microbiological methods (8). Chloramphenicol resistance is due to the production of chloramphenicol acetyl transferase (CAT), which inhibits the activity of this antibiotic. Various methods allow assessment of enzyme production in conjunction with agar diffusion studies (standard antibiotic susceptibility tests) (8).

Although the development of strains resistant to antibiotics was first seen in the 1970s, before 1980 the frequency of ampicillin resistance, in particular of the invasive strains, was generally low — below 10%. Major variations have been seen with time and area, however, and detailed information is available for the various European countries, including the UK, Switzerland, Belgium and Finland. In France, a national survey carried out in 1981 showed that 7·5% of the causal pathogens in meningitis were resistant to ampicillin (9).

Results of a French collaborative study

Our French data are based on the work of the Centre d'Etude des Haemophilus GEEP which functions in the framework of the Network for Permanent Monitoring of *Haemophilus influenzae* Infections. Correspondents are distributed throughout France at the General and University Hospitals (Fig. 1). Hospital laboratories

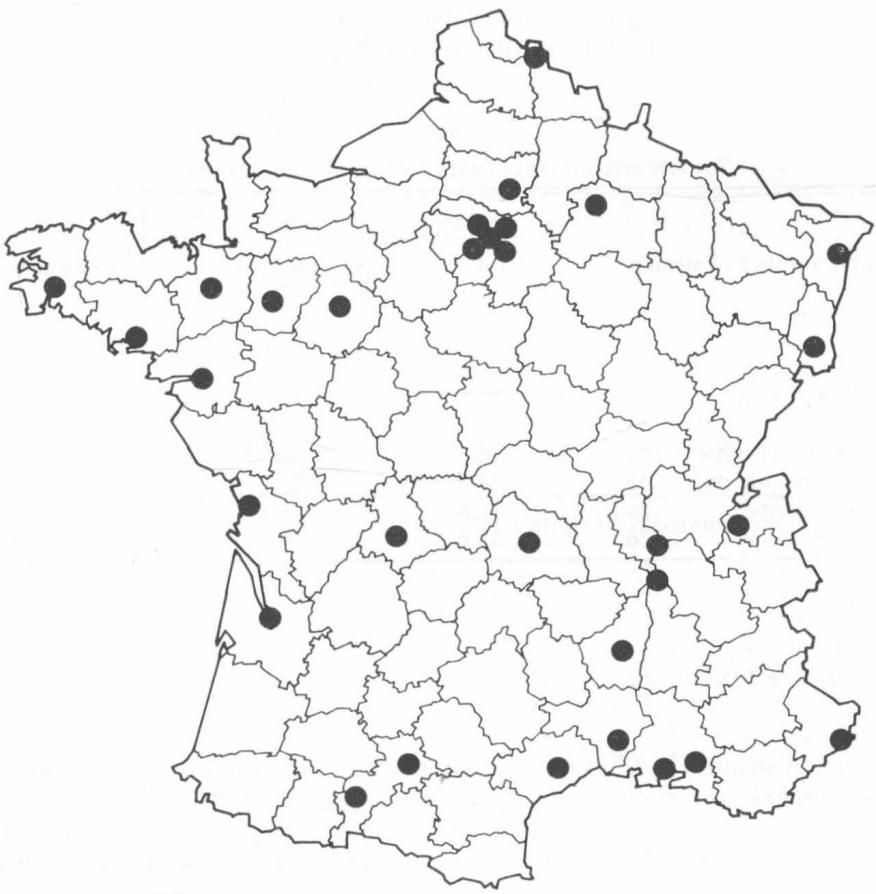

Figure 1. Geographical origin of Haemophilus influenzae *strains studied.*

despatch all strains isolated from pathological specimens to the 'Centre d'Etude des Haemophilus', and the following parameters are determined for each strain: serotype, biotype, antibiotic susceptibility and, for type b strains, sub-type defined by the electrophoretic profile of outer membrane proteins.

Bacteriological results

In 1985, 705 strains isolated from clinical infections were studied. Distribution by type of specimen and primary characteristics are shown in Table 2. It was seen that 84% of meningitis cases occurred in children aged 3 months to 3 years. Among the adults, we would note one case of recurrent meningitis in a 33-year-old man with non-encapsulated biotype II and III strains of *H. influenzae*, developing some time after a complex fracture of the pars petrosa.

