Clinical recognition of meningococcal disease in children and adolescents

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Summary

Background Meningococcal disease is a rapidly progressive childhood infection of global importance. To our knowledge, no systematic quantitative research exists into the occurrence of symptoms before admission to hospital.

Methods Data were obtained from questionnaires answered by parents and from primary-care records for the course of illness before admission to hospital in 448 children (103 fatal, 345 non-fatal), aged 16 years or younger, with meningococcal disease. In 373 cases, diagnosis was confirmed with microbiological techniques. The rest of the children were included because they had a purpuric rash, and either meningitis or evidence of septicaemic shock. Results were standardised to UK case-fatality rates.

Findings The time-window for clinical diagnosis was narrow. Most children had only non-specific symptoms in the first 4–6 h, but were close to death by 24 h. Only 165 (51%) children were sent to hospital after the first consultation. The classic features of haemorrhagic rash, meningism, and impaired consciousness developed late (median onset 13–22 h). By contrast, 72% of children had early symptoms of sepsis (leg pains, cold hands and feet, abnormal skin colour) that first developed at a median time of 8 h, much earlier than the median time to hospital admission of 19 h.

Interpretation Classic clinical features of meningococcal disease appear late in the illness. Recognising early symptoms of sepsis could increase the proportion of children identified by primary-care clinicians and shorten the time to hospital admission. The framework within which meningococcal disease is diagnosed should be changed to emphasise identification of these early symptoms by parents and clinicians.

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Introduction

Meningococcal disease is a global problem. In epidemics in developing countries, the incidence can be higher than 500 per 100 000.[1] In endemic periods in developed countries, it is the leading infectious cause of death in children, with an incidence of at least four per 100 000, and killing 10% of those with the disease.[2–6] Despite the disease's prevalence, several researchers have reported that many children who are admitted to hospital with meningococcal disease had been initially misdiagnosed by a doctor before admission.[7–9] Since infection can progress from initial symptoms to death within hours, individuals must be diagnosed as early as possible.

One reason why clinicians working in the community may find it difficult to identify meningococcal disease is that they see so few cases in their lifetime—many children will be first examined by a clinician who has never before seen a case outside hospital. Identification of the disease will therefore depend on clinicians' experience in hospital and on textbook descriptions of classic features such as haemorrhagic rash, meningism, and impaired consciousness that occur late in the illness.[10–16]

As far we are aware, there has been no systematic assessment of the sequence and development of early symptoms of meningococcal disease before admission to hospital. We sought to determine the frequency and time of onset of clinical features of the disease to enable clinicians to make an early diagnosis before the individual is admitted to hospital. Parents also need to be aware of the importance of early symptoms to avoid delay in seeking medical care.

Methods

Participants

Participants came from a study originally designed to determine the clinical and health service factors associated with fatal and non-fatal outcomes from meningococcal disease in hospitals.[17] Between Dec 1, 1997, and Feb 28, 1999, we identified children aged 0–16 years who died from meningococcal disease. We did this by using the Public Health Laboratory Service network of regional epidemiologists and consultants in communicable disease control in England, Wales, and Northern Ireland.

In addition to cases confirmed through microbiological techniques, we included as probable cases children with a purpuric rash and either meningitis or evidence of septicaemic shock, in whom alternative diagnoses had been excluded.[18] 190 fatal cases were identified, and a sample of 755 non-fatal cases was drawn after matching for age group (four strata) and region.[19]

An expert panel of consultants in paediatric emergency medicine, infectious disease, and intensive care reviewed, without knowing the final outcome, the clinical records of all children to determine the clinical presentation (meningitis, septicaemia, or both), and any hospital complications (eg, cardiovascular failure). A case

