J. Hyg., Camb. (1971), **69**, 453
Printed in Great Britain

Control at hospital level of infections by methicillin-resistant staphylococci in children

By M. F. MICHEL and CATHARINA C. PRIEM

Department of Bacteriology, Sophia Children's Hospital and Neonatal Unit, Academical Hospital, Medical Faculty Rotterdam, 160 *Gordelweg, Rotterdam* 4, *The Netherlands*

(*Received* 10 *March* 1971)

SUMMARY

Rapid spread of methicillin-resistant staphylococci (MeRS) in a children's hospital is described. Within 4 months of the first isolation MeRS had been isolated from infections in all clinical units. MeRS were also regularly isolated at the out-patient department. Protective isolation of one of the clinical units had no effect on the infection rate by MeRS. The use of antiseptics (Hexachlorophene and chlorhexidine) and gentamicin nose cream in children and staff members in three out of five clinical units resulted in a significant reduction of the prevalence of nose colonization by MeRS in children. In staff members a non-significant reduction of the prevalence of colonization and a significant reduction of the acquisition of MeRS was found. After a few months the infection rate decreased to zero in the units where the measures were introduced. It remained unchanged in the other units. Phage typing of two sets of strains collected at an interval of 6 months showed that the infections were mainly caused by two endemic strains of MeRS. The majority of the infections caused by MeRS was of minor importance. In 16 % of the infections a strain was isolated repeatedly and for more than 1 week. After the introduction of antiseptics a relative increase of infections by Gram-negative bacteria was observed. The significance of this phenomenon is discussed.

INTRODUCTION

Naturally occurring strains of methicillin-resistant staphylococci (MeRS) were initially described by Jevons (1961), Knox & Smith (1961) and Barber (1961). Evidence has been presented that they differ in several respects from other strains of *Staphylococcus aureus* (Knox, 1961; Sutherland & Rolinson, 1964; Barber, 1964; Annear, 1968; Sabbath, Leaf, Gerstein & Finland, 1970).

Strains of MeRS invariably show resistance to other penicillins and with few exceptions to streptomycin and tetracyclin. Resistance to methicillin is not due to an increased destruction of the antibiotic by a modified penicillinase but to intrinsic insensitivity for all penicillins. Penicillinase-negative variants of MeRS are therefore also resistant to methicillin (Dyke, Jevons & Parker, 1966).

The frequency of resistance to methicillin among staphylococcal strains investigated at the Staphylococcal Reference Laboratory in Colindale was initially

very low. It increased slowly in the period 1960–3 to 1 % and remained stationary for several years thereafter (Parker & Hewitt, 1970). During this time higher frequencies were, however, observed locally in England and abroad (Chabbert & Baudens, 1962; Cetin & Ang, 1962; Courtieu *et al.* 1964; Chabbert, Baudens, Acar & Gerbaud, 1965; Colley, NcNicol & Bracken, 1965; Chabbert & Pillet, 1967). After 1967 the frequency of methicillin-resistant strains observed in Colindale rose sharply to 5 %.

There are numerous publications on the epidemic spread and infections by MeRS in different countries. They were surveyed by Barrett, McGehee & Finland (1968). Additional reports have been published by Rountree & Beard (1968), Benner & Kayser (1968), Jessen *et al.* (1969), Mouton & van Boven (1969) and O'Toole, Drew, Dahlgren & Beaty (1970).

The present study deals with the epidemic spread of MeRS after their first isolation in a hospital for children. Emphasis is placed on the effect of several measures to restrict the colonization and infection rates on a hospital level.

MATERIAL AND METHODS

Population studied

Observations were made in a 180-bed hospital for children, in both the wards and the out-patient department. Patients are nursed in five separate units: a neonatal unit (24 beds), an infant unit (24 beds), a quarantine unit (24 beds), a medical unit (48 beds) and a surgical paediatric unit (60 beds).

Nasal swabs were taken fortnightly and later monthly from patients and staff members as indicated. Colonization rates are reported on a monthly basis.

Bacteriological methods

Conventional bacteriological methods were used for the isolation of coagulase-positive staphylococci and other bacterial species.