Conjunctivitis is primarily seen in children (97·3% of cases before 15 years and 67.7% between 3 months and 3 years). Strains were of biotypes II and III in 56% and 31% of cases, respectively. Only 10% of strains were encapsulated, including 8% of type b. Biotype III strains did not meet criteria defined for *H. aegyptius*. In otitis, the isolated strains were of biotypes II (39%), I (25·4%) and III (17%): 15·25% of strains were serotype b and 81·3% were non-encapsulated. The main strains isolated from bronchial secretions were biotype II (36%); biotypes I, II, and III together accounted for 83·3% of isolates. A total of 82·6% of the strains were non-encapsulated, and 11% were of serotype b (Table 2).

Table 2

Source and characteristics of H. influenzae *strains*

Source and number of strains		Percentage of strains		
		Biotype I	Serotype b	Non-encapsulated
CSF	98	90	91.8	8.1
Blood	76	79	80.2	18.4
Bronchial secretions	144	25.6	11.1	82.6
Pus from otitis	118	25.4	15.2	81.3
Pus from conjunctivitis	164	7.3	7.9	90.8
Other ENT specimens	45	24.4	22.2	73.3
Genital specimens	28	17.8	7.1	89.2
Other suppurations	26	34.6	19.2	76.9

Antibiotic resistance

A total of 613 strains (86·9%) were susceptible to the antibiotics tested. Resistance to one or several antibiotics was observed in 92 strains (13%).

Tables 3 and 4 show the distribution of resistant strains as a function of biotype (Table 3) as well as serotype (Table 4). The highest percentage of resistant strains was seen in biotype I and serotype b.

Table 3

Distribution of H. influenzae resistant strains according to the biotype

Biotype and number of strains		Percentage of resistant strains				
		Overall	Ap	Tc	Cm	Km
I	255	17.6	14.5	14.1	4.7	11
II	248	8.8	7.6	6	1.2	5.6
III	128	10.1	8.5	4.6	4.6	2.3
IV	22	9	9	9	9	9
V, VI, VII	52	19.2	19.2	9.6	1.9	1.9

Ap = ampicillin; Tc = tetracycline; Cm = chloramphenicol; Km = kanamycin

Table 4

Distribution of H. influenzae *resistant strains according to the serotype*

Serotype and number of strains		Percentage of resistant strains				
		Overall	Ap	Tc	Cm	Km
b	220	20	16.8	15	5.5	9
a, c–f	21	4.7	4.7	–	–	–
non-typable	464	10	8.8	6.6	2.5	6

Ap = ampicillin; Tc = tetracycline; Cm = chloramphenicol; Km = kanamycin

Table 5

Distribution of H. influenzae *resistant strains according to antibiotic and to specimen sources*

Specimens and number of strains		Percentage of resistant strains				
		Overall	Ap	Tc	Cm	Km
All specimens	705	13.0	11.2	9.0	3.4	6.8
CSF	98	15.3	12.2	14.2	4.0	11.2
Blood	76	11.8	10.5	10.5	5.2	9.2
Conjunctival pus	164	9.1	6.7	4.8	2.4	3.6
Otitis pus	118	16.1	16.1	7.6	3.3	6.7
Bronchial secretions	144	13.8	12.5	10.4	1.3	6.9
Other ENT specimens	45	8.8	8.8	4.4	4.4	4.4
Pus and fluids	26	19.2	19.2	15.3	7.6	11.5
Genital specimens	28	14.2	3.5	14.2	7.1	3.5

Ap = ampicillin; Tc = tetracycline; Cm = chloramphenicol; Km = kanamycin

Table 6

Distribution of H. influenzae *resistant strains according to resistance phenotype and to specimen source*

Phenotype	Number of strains	CSF (98)	Blood (76)	Bronchial secretions (144)	Pus from otitis (118)	Pus from conjunctivitis (164)	Other ENT specimens (45)	Genital specimens (28)	Pus and fluids (26)	Not indicated (6)
Ap-Km-Tc	24	6	3	8	4	1	–	–	2	–
Ap	14	–	–	2	6	2	2	–	1	1
Ap-Km-Cm-Tc	13	4	3	–	1	1	2	1	1	–
Ap-Tc	11	1	–	5	3	2	–	–	–	–
Ap-Km	10	1	1	2	2	4	–	–	–	–
Tc	9	3	1	1	–	2	–	2	–	–
Ap-Cm-Tc	4	–	1	–	1	1	–	–	1	–
Cm-Tc	3	–	–	1	–	1	–	1	–	–
Ap-Cm	2	–	–	1	1	–	–	–	–	–
Ap-Km-Cm	1	–	–	–	1	–	–	–	–	–
Cm	1	–	–	–	–	1	–	–	–	–