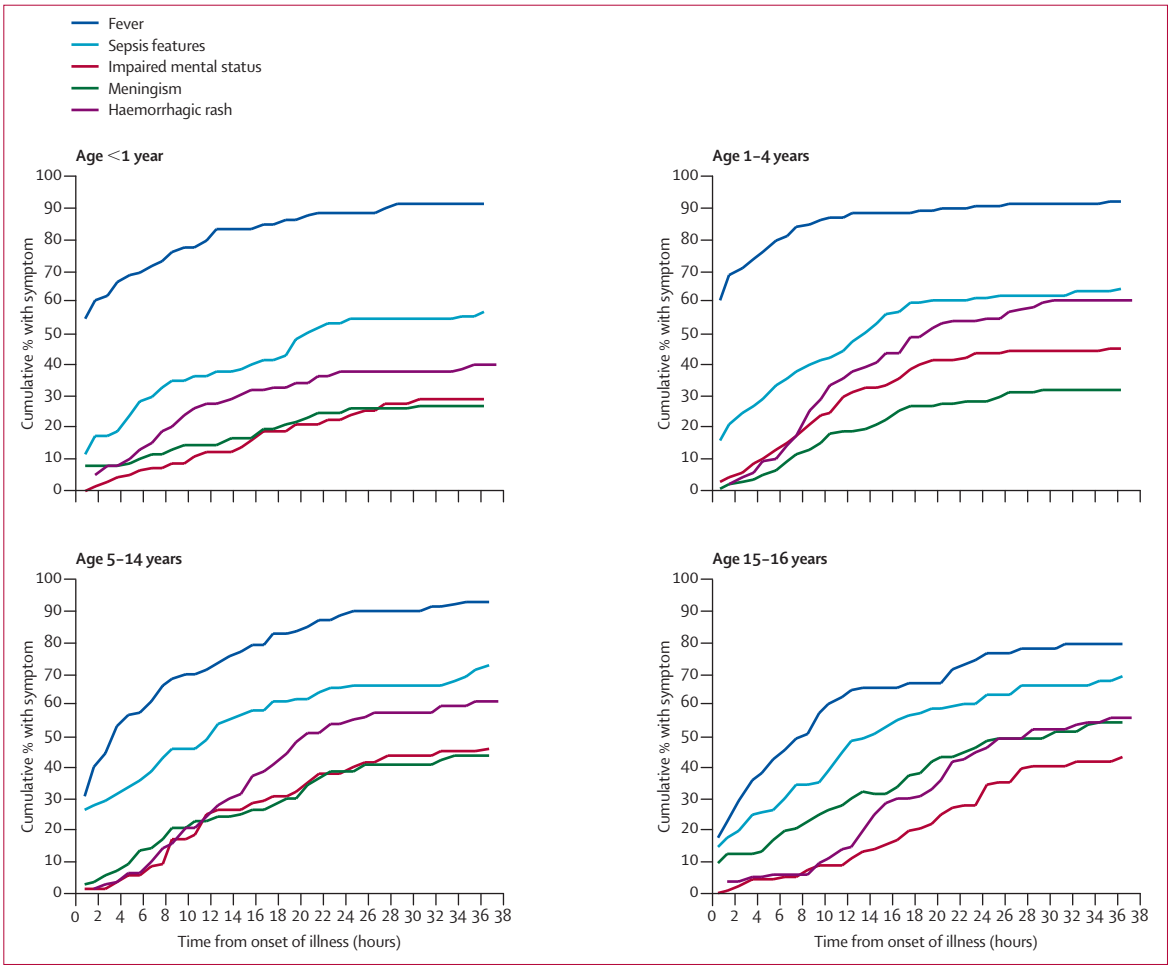

Figure: **Development of clinical features over time**
Sepsis features=abnormal skin colour, cold hands and feet, or leg pain; impaired mental state=unconsciousness, confusion or delirium, or seizure; meningism=neck stiffness or photophobia.

was categorised as meningitis if the child had neck stiffness, photophobia, or other CNS signs, and as septicaemia if the child had cardiovascular shock or multiorgan failure but no signs of meningitis. Some children had features of both meningitis and septicaemia.

After review, we excluded two fatal cases and 106 non-fatal cases because their diagnoses did not meet the criteria for inclusion, and excluded a further 74 fatal cases and 219 non-fatal cases because we did not get parental consent. Of the remaining 114 fatal cases and 430 non-fatal cases, completed questionnaires were returned for 103 (90%) fatal cases and 345 (80%) non-fatal cases. Of the 448 children in the study, 373 were confirmed through microbiological techniques (99 died) and 75 were probable cases (four died).

This study has been approved by the South Thames Multi-Research Ethics Committee and by all Local Research Ethics Committees in England, Wales, and Northern Ireland.