Sensitivities to the antibiotics mentioned in the next section were determined on Diagnostic Sensitivity Test (DST) agar (Oxoid) using paper disks (Oxoid). Readings of the tests were normally made after 24 hr. incubation at 37° C. At this time methicillin-resistant strains usually showed a narrowing of the critical zone of inhibition with or without visible growth of resistant colonies within this zone. Additional methicillin-resistant strains were detected by reincubation of the plates for 24 hr at 37° C.

Phage-typing was carried out at 1 RTD and 1000 RTD by Dr R. Scholtens, Rijksinstituut voor de Volksgezondheid, Bilthoven.

RESULTS

Primary isolation and spread of MeRS

MeRS were observed for the first time in January 1969. These and subsequently isolated strains were as a rule resistant to penicillin, streptomycin, tetracylin, erythromycin, kanamycin, methicillin and cephaloridin but sensitive to chloram-

phenicol, lincomysin, gentamicin and fucidin. The number of isolations from infections rose from seven in the second month to ten in the third month. The strains were isolated from patients of the infant and surgical units. From the fourth month onwards new infections were seen on all units, the infection rate varying between 7 and 17 per month.

Both the rapid increase and the spread of infections over all units strongly suggested the existence of an epidemic of hospital infections due to one or more strains of MeRS. Therefore from April 1969 efforts were made to reduce the number of these infections by MeRS. Measures to prevent recolonization of the infant unit previously freed of MeRS were only partially successful and are not reported here.

Use of antiseptics

When after 1 year the number of infections caused by MeRS did not show any sign of spontaneous decline an attempt was made to reduce the colonization and acquisition rates of MeRS by means of skin antiseptics. It was hoped that by this measure a secondary reduction of the infection rate could be effected. Skin disinfection was not used throughout the whole hospital but on three units where most infections were observed, i.e. the infant, neonatal and surgical unit. Starting in March 1970 the following regulations were put into operation on these units. Children were washed daily with 3% hexachlorophene emulsion (pHisoHex). After rinsing with water the skin was treated with 1% chlorhexidine in water. Staff members on duty used hexachlorophene bar-soap for hand washing. Carriers of MeRS were treated once or several times during 1 week with 0·3% gentamicin nasal cream until three consecutive nasal swabs taken at weekly intervals were negative.

Prevalence and acquisition of MeRS in staff members

The influence of the measures on the prevalence and acquisition of MeRS in the nose of staff members is shown in Table 1. Both phenomena are compared during a period of 6 months preceding and following the introduction of the measures. It can be seen that the prevalence of MeRS decreased from 37 carriers in the first period to 23 in the second period. This decrease is statistically non-significant ($0{\cdot}1 < P < 0{\cdot}2$). The acquisition of MeRS on the other hand declined significantly from a total of 16 persons in the first period to 3 persons in the second period ($0{\cdot}005 < P < 0{\cdot}01$). These data indicate that the measures, although effective in preventing acquisition, were much less so in curing existing nasal colonization.

Prevalence of MeRS in patients

The prevalence of the nasal colonization in patients in each unit was compared in the same 6 months periods as above. It is shown in Table 2 that a significant reduction of the colonization occurred in the neonatal and surgical units ($P < 0{\cdot}0005$). For no obvious reason the reduction in the infant unit, although marked, was less and not significant ($0{\cdot}1 < P < 0{\cdot}2$).

Table 1. *Effect of the introduction of the use of antiseptics on the prevalence and acquisition of MeRS in the nose in staff members*

Period	n	Prevalence	n^{acq}	Acquisition
October 1969	80	7 (8·7%)	—	—
November 1969	133	7 (5·3%)	126	2 (1·5%)
December 1969	149	5 (3·4%)	144	1 (0·7%)
January 1970	145	4 (2·8%)	141	4 (2·8%)
February 1970	150	6 (4·0%)	144	5 (3·3%)
March 1970	127	8 (6·3%)	119	4 (3·2%)
Total	704	37 (5·3%)	674	16 (2·4%)
April 1970	136	6 (4·4%)	130	1 (0·7%)
May 1970	133	7 (5·3%)	126	0
June 1970	121	3 (2·5%)	118	0
August 1970	136	4 (2·9%)	132	0
September 1970	132	3 (2·3%)	129	2 (1·5%)
Total	658	23 (3·5%)	635	3 (0·5%)

The use of antiseptics was started in March 1970.

n, Number of nasal cultures; n^{acq}, number of nasal cultures diminished by the number of carriers.