Ap = ampicillin; Tc = tetracycline; Cm = chloramphenicol; Km = kanamycin

Resistance to ampicillin, tetracycline, kanamycin and chloramphenicol were seen in 11·2%, 9%, 6·8% and 3·4% of strains, respectively. Resistance to co-trimoxazole (or to trimethoprim and sulphonamides separately) was not taken into account due to technical difficulties in interpretation. Distribution of resistant strains as a function of antibiotic and type of specimen is shown in Table 5. Resistance to ampicillin was seen in 12% of specimens from meningitis and bronchopulmonary infections, and in 16% of cases of otitis. Chloramphenicol resistance in these same specimens was always lower, less than 4%.

Resistant strains showed 11 different resistance phenotypes (Table 6). Simultaneous resistance to ampicillin and chloramphenicol was seen in 20 strains (21·7% of resistant strains and 2·8% overall) and simultaneous resistance to ampicillin and tetracycline was seen in 52 strains (56·5% of the resistant strains, and 7·3% of all strains). Resistance to ampicillin was always attributable to production of beta-lactamase, except in one strain isolated from bronchial secretions.

Discussion

These data show the prevalence of resistance in France and are based on the pooled data from different geographical areas over a large period of time in order to offset local and temporal variations. Changes have occurred since the 1981 survey (9) and the incidence of ampicillin strains in meningitis has now increased from 7·5% in 1981 to 12% today.

Because of the dire consequences for the patient, particular attention was devoted to the investigation of ampicillin resistance. An upward trend has been observed in many countries, though major intralaboratory and geographical variations have sometimes been seen (10,11,12). Following the isolation of the first resistant strains in 1973–74, there was a gradual increase until 1980 with a resistance rate approaching 5% of the invasive strains noted in the UK (1·6% in 1977) (11), in some states of the USA (from 0 to 4·2% in 1977) (10,12,13) in Canada (14), Belgium (15), Australia (16), Finland (17) and New Zealand (18) (Table 7).

During the 1980s, however, the rate of beta-lactamase-producing strains increased, almost universally, to above 10%. Concurrently, the first non-enzyme-producing ampicillin resistant strains (6,7,10,11,17,21,22,) and multiple resistant strains were isolated. Multiple resistance is known to involve ampicillin, chloramphenicol and tetracycline; it may or may not be associated with resistance to other antibiotics (kanamycin or trimethoprim) (20,24,25,26,27).

Chloramphenicol resistance development has not paralleled that of ampicillin, and the resistance incidence is low — no higher than 1% in many countries such as the UK (11), USA (22) and Switzerland (19), and sometimes there is no evidence of it (21,23). However, the data reported by Campos *et al* in Barcelona, Spain, are quite different since 50% of the strains causing meningitis show multiple resistance (e.g. to ampicillin, chloramphenicol and tetracycline) (20).

In the case of tetracycline, resistance rates also vary: most commonly they are low — no higher than 5% (11,19,22) — but sometimes the incidence is much greater, i.e. 23% of the strains from the respiratory source (23) and 50% of the strains isolated from meningitis (Table 7) (20).

It should be emphasized that ampicillin resistance is more frequent in type b capsulated strains (11,14,22). Today the incidence of ampicillin resistant strains is

Table 7

Percentage incidence of resistance to antibiotics among H. influenzae *in various countries*

				Ap	Tc	Cm	Cot	Reference
Finland	Jokipii (1977–78)	1980	ENT	13	–	0	–	17
Switzerland	Borer-Bigliardi	1984		4	–	1.4	–	19
Spain	Campos	1984	IS	50	54.5	52.2	63.6	20
(Barcelona)			NIS	11.6	11.6	11.6	10.5	
UK	Philpott-Howard	1978		1.6	2.7	0.25	0.2	
		1982		6.2	3.1	1	1.4	11
Canada	Scheifele (1979)	1977	IS	6.3	–	–	–	
		1978	IS	13	–	–	–	14
	Bannatyne (1976–1983)	1985	IS	14.8	–	0	–	21
USA	Ward	1978	IS	4.5	–	0	–	12
	Istre (Colorado)	1977	IS	4.2	–	–	–	
		1981	IS	31.3	–	–	–	10
	Doern (Collaborative study)	1985		15.2	6.4	0.6	–	22
New Zealand	Green	1979	BR.S	3.4	1.6	0	0.42	18
Hong Kong	Ling	1983	BR.S	3	23	0	–	23

ENT = ear, nose and throat specimens; IS = invasive strains; NIS = non-invasive strains; BR.S = bronchial secretions; Ap = ampicillin; Tc = tetracycline; Cm = chloramphenicol; Cot = Co-trimoxazole

such that this antibiotic should be ruled out in the treatment of systemic *H. influenzae* infections, particularly meningitis but also otitis media.

