Resistance of clinical isolates of *Haemophilus influenzae* in United Kingdom 1986

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Abstract

Between 1 January and 31 March 1986, 2434 strains of *Haemophilus influenzae* collected from 23 laboratories in the United Kingdom were examined. With the same criteria as previous studies in 1977 and 1981 the prevalence of resistance was: ampicillin 7.8% (6.2% β -lactamase producers and 1.6% non-producers), tetracycline 2.7%, chloramphenicol 1.7%, trimethoprim 4.2%, and sulphamethoxazole 3.5%. Of the 87 capsulated strains, 15 produced β -lactamase, nine were resistant to ampicillin but did not produce β -lactamase, and two strains, one of which produced β -lactamase, were resistant to chloramphenicol and tetracycline.

Since 1977 the prevalence of resistance to ampicillin, chloramphenicol, and trimethoprim has increased significantly. During 1981-6 strains resistant to ampicillin but not producing β -lactamase and strains resistant to trimethoprim have significantly increased.

Introduction

Many countries have reported increasing resistance to antibiotics by *Haemophilus influenzae* over the past decade.¹⁻³ An increase in the prevalence of resistance to ampicillin or chloramphenicol, or both, in Pittman type b strains is particularly important for patients who have meningitis, septicaemia, epiglottitis, and septic arthritis, in whom treatment starts before the results of susceptibility testing are available.

During the first three months of 1986, 23 of the 24 laboratories that formed the 1981 *H. influenzae* study group participated in a new survey. All 17 laboratories of the 1977 study group were included in this number.

Methods

IDENTIFICATION AND DISC DIFFUSION SUSCEPTIBILITY TESTING

Strains of *H. influenzae* that were isolated in the participating laboratories were sent to this college on chocolate agar slopes. One strain was accepted for each episode of infection. Pure subcultures of each strain were inoculated into phials of nutrient broth (Oxoid) supplemented with 5% inactivated Fildes' extract (Oxoid) and incubated for five hours at 37°C.

Each suspension was diluted 1/100 in peptone water and used to inoculate

a nutrient agar plate (Southern Group Laboratories) for X and V factor disc testing, incubated in air for 18 hours at 37°C and a DST agar (Oxoid) plate supplemented with 0.25% lysed horse blood and 10 mg nicotinamide-adenine dinucleotide/1 (BDH Chemicals), to which the following 6 mm discs were applied: 2 μ g ampicillin, 10 μ g tetracycline, 10 μ g chloramphenicol, 1.25 μ g trimethoprim, and 100 μ g sulphamethoxazole. The plates were incubated in an atmosphere of 5% carbon dioxide and 95% air for 18 hours at 37°C.

Each strain was biotyped according to the methods of Kilian,⁴ with the revised classification of Oberhofer and Back.⁵ Kilian's test for porphyrin production⁶ was used to check the haemin dependency of all strains. Organisms that were dependent on X and V factors, gave negative results for the porphyrin production test, and did not require carbon dioxide were accepted as being *H. influenzae*.

DETERMINATION OF MINIMUM INHIBITORY CONCENTRATIONS

The minimum inhibitory concentrations of the five antibiotics were determined by an agar dilution method with DST agar supplemented as above. A Denley multipoint inoculator was used to deliver 0.003 ml 1/100 dilution of organisms prepared as for disc testing; about 10 000 organisms were applied to the agar surface. All plates were incubated in an atmosphere of 5% carbon dioxide and 95% air for 18 hours at 37°C.

Those strains that grew with a zone diameter of less than 20 mm around one or more antibiotic discs were tested against all five antibiotics at final concentrations ranging from 256 mg/l to 0.008 mg/l. All other strains were tested only on plates containing the following final antibiotic concentrations: ampicillin 2 mg/l, tetracycline 4 mg/l, chloramphenicol 4 mg/l, trimethoprim 2 mg/l, and sulphamethoxazole 32 mg/l.

DETECTION OF β -LACTAMASE

All strains that grew with a reduced zone diameter around the ampicillin 2 μ g disc and those strains considered to be resistant by the sending laboratories but that grew with zone diameters ≥ 20 mm were tested for β -lactamase production by an acidometric method (Oxoid β -lactamase detection papers) and a cell suspension iodometric method.⁷

SEROTYPING

Strains showing iridescence on Fildes' agar were serotyped with agglutinating antiserum (Wellcome).