Data collection

Parents completed a questionnaire by post (313, 69·9%) or during a personal interview (135, 30·1%) with one of the investigators (NN) after a mean of 144 days (SD 125) for fatal cases and 139 days (331) for non-fatal cases (independent *t* test for difference, p=0·72) after either admission to hospital or death before admission to hospital. Parents were asked the time of day that the initial symptoms of their child's illness began and, using a checklist, to record the presence and time of appearance of pre-defined clinical features.

To identify the time of onset as precisely as possible, we also asked parents about any episodes of illness in the previous 2 weeks. We used telephone interviews with patients' general practitioners (GPs) in 173 cases, copies of GP clinical records in 87 cases, GP referral letters in 72 cases, and complaints made to health authorities regarding alleged malpractice in three cases to verify timings where possible. When there was a discrepancy, we used the timing from the medical record.

Analysis of symptom frequency

The method of recruitment determined the proportion of fatal cases. To better represent the frequency of clinical features that would be found in a typical sample of children with meningococcal disease, we calculated the weighted mean frequency of each clinical feature in each age group. We used published age-specific case fatality rates for meningococcal disease[20] to weight the frequency of each clinical feature based on the following formula:

> Weighted mean frequency=(mean frequency in fatal cases×age-specific case fatality rate)+(mean frequency in non-fatal cases×1–age-specific case fatality rate).

Non-parametric bootstrapping was done to calculate 95% CIs around the mean frequencies with the statistical computing program R, version 2.0.1. This calculation involved creating 1000 random samples from the data, each containing 100 children with the correct mix of fatal and non-fatal cases.

Analysis of time course

We calculated the number of hours from the onset of illness to GP consultation, and to hospital admission (or death before admission) for all children. The exact time of death was not available for four of the 13 children who died before admission to hospital, and they were excluded from the time-course analyses. The onset of illness was taken as the time when the parents noticed the first symptom. The time at which each subsequent symptom developed was then calculated from the time of illness onset, rounded to the nearest hour. The median time of onset and interquartile range for each symptom in a typical cohort of UK children with meningococcal disease was then adjusted by the same mechanism as for symptom frequency.

Role of the funding source

The Meningitis Research Foundation funded the initial design of the study, and initial data collection and analysis. The UK Medical Research Council funded the analysis and interpretation of the primary-care data. Neither funding body influenced study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 448 children with meningococcal disease, 103 died. 296 (66%) children were classified by the expert panel as having predominant septicaemia, 99 (22%) with meningitis, and 53 (12%) with features of both. In the 307 (68%) children in whom meningococcal serogrouping data were available, those in serogroup B accounted for 152 (50%) cases, serogroup C for 146 (47%), and W135 and Y serogroups collectively for 9 (3%).

Children who died were more likely to have had septicaemia (84% *vs* 61%, $p<0·001$) and more likely to have serogroup C disease (47% *vs* 28%, $p<0·001$) than those who did not die. A total of 324 children were seen by a GP and 165 (51%) were sent to hospital from the first consultation.

In most children, the disease progressed very rapidly. The median time between onset and admission to hospital was 22 h in the oldest children (aged 15–16 years) and even less in younger children (13 h in those younger than 1 year, 14 h in those aged 1–4 years, 20 h in those aged 5–14 years). 113 (25%) children had symptoms in the two weeks before the onset of meningococcal disease, most of which (in 107) were suggestive of upper or lower respiratory tract infection. Only 32 (7%) children had seen a doctor in the week before the onset of disease.

Table 1 shows the median time that clinical features developed after onset of illness, and median time to first medical consultation. The features that appeared earliest were common to many self-limiting viral illnesses seen in primary care. Fever was the first symptom to be noticed in children younger than 5 years; headache the first to be seen in those older than 5 years. 94% of children developed fever at some point and most young children were irritable. Loss of appetite, nausea, and vomiting were early features for all age groups, with many children also having upper respiratory symptoms (sore throat and coryza). These features, which are not specific to meningococcal disease, lasted for about 4 h in younger children but as long as 8 h in adolescents.

In all age groups, the first specific clinical features were signs of sepsis—leg pain, abnormal skin colour, cold hands and feet, and, in older children, thirst. Parents of younger children also reported drowsiness and difficulty in breathing (usually described as rapid or laboured breathing) and occasionally diarrhoea, at this stage. Most sepsis symptoms occurred before the first medical contact.