With a third generation cephalosporin, ampicillin and chloramphenicol resistance is covered and meningitis can be treated successfully. In other indications the choice of the antibiotic will have to rely on the susceptibility of the causative strains and on the site of infection. Non-beta-lactamase-producing strains, isolated primarily from adult respiratory tract infections, which are not frequent at the moment, may become a major concern in the future.

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The significance of *Haemophilus influenzae* and other micro-organisms in the pathogenesis and treatment of chronic respiratory infection

P. J. COLE

Host Defence Unit, Cardiothoracic Institute, Brompton Hospital, London, UK

Introductory concepts

To understand the significance of *Haemophilus influenzae* in chronic respiratory infection it is necessary to be aware of recent concepts of the pathogenicity of such infection which have developed from the study of bronchiectasis – one of the conditions encompassed by the syndrome of chronic bronchial sepsis (chronic, usually daily, expectoration of purulent sputum).

Evolutionary background

The lung develops from foregut and therefore local respiratory defences have evolved from those which formerly protected the foregut. Not being custom built to protect the respiratory tract, they are therefore prone to be fallible in certain situations; furthermore they can, under certain conditions, be subverted against the host itself and cause it actual damage.

Microbial supremacy

In the evolutionary struggle for survival the micro-organism has enormous adaptive powers because of its rapid rate of division and therefore considerable capacity for genetic change — in contrast to man who is ultimately at a disadvantage in spite of his ability to develop antimicrobial agents. So, for the forseeable future, the question is how successfully can man restore equilibrium in the host-parasite relationship thus minimizing mortality and morbidity due to microbial challenge?

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Facts about chronic bronchial sepsis

As exemplified by bronchiectasis, the major facts about patients suffering from the condition (1) are:

1. they are relatively young (mean age approximately 40 years)
2. they are mainly non-smokers (although this may be an artefact of their referral to hospital since primary care physicians commonly ask patients with persistent expectoration whether they smoke cigarettes and, if they reply 'yes', advise them 'there is nothing I can do for you until you stop smoking' — in which case such patients are less likely to be referred to hospital and fail to appear in the statistics)
3. they are wheezy — with partially or completely reversible airflow obstruction
4. they are infected in the bronchial tree by a variety of micro-organisms *not* usually associated with invasive disease (e.g. uncapsulated *H. influenzae*, mucoid *Pseudomonas aeruginosa* etc.)
5. they respond to the bronchial microbial load with a normal or exuberant immunological and non-immunological host response in approximately 80% of cases (the prevalence of immunity deficiency being <10% — apparently a paradox)
6. they are affected in the upper respiratory tract in 80% cases — with one third suffering frank, purulent chronic sinusitis
7. they are, in a proportion of cases, affected by rapidly progressive disease which causes severe shrinkage and scarring of the bronchial tree with serious morbidity and often death within a few years.

The 'vicious circle' hypothesis

To accommodate these facts it is attractive to postulate that the host's respiratory defences are subverted by persistent micro-organisms into a tissue-damaging chronic inflammatory response.

Normally, the majority of attacks upon the lung by bacteria will be repelled by the efficient first-line defence mechanism, the mucociliary system with, in a few instances, the assistance of an acute, short-lived, useful and controlled inflammatory response. If, for reasons of pre-existing damage (e.g. from a virus infection) or underlying disease (e.g. cystic fibrosis), clearance in the respiratory tract is impaired and elimination of the attacking microbes is not effected — microbial colonization of that part of the bronchial tree will result in amplified inflammation. This host response will produce symptoms in the host so that the colonization can then correctly be termed infection. The host's inflammatory response, if unsuccessful in eliminating the attacking microbes, will become chronic and damage normal 'bystander' lung tissue resulting in progressive disease (Fig. 1).

Mucociliary impairment

Central to the concept of the 'vicious circle' pathogenesis of chronic bronchial sepsis is impairment of the first-line mucociliary clearance mechanism. That this occurs in bronchiectasis has been established by two studies (2,3) — the one by Currie *et al* also showing that the magnitude of impairment was of the same order as that seen in chronic bronchitis. Impaired mucociliary clearance has also been