Results

Of the 2805 live cultures received, 2434 met the stated requirements for inclusion in the study. Calculations of the proportional contribution of isolates from the participating laboratories showed excellent agreement between 1981 and 1986, with only seven centres having a difference of more than 2%. These differences in proportion were all 5% or less, and none of the seven had appreciably different prevalences of resistance to any one antibiotic from the overall figures.

Table I shows the distribution of minimum inhibitory concentrations obtained from strains that showed a reduced zone diameter (<20 mm) for each of the antibiotics tested. Table II shows the total numbers of strains that showed a reduced zone diameter and minimum inhibitory concentration greater than the breakpoint chosen for each of the five antibiotics and compares the proportions of such strains in the three surveys. Identical methods for testing susceptibility were used in all three surveys^{8,9} except that a tube dilution method for determining sulphamethoxazole minimum inhibitory concentrations was used in 1981.

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Ampicillin

Two hundred and eighty three strains showed a reduced zone diameter around the ampicillin 2 µg disc, and 189 were considered to be resistant. Of these, 151 produced β-lactamase and had minimum inhibitory concentrations of ≥2 mg/l, and 38 were β-lactamase negative and had minimum inhibitory concentrations of ≥4 mg/l. The proportions of these two groups as a percentage of the total strains resistant to ampicillin were 80% and 20%, respectively, compared with 92% and 8%, respectively, in 1981.

The remaining strains with zone diameters <20 mm were all β-lactamase negative. Sixty of these required a minimum inhibitory concentration of 1 mg/l or 2 mg/l—an intermediate degree of resistance. Two β-lactamase negative strains with zone diameters ≥20 mm grew on 2 mg ampicillin/l

plates, and two β-lactamase positive strains seemed initially to be sensitive on disc testing and minimum inhibitory concentration determination.

Table III shows the changes in the total prevalence of resistance to ampicillin as defined above for the participating laboratories. The centres with the highest percentage resistance values were scattered geographically, and there were no clear correlations with large industrial cities or less urban centres.

Table IV shows the resistance patterns seen in the strains sensitive to ampicillin and the two resistant groups of strains. Of 14 isolates that were resistant to four or five of the antibiotics tested, six produced β-lactamase. None of the β-lactamase negative ampicillin resistant strains was also resistant to chloramphenicol or tetracycline, or both, but 23 β-lactamase positive isolates were.

TABLE I—Distribution of minimum inhibitory concentrations obtained from strains with zone diameters <20 mm for each antibiotic tested

	Minimum inhibitory concentration (mg/l)											
	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Ampicillin β-lactamase positive					6	14	16	29	36	33	14	3
Ampicillin β-lactamase negative	1	6	27	36	24	21	6	4	5	2		
Tetracycline				1		5	33	20	6	2		
Chloramphenicol					2	1	18	9	2			
Trimethoprim			1	1	1	3	5	16	25	53		
Sulphamethoxazole					2	12	26	66	25	22	16	22

TABLE II—Numbers of strains with reduced zone diameters (<20 mm) and minimum inhibitory concentration ≥ value stated of each antibiotic tested in the three United Kingdom surveys

Antibiotic (minimum inhibitory concentration)	1986 % (No) of strains	1981 % Of strains	1977 % Of strains
Ampicillin (total)	7.8 (189)	6.2	1.6
β-lactamase positive (≥2 mg/l)	6.2 (151)	5.75	1.6
β-lactamase negative (≥4 mg/l)	1.6 (38)	0.45	—
Tetracycline (≥4 mg/l)	2.7 (66)	3.1	2.7
Chloramphenicol (≥4 mg/l)	1.7 (42)*	1.0	0.2
Trimethoprim (≥2 mg/l)	4.2 (102)	1.4	0.2
Sulphamethoxazole (≥32 mg/l)	3.5 (85)	1.5†	

*Two strains had zone diameter <20 mm and minimum inhibitory concentrations of 2 mg/l, and 10 strains had zone diameters 20-25 mm and minimum inhibitory concentrations ≥4 mg/l.