Prevalence $\chi^2_{(1)} = 2{\cdot}10$ ($0{\cdot}10 < P < 0{\cdot}20$); acquisition $\chi^2_{(1)} = 6{\cdot}99$ ($0{\cdot}005 < P < 0{\cdot}01$).

Table 2. *Prevalence of MeRS in the nose in children*

Unit	Period	n	Prevalence	$\chi^2_{(1)}$
Neonatal	Before	173	48 (27·7%)	37·58
	After	148	3 (2%)	$P < 0{\cdot}0005$
Infant	Before	206	21 (10·1%)	1·77
	After	115	6 (5·25%)	$0{\cdot}10 < P < 0{\cdot}20$
Surgical	Before	427	68 (15·9%)	24·61
	After	314	13 (4·1%)	$P < 0{\cdot}005$

The prevalence is compared in each unit for a period of 6 months before and 6 months after the introduction of the use of antiseptics.

Infection rate

The number of new isolations of MeRS from infections on all clinical units and the out-patient department during a 12-month period (October 1969 to October 1970) is shown in Table 3. Isolations on the quarantine and medical units were evenly distributed over the whole of the observation period. Introduction of antiseptics on the infant, neonatal and surgical units in March 1970 rapidly reduced the infection rate on these units to zero ($P < 0{\cdot}0005$). Although the number of positive cultures originating from the out-patient department seems remarkably high it should be remembered that they were frequently obtained in children with previous hospital contacts.

Source and types

All strains newly isolated 1 month before (53 strains) and 3 months after (10 strains) the introduction of the restrictive measures in March 1970 were phage-typed. The origin and the types of these strains are shown in Table 4.

https://doi.org/10.1017/S0022172400021707 Published online by Cambridge University Press

Arranged in decreasing order of frequency the source of the strains in both periods was the following: nasal swabs, pus and sputum. One additional strain was isolated from blood and from urine in the first period.

Table 3. *Monthly isolations of MeRS from infections in clinical units and the out-patient department*

	Unit						
	Neonatal	Infant	Surgical	Quarantine	Medical	O.D.	Total
1969							
Oct.	0	1	6	0	2	0	9
Nov.	0	1	1	1	0	0	7
Dec.	5	0	2	2	1	1	11
1970							
Jan.	1	1	4	2	0	3	12
Feb.	1	2	4	3	1	5	17
Mar.	0	1	4	2	0	0	8
Apr.	0	0	0	1	0	0	3
May	0	1	0	2	0	0	4
June	0	1	0	2	0	1	5
July	1	0	0	2	2	1	6
Aug.	0	0	0	1	1	0	2
Sept.	0	0	0	2	1	0	5

In March 1970 the use of antiseptics was introduced in three out of five clinical units, i.e. the neonatal, infant and surgical unit.

O.D., Outpatients' Department.

$\chi^2_{(1)} = 12{\cdot}4$ ($P < 0{\cdot}0005$).

Table 4. *Type and source of MeRS collected during February and June* 1970

	Strains						
		Source					
Period	No.	Nose	Sputum	Pus	Blood	Urine	Phage type
February 1970	37	27	2	7	1	—	85/+
	12	8	2	2	—	—	6/47/77/84/85/+
	2	1	—	1	—	—	6/7/47/53/54/88/83A/85/+
	1	—	—	—	—	1	53/88/85
	1	1	—	—	—	—	29/52/+
June 1970	5	3	1	1	—	—	85/+
	3	—	2	1	—	—	6/42/77/84/85/+
	1	—	—	—	—	—	6/7/47/53/54/88/83A/85/+
	1	—	—	1	—	—	7/47/54/77/+

Two major (85/+, 6/47/77/84/85/+) and one minor (6/7/47/53/54/88/83A/85/+) type prevailed in both periods. Strains with type 53/88/85, 29/52/+, 7/47/54/77/+ were observed only once. The frequent isolation of two sets of multiple-resistant strains of the same type both from nasal swabs and from infections over a long period of time substantiates the endemic character of these strains.

https://doi.org/10.1017/S0022172400021707 Published online by Cambridge University Press