The first classic symptom of meningococcal disease to emerge was rash, although at onset this was sometimes non-specific and only developed into a petechial and then a large haemorrhagic rash over several hours. The close correspondence of the median time of onset of rash and of first medical contact is unlikely to be coincidental—the importance of non-blanching rash is the central message of most public education campaigns about meningitis.

The median time of onset of specific meningitis symptoms (neck stiffness, photophobia, bulging fontanelle) was later, around 12–15 h from onset of illness. The last signs (such as unconsciousness, delirium, or seizures) were seen at a median of 15 h in infants (under 1 year of age), and about 24 h in older children.

Table 2 shows the frequency of specific clinical features and how this varied with age. The most common early features were cold hands and feet

	Age <1 year		Age 1–4 years		Age 5–14 years		Age 15–16 years	
	Symptom	Median (IQR)*	Symptom	Median (IQR)	Symptom	Median (IQR)	Symptom	Median (IQR)
Hours from onset								
0–4	Fever	0 (0–6)	Fever	0 (0–3)	Headache	0 (0–12)	Headache	0 (0–2)
	Irritable	0 (0–7)	Irritability	2 (0–10)	Nausea/vomiting	2 (0–12)	Sore throat/coryza	0 (0–9)
	Poor feeding	1 (0–9)	Nausea/vomiting	3 (0–11)			Thirst	4 (1–39)
	Nausea/vomiting	1 (0–11)	Decreased appetite	3 (0–13)	Fever	3 (0–13)		
	Coryza	2 (0–13)	Drowsy	4 (0–11)	Abnormal skin colour	5 (0–29)		
	Drowsy	4 (0–14)	Leg pain	6 (0–13)	Decreased appetite	6 (1–17)		
5–8	Diarrhoea	5 (0–9)	Headache	6 (1–17)	Thirst	6 (2–16)	General aches	6 (0–20)
	Abnormal skin colour	5 (0–18)	Sore throat/coryza	7 (1–19)	Sore throat/coryza	7 (0–16)	Fever	6 (1–16)
	Breathing difficulty	5 (0–19)	Breathing difficulty	7 (1–17)	Leg pain	7 (0–15)		
	Leg pain	7 (0–15)			General aches	7 (1–18)		
	Floppy muscle tone	8† (1–19)						
	Rash	8 (4–18)						
9–12	Cold hands and feet	9 (1–20)	Abnormal skin colour	9 (3–18)	Drowsy	9 (1–21)	Decreased appetite	9 (3–21)
	General aches	9 (4–22)	General aches	9 (4–18)	Irritable	12 (2–22)	Nausea/vomiting	10 (3–19)
			Rash	9 (6–18)	Confusion/delirium	12 (8–24)	Leg pain	12 (5–23)
			Seizure	9 (1–18)			Miserable/irritability	12 (3–25)
			Diarrhoea	10† (6–14)				
			Cold hands and feet	11 (2–17)				
			Confusion/delirium	11 (5–17)				
			Neck stiffness	11 (8–17)				
			Photophobia	12 (6–27)				
13–16	Photophobia	13 (5–17)	Floppy muscle tone	13 (8–20)	Cold hands and feet	13 (7–26)	Drowsy	14 (6–27)
	Unconsciousness	15 (6–17)			Rash	14 (8–21)	Breathing difficulty	15 (13–17)
	Bulging fontanelle	15 (3–20)			Neck stiffness	15† (6–25)	Diarrhoea	16 (8–26)
	Neck stiffness	15 (2–27)					Neck stiffness	16 (6–30)
	Seizure	16 (14–31)					Cold hands and feet	16 (6–32)
17–20	Thirst	17 (7–27)			Photophobia	17 (5–39)	Photophobia	17 (5–29)
							Abnormal skin colour	18 (4–29)
							Rash	19† (11–26)
21–24			Unconsciousness	23 (17–42)	Diarrhoea	22 (20–25)	Confusion/delirium	23 (13–30)
					Seizure	24 (9–79)	Unconsciousness	24 (19–41)
>24					Breathing difficulty	34 (10–57)	Seizure	26 (25–27)
					Unconsciousness	34 (11–52)		

IQR=interquartile range. *Median and IQRs rounded to nearest hour. †Median times of first consultation with GP, according to age group (age <1 year=8 h; 1–4 years=10 h; 5–14 years=15 h; 15–16 years=19 h).