†Tube dilution method used.

TABLE III—Prevalence of total ampicillin resistance in isolates from participating laboratories

	1986			1981 % Resistant	1977† % Resistant
	No of isolates examined	Total No (%) resistant to ampicillin*			
Aberdeen	75	6 (8.0)	9.6		
Ayr	189	19 (10.0)	7.4		
Barking	80	3 (3.8)	9.5		
Birmingham	111	11 (10.0)	8.8		
Bristol	79	8 (10.0)	10.6		3.8
Edinburgh	261	20 (7.7)	5.7		2.8
Epping	28	2 (7.1)	10.2		4.3
Glasgow	57	4 (7.0)	8.1		
High Wycombe	53	8 (15.0)	5.3		13.3
Inverness	80	4 (5.0)	2.7		
Liverpool	130	12 (9.2)	3.4		
London (total)	306	38 (12.4)			
Guy's	61	6 (9.8)	8.2		3.0
The London Hospital					
Medical College	84	10 (11.9)	6.5		1.4
St Thomas's	137	20 (14.6)	3.0		
University College Hospital	24	2 (8.3)	4.9		
Manchester	76	8 (10.5)	0.9		
Newcastle	124	11 (8.9)	8.3		
Nottingham	395	32 (8.1)	6.4		1.1
Plymouth	141	6 (4.3)	4.9		0.7
Portsmouth	128	15 (11.7)	11.5		
Salford	25	3 (12.0)	5.9		
Stockport	7				
York	89	3 (3.4)	2.9		

*Reduced zone diameter (<20mm) and minimum inhibitory concentration ≥1mg/l.

†Seventeen laboratories only.

Chloramphenicol

Thirty strains had both a reduced zone diameter and minimum inhibitory concentration ≥4 mg chloramphenicol/l, two strains had a zone diameter <20 mm and minimum inhibitory concentrations of 2 mg/l, and another 10 strains had zone diameters 20-25 mm and minimum inhibitory concentrations ≥4 mg/l. All 42 strains were shown to produce chloramphenicol acetyltransferase by the spectrophotometric method of Shaw and Brodsky¹⁰ and were resistant to tetracycline. Thirteen produced β-lactamase, and 11 were resistant to trimethoprim and sulphamethoxazole. Two strains were resistant to all five antibiotics tested (both produced β-lactamase). When the additional 12 strains were taken into account the overall figure for chloramphenicol resistance increased from 1.2% to 1.7%. Isolates from eyes did not show the increased prevalence of resistance to chloramphenicol found in 1981.

Tetracycline

Of the 66 strains (2.7%) with a reduced zone diameter and minimum inhibitory concentration ≥4 mg/l, 23 also produced β-lactamase. Twenty four strains were not resistant to chloramphenicol, but 10 of these produced β-lactamase. There was no increased prevalence of resistance to trimethoprim and sulphamethoxazole in this group.

Trimethoprim

One hundred and two strains (4.2%) were resistant to trimethoprim, showing a reduced zone diameter and minimum inhibitory concentration ≥2 mg/l. Of these, 47 were also resistant to sulphamethoxazole and 12 produced β-lactamase.

Sulphamethoxazole

Determining the minimum inhibitory concentrations of sulphamethoxazole by the agar dilution method produces a larger range of values compared with results of tube dilution assays. Of the 193 strains with a reduced zone diameter, however, 85 required a minimum inhibitory concentration ≥32 mg/l while only seven strains with zone diameters ≥20 mm were able to grow on the 32 mg sulphamethoxazole/l plate.

CAPSULATED STRAINS

Of 87 typable strains (3.6%), 66 (76%) were type b. Table V shows the prevalence of resistance as defined above in type b capsule and non-capsulate strains.