Infections by Gram-positive and Gram-negative bacteria

The favourable effect exerted by the use of hexachlorophene on the incidence of infections in newborn infants has been well documented (Williams, Blowers, Garrod & Shooter, 1966; Baber *et al.* 1967). Recently several authors drew attention to the fact that the use of this antiseptic might involve colonization followed by a rise of infections by Gram-negative bacteria (Forfar, Gould & Maccabe, 1968; Light, Sutherland, Cockran & Sutorius, 1968; Conn, 1969). Chlorohexidine was added to the restrictive measures described here in an attempt to prevent

Table 5. *Isolations of Gram-positive and Gram-negative bacterial species from pus, blood and cerebrospinal fluid*

	Units with skin disinfection			Units without skin disinfection		
	Jan. 1970	Aug. 1970	$\chi^2_{(1)}$ P	Jan. 1970	Aug. 1970	$\chi^2_{(1)}$ P
Total no. of cultures	53	29	—	40	28	—
No. of cultures from which Gram-positive bacteria were isolated	33	8	7·68 $0{\cdot}005 < P < 0{\cdot}01$	20	5	6·00 $0{\cdot}01 < P < 0{\cdot}02$
No. of cultures from which Gram-negative bacteria were isolated	9	13	6·05 $0{\cdot}01 < P < 0{\cdot}025$	3	7	2·74 $0{\cdot}05 < P < 0{\cdot}10$

such an effect of hexachlorophene. Information about the frequency of new isolations of pathogenic Gram-positive and Gram-negative bacteria from pus, blood and cerebrospinal fluid during fixed periods before and after March 1970 in different parts of the hospital is given in Table 5. A significant decrease ($0{\cdot}005 < P < 0{\cdot}01$) of Gram-positive and increase of Gram-negative bacteria ($0{\cdot}01 < P < 0{\cdot}025$) was observed in the units where the measures were put into effect (Table 5). The same trend was observed in the other units (Table 5), although in this case the increase of Gram-negative bacteria did not attain the level of significance ($0{\cdot}05 < P < 0{\cdot}10$).

DISCUSSION

It is assumed that the close contact between children and between staff and children contributed greatly to the rapid spread followed by endemic infections by several strains of MeRS. This assumption is supported by the independent observation that similar infections occurring simultaneously in another hospital in adults hardly gave rise to colonization and rarely to cross-infections.

There are several reports (Stewart & Holt, 1963; Benner & Kayser, 1968) indicating that infections by MeRS are often seen in patients suffering from debilitating diseases. This might very well imply that the virulence of MeRS is reduced.

In our experience most infections caused by MeRS were of minor importance. Multiple isolations, mainly from sputum or pus during 1 week or longer, were observed in 12 out of 75 children in hospital in the last 12 months. One child with debilitating disease died from septicaemia. In this case *Streptococcus faecalis* and indifferent streptococci as well as MeRS were isolated from the blood.

Reversed isolation of a complete unit was only temporarily effective in the control of infections by MeRS. The high degree of contamination of the environment must undoubtedly be held responsible for this result (Shooter, 1965).

It was expected that by the use of antiseptics and gentamicin nose-cream a primary reduction of the colonization rate in staff members and children would be followed by a secondary reduction in the infection rate (Gillespie, Simpson & Tozer, 1958). Although both objectives were attained the following epidemiological details are worth mentioning. The reduction of the colonization was rapid and pronounced in children but much less so in staff members. This difference may be more apparent than real when one keeps in mind that the data of the children were favourably biased by the high turnover rate of patients. The reduction of the infection rate was further strictly confined to the units where the measures were applied. The expectation that the reduction of the colonization and infection rate would become manifest after a certain time in other units was not fulfilled.

It was established in this study that infections by endemic strains of MeRS can be successfully controlled on a hospital level. Although weakened by a similar development in other clinical units evidence was obtained that the introduction of antiseptics was followed by a relative increase of infections caused by Gram-negative bacteria. The incompatible consequences of the measures creates a dilemma which may be difficult to solve. In a given situation one may have to decide whether the suppression of staphylococcal infections justifies the risk of an increase of infections by Gram-negative bacteria. Further work on the relative importance of both kinds of infections for patients is needed before a final judgement can be expressed on the course which should be taken in this matter.

We want to thank the members of the infection committee for the constructive interest and the members of the medical and nursing staff for their help in this project. We are indebted to Professor H. A. Valkenburg, Department of Epidemiology, Medical Faculty Rotterdam, for the statistical analysis of the results.

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