Table 1: **Time of onset of clinical features of meningococcal disease before hospital admission**

(35–47%), leg pain (31%–63%, excluding infants) and abnormal colour (17–21%) described as pallor or mottling. Thirst, diarrhoea, and breathing difficulty presumably also indicate sepsis but were less common.

The most common classic feature was haemorrhagic rash, but even this was seen in only 42–70% of cases. Meningism was more common in older children, being present in about half the children aged over 5 years (46–53%) with about half these children also showing photophobia. The most common late feature was confusion or delirium, also occurring in almost half the children (43–49%). Between 7% and 15% were unconscious by the time they were admitted to hospital.

The figure shows by age group the proportion of children who developed specific groups of clinical features over the 36 h after the onset of illness. It shows that few children developed any new symptoms after 24 h after onset. The order of symptom progression in all age groups was fever followed by sepsis symptoms, and then the classic symptoms of haemorrhagic rash, impaired consciousness, and meningism. The progression of illness was slower in the oldest children (aged 15–16 years) who were the only age group in which meningism was an earlier and more frequent feature than haemorrhagic rash and impaired consciousness.

Table 3 integrates the time course and frequency data for all age groups. Features that were present in more than half the children before admission to hospital were non-specific (ie, common in self-limiting viral illness) except for haemorrhagic rash, which emerged late (median 13 h).

However, three features of sepsis occurred earlier in the illness and were not uncommon—leg pain (median 7 h, 37%), abnormal skin colour (10 h, 18·6%), and cold hands and feet (12 h, 43·2%). Thirst (8 h), diarrhoea (9 h), and breathing difficulties (11 h) were also early symptoms, but they were seen in fewer children (7–11%).

The sequence of symptom development remained the same whether or not children died of the disease (table 4). The median time of onset of the classic meningococcal features of haemorrhagic rash, meningism, and impaired consciousness was 13–22 h. By contrast, the median time of onset of the early, non-specific symptoms was 7–12 h.

The parents of three-quarters (76·1%) of children had noticed one or more of the early symptoms before hospital admission. Fewer than 10% of children presented with the classic signs of meningism or impaired consciousness without parents having previously recognised a haemorrhagic rash or early signs of sepsis. Taking into account only the three sepsis symptoms of leg pain, abnormal skin colour, and cold hands and feet, 72% of children had one or more that was first noticed at a median time of 8 h, which was 11 h sooner than the median time of 19 h from onset to hospital admission.

Discussion

Our results provide the first description—as far as we are aware—of the time course of the clinical features of meningococcal disease in children and adolescents before admission to hospital. We have identified three important clinical features—leg pain, cold hands and feet, and abnormal skin colour—that are signs of early meningococcal disease in children and adolescents. These features generally occur within the first 12 h of the onset of illness, and are present at the first consultation with a primary-care physician.

The classic symptoms of rash, meningism, and impaired consciousness generally occur later in the pre-hospital illness. We believe that primary-care clinicians are over-reliant on using these three symptoms to diagnose meningococcal disease in children, and that parents may be influenced by doctors or public health campaigns to seek medical advice only on the appearance of features such as a rapidly evolving rash. Moreover, clinicians and parents may be falsely reassured by the absence of these features.

Cold hands and feet, and abnormal skin colour are features of early sepsis that represent changes in the peripheral circulation. Leg pain is less well recognised, although pain in the limbs, with or without refusal to walk, has been reported in children with meningococcal disease and other causes of septicaemia.[21] The pathophysiology of this pain is not entirely clear since only two patients in our study had septic arthritis. These features could be a response to a range of inflammatory mediators released during the early septic process. Since rigors are often associated with meningococcal disease, intense muscle contraction or membrane damage due to the release of tumour necrosis factor (TNF) or other cytokines, or other pro-inflammatory mediators could be the cause of these features. The presence of these three features also suggests that vital signs (pulse, respiratory rate, and capillary return) might also be abnormal.

Our data also raise another important issue for primary-care doctors. Within the first 4–6 h of the onset of meningococcal disease, children have non-specific features such as fever, poor feeding or decreased appetite, nausea, vomiting, and irritability. This presentation does not mean that all parents of children with a coryza or sore throat should be warned that their child may have meningococcal disease. But it does mean that such disease can rarely be excluded by clinical examination in the first 4–6 h. Our data confirm that symptoms progress rapidly over a period of a few hours. It is therefore extremely important that parents who have received clinical reassurance early in the illness are easily able to re-consult the doctor if their child's condition worsens. If the clinician has concerns that are not serious

	<1 year	1–4 years	5–14 years	15–16 years
Early features				
Leg pain	5·1%	30·6%	62·4%	53·3%
Thirst	3·4%	6·4%	11·4%	12·6%
Diarrhoea	9·9%	7·8%	3·1%	5·5%
Abnormal skin colour	20·6%	16·8%	18·5%	19·0%
Breathing difficulty	16·2%	9·7%	7·1%	12·1%
Cold hands and feet	44·0%	46·7%	34·9%	44·4%
Classic features				
Haemorrhagic rash	42·3%	64·2%	69·8%	65·9%
Neck pain or stiffness	15·5%	28·1%	45·9%	52·9%
Photophobia	24·5%	24·1%	26·4%	35·5%
Bulging fontanelle	11·5%	n/a	n/a	n/a
Late features				
Confusion or delirium	n/a	42·8%	49·4%	47·6%
Seizure	8·9%	12·8%	7·8%	7·3%
Unconsciousness	7·0 %	9·1%	5·9%	15·1%

Percentages are standardised to UK case-fatality rates. Age-specific data on frequency of other symptoms are available from the investigators.

Table 2: **Age-specific frequency of clinical features of meningococcal disease before hospital admission**

	Percentage of children (95% CI)	Median hour of onset
Clinical features present in >50% of children		
Fever	93·9% (89–98)	1
Drowsiness	81·1% (74–88)	7
Nausea or vomiting	76·4% (67–84)	4
Irritability	66·6% (57–75)	4
Haemorrhagic rash	61·0% (51–70)	13
Poor appetite or feeding	59·9% (50–70)	5
Clinical features present in 20–50%		
General aches	48·5% (39–58)	7
Confusion or delirium*	45·1% (36–55)	16
Cold hands and feet	43·2% (33–53)	12
Headache*	40·5% (31–50)	0
Leg pain	36·7% (28–47)	7
Neck pain or stiffness	35·0% (26–44)	13
Photophobia	27·5% (19–36)	15
Sore throat or coryza	23·6% (15–32)	5
Clinical features present in <20%		
Abnormal skin colour	18·6% (11–27)	10
Floppy muscle tone†	18·3% (12–26)	13
Bulging fontanelle‡	11·5% (5-18)	15
Breathing difficulty	10·8% (5–18)	11
Seizure	9·8% (4–16)	17
Unconsciousness	9·5% (4–15)	22
Increased thirst	8·1% (3–14)	8
Diarrhoea	6·6% (2–12)	9

Percentages and median hours of onset are standardised to UK case-fatality rate. *Data only available for children aged >1 year. †Data only available for children aged <5 years. ‡Data only available for children aged <1 year.

Table 3: **Overall frequency and time of onset of clinical features of meningococcal disease in children before hospital admission**

	Cumulative proportion of children with clinical feature			
	Fatal cases (n=103)	Non-fatal cases (n=345)	Overall (95% CI)	Median hour of onset
Early symptoms				
Leg pain	22·3%	37·7%	36·7% (28–47)	7
Thirst	41·7%	40·6%	40·7% (31–50)	8
Diarrhoea	54·4%	44·6%	45·2% (36–56)	9
Abnormal skin colour	73·8%	53·9%	55·1% (45–65)	10
Breathing difficulty	75·7%	58·0%	59·1% (50–69)	11
Cold hands and feet	81·6%	75·7%	76·1% (67–85)	12
Classic symptoms				
Haemorrhagic rash	94·2%	88·4%	88·8% (82–95)	13
Neck pain or stiffness	94·2%	91·6%	91·8% (86–97)	13
Photophobia	94·2%	92·5%	92·6% (87–97)	15
Bulging fontanelle	94·2%	93·0%	93·1% (88–98)	15
Late symptoms				
Confusion or delirium	94·2%	95·1%	95·0% (90–99)	16
Seizure	96·1%	95·4%	95·4% (91–99)	17
Unconsciousness	97·1%	95·9%	96·0% (92–99)	22

Percentages and median time of onset are standardised to UK case-fatality rate. Median time of onset is rounded to nearest hour.

Table 4: **Cumulative proportion of children developing clinical features during the course of meningococcal disease**

enough to warrant urgent admission after the initial consultation, they should reschedule a repeat clinical examination within 4–6 h—rather than the next day.

Our study has several limitations, particularly with respect to retrospective data collection and associated recall bias. The parents who were interviewed said they remembered events with great clarity, presumably reflecting their life-changing importance. However, their recall is likely to be biased by selective memory of symptoms (such as haemorrhagic rash) that are well-known features of meningococcal disease. This bias might lead to overestimation of the importance of classic symptoms. But it would not explain our findings of the importance of the early sepsis symptoms, nor would it have led to incorrect reporting of the sequence of symptoms.

Most parents seemed to have no difficulty in deciding when the episode of illness started, and said their child had been completely well up to that point. A quarter of parents (107, 24%) reported that their children had had some symptoms of respiratory tract infection (eg, cold, cough, or influenza) in the previous 2 weeks. However, all but one of the parents of the few children who had prolonged respiratory symptoms were clear about the timing of the change in the illness. It therefore seems unlikely that the non-specific early symptoms reported simply indicate continuation of a previous episode of upper respiratory illness.

For clinicians, the most important limitation of our study is that we do not have data for children with other illnesses to compare symptom frequency. Historical data for the frequency and course of symptoms outside hospital do exist, but they are insufficient. All the current databases and morbidity surveys of which we are aware focus only on final diagnosis or main presenting symptom. This absence of data means that we cannot make any quantitative estimate of how well early symptoms could be used as diagnostic markers.

So how far can we go in making firm clinical recommendations? We believe our evidence is sufficiently robust to argue that we need a diagnostic paradigm shift. Although we must avoid undermining the importance of classic symptoms, we could substantially speed up diagnosis if the emphasis was shifted to early recognition of sepsis. Leg pain, cold hands and feet, and abnormal skin colour are rarely reported by parents to a primary-care doctor, and are therefore likely to have high diagnostic value. Until we have precise quantitative evidence on predictive values of these sepsis features, we believe that there would be little risk of harm and considerable potential benefit if these symptoms were to be promoted to both parents and doctors as warnings of potential meningococcal disease.

Our findings also have important implications for parents, since the median time of first GP consultation was 4 h or longer after the first signs of sepsis. Clinicians cannot make a diagnosis of meningococcal disease until a parent seeks their advice. The timing of first consultations suggests that parents, like clinicians, are motivated to act only on the basis of classic symptoms, particularly haemorrhagic rash. Encouraging recognition of sepsis symptoms (and perhaps measurement of vital signs) in primary care could reduce the proportion of cases missed at first consultation from a half to a quarter. However, achieving earlier diagnosis for the final 25% needs increased awareness of the early symptoms of sepsis and a change in help-seeking behaviour by parents as well as clinicians. At the other end of the timescale, meningococcal disease is a less likely diagnosis if the illness has lasted more than 24 h.

Early diagnosis of rare but important diseases outside hospital is extremely difficult. If diagnostic decisions are driven by clinical observations derived from hospital case-series, rather than the course of symptoms before admission, a diagnostic delay is inevitable. Further research into the diagnostic value of clinical symptoms and signs in serious childhood infection before admission to hospital is necessary to enable clinicians working in primary care to make an accurate assessment and an early diagnosis.

Contributors

The study was designed by N Ninis and M Levin. M Thompson, N Ninis, M Levin, A Harnden, R Mayon-White, R Perera, and D Mant contributed to the design of the primary-care data analysis. N Ninis and C Phillips recruited the parents, collected the data and interviewed parents and general practitioners. L Bailey participated in data collection and interpretation, provided administrative and technical support, and did some of the initial analysis. M Thompson, R Mayon-White