TABLE IV—Patterns of resistance for three groups by susceptibility to ampicillin. Values are numbers of strains

	Ampicillin alone	Tetracycline	Chloramphenicol and tetracycline	Chloramphenicol, tetracycline and trimethoprim	Chloramphenicol, tetracycline, trimethoprim and sulphamethoxazole	Trimethoprim	Sulphamethoxazole	Trimethoprim and sulphamethoxazole
Ampicillin sensitive: zone ≥ 20 mm, minimum inhibitory concentration < 2 mg/l (n=2149)		14	13	6	8	42	32	27
Ampicillin resistant: zone < 20 mm, minimum inhibitory concentration ≥ 2 mg/l, β -lactamase positive (n=151)	122	10	7	4	2	1		5
zone < 20 mm, minimum inhibitory concentration ≥ 4 mg/l, β -lactamase negative (n=38)	28					2	3	5

TABLE V—Prevalence of resistance for type b and non-capsulate strains

	No (%) type b	No (%) non-capsulated
Ampicillin:		
β -lactamase positive	12 (18)	136 (6)
β -lactamase negative	6 (9)	29 (1)
Tetracycline	3 (5)	62 (3)
Chloramphenicol	2 (3)	40 (2)
Trimethoprim	3 (5)	98 (4)
Sulphamethoxazole	2 (3)	82 (4)

As in previous surveys, there was an increased prevalence of β -lactamase production in type b strains (14% in 1981). The current survey also showed an increased resistance to ampicillin without β -lactamase production in type b strains ($p < 0.001$). Two type b strains were resistant to chloramphenicol; no such isolates were found in previous surveys. These two strains were also resistant to tetracycline and trimethoprim, and one produced β -lactamase, but they were not isolates from blood or cerebrospinal fluid.

BIOTYPE AND SITE OF ISOLATION

The distribution of strains in the seven biotype groups, the pattern of association with the site of isolation, and the strong correlation of biotype I with capsulation agreed well with other studies.^{2,5,11} Twenty four isolates from blood or cerebrospinal fluid were received, of which 16 were both biotype I and capsule type b, four were biotype I but non-typable, and four were of other biotypes and non-typable. Six (25%) of these 24 strains produced β -lactamase. The scatter of resistant strains among the biotypes was unremarkable except that the prevalence of β -lactamase production was higher in biotypes IV (16.5%) and V (14%).

Discussion

The overall prevalence of β -lactamase production by *H influenzae* in the United Kingdom is still low (6.2%) compared with many countries (France 11%, Spain $> 50\%$ in type b strains in some regions, United States $> 30\%$ in some regions). Type b strains have shown an increased prevalence of β -lactamase production in all three surveys—a phenomenon noted in many other national studies. The prevalence of β -lactamase production has not changed appreciably between 1981 and 1986, but there has been a significant increase in the prevalence of β -lactamase negative strains, with minimum inhibitory concentrations ≥ 4 mg/l increasing from 0.45% of isolates in 1981 to 1.6% in 1986 ($p < 0.001$). In addition, the prevalence of β -lactamase negative strains with reduced zone diameters and minimum inhibitory concentrations of 1 mg/l or 2 mg/l has increased from 1.6% in 1981 to 2.5% in 1986.

The prevalence of strains resistant to chloramphenicol and tetracycline has not increased significantly, but the distribution of such strains is interesting. Resistance to chloramphenicol was

highest among isolates from Bristol and Liverpool (both 3.8%) and was accompanied by an increased prevalence of resistance to tetracycline (6.3% and 7.7%, respectively). Liverpool was also remarkable in that the prevalence of resistance to all five antibiotics there was greater than the national average (ampicillin 9.2%, trimethoprim 6.9%, and sulphamethoxazole 5.4%). Resistance to trimethoprim has increased significantly (1.4% in 1981 to 4.2% in 1986; $p < 0.001$). The vogue for using trimethoprim alone during this period may have contributed to this.

The methods used for testing susceptibility have produced several interesting results, including the two β -lactamase positive strains and the 10 strains producing chloramphenicol acetyltransferase, which would have been missed by testing only with discs with a < 20 mm zone demarcation line. A further analysis of laboratory methods applied to *H influenzae* in the United Kingdom will be described elsewhere.

Isolates of *H influenzae* in the United Kingdom are still rather susceptible to the commonly used antibacterial agents compared with those in other countries. One quarter of the isolates collected from blood and cerebrospinal fluid in this survey produced β -lactamase, but at present chloramphenicol still seems to be suitable as initial treatment for invasive disease caused by *H influenzae*. The increasing prevalence of non- β -lactamase producers resistant to ampicillin may pose problems for treatment. The mechanism of resistance has not been fully elucidated, and work published so far suggests that changes in penicillin binding proteins or outer membrane proteins, or both, may be responsible,^{12,14} so that varying degrees of cross resistance to other β -lactams may occur. Strains collected during this survey have been tested against some of the more recent β -lactam antibiotics, and the data accumulated will be published later.

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SHORT REPORTS

The staphylococcal scalded skin syndrome in two elderly immunocompromised patients

The staphylococcal scalded skin syndrome, mainly seen in neonates and young children, presents with the rapid development of large, extremely superficial blisters in the epidermis, which rapidly rupture, leaving raw, denuded areas.¹ It is caused by staphylococci, usually of group II, which produce an exotoxin (exfoliatin), which is responsible for the epidermal split.² Outbreaks of staphylococcal scalded skin syndrome have been reported from neonatal nurseries³ and may be traced to a carrier of staphylococci in the staff. Only 18 cases have been recorded in adults, most in association with renal impairment or immunosuppression.⁴ We describe two cases in adults in "at risk" categories who were nursed in the same ward.

Case reports

Case 1—A 67 year old woman with polymyalgia rheumatica was admitted for investigation of right hip pain. She had been receiving prednisolone in doses of up to 40 mg/day for about three months and indomethacin 25 mg three times a day. An eroded area had been seen on her left thigh a few days before admission. Over the next five days extensive blisters and erosions developed on her buttocks and thighs. Skin biopsy showed a high level intraepidermal blister. Direct and indirect immunofluorescence tests for pemphigus antibodies yielded negative results. *Staphylococcus* group II type 3A/3C was cultured from the eroded areas. Serum creatinine concentration was normal. She was treated with intravenous flucloxacillin and topical mupirocin, and healing occurred within a few days.

Case 2—An 81 year old woman with non-Hodgkin's lymphoma shared a four bedded ward with the patient in case 1 for two weeks and two weeks later was readmitted for cytotoxic chemotherapy. After the first day of chemotherapy an eroded area was noted on her left arm. She rapidly developed extensive erosions and blisters (figure). Skin biopsy showed a high level intraepidermal blister. Swabs from her nose and cutaneous lesions grew *staphylococcus* group II type 3A/3C, and the same organism was also found in blood, sputum, and urine cultures. Serum creatinine concentration was normal and creatinine clearance 47 ml/minute. She was treated with intravenous flucloxacillin and topical mupirocin, and healing occurred rapidly.

Comment

It is not known why most patients with the staphylococcal scalded skin syndrome are young. Of 18 adult patients reported on, 14 were regarded as immunosuppressed as a result of cytotoxic or corticosteroid treatment, chronic illness, diabetes mellitus, or alcoholism. Of the 11 patients whose renal function was known, eight showed renal impairment. In the mouse model developed by Melish and Glasgow² adult mice do not develop the staphylococcal scalded skin syndrome unless they have undergone nephrectomy or been treated with corticosteroids. One of our patients had received oral prednisolone for 10 weeks, and the other had received cytotoxic chemotherapy immediately before her lesions developed.

These two cases occurring in one ward show the importance of early recognition of the syndrome and barrier nursing. After the identification of

Low power (top) and high power (bottom) views of lesions in case 2, showing typical rolled back appearance at edge of lesion (arrowed).

the second case all members of the nursing, medical, and paramedical staff and all other patients were swabbed, but no carrier was found. We therefore assume that our second patient contracted the infection from the first.

The investigation of elderly patients with a blistering disorder should include a skin biopsy with frozen section to identify rapidly the site of the blister,⁵ direct and indirect immunofluorescence tests on skin and blood to identify autoantibodies of the type diagnostic of either bullous pemphigoid or pemphigus vulgaris, and full bacteriological examination, with phage typing of the staphylococci if necessary, to exclude the possibility of the staphylococcal scalded skin syndrome. As the use of immunosuppressive and cytotoxic agents increases and the proportion of elderly in the population becomes larger the staphylococcal scalded skin syndrome may occur more commonly in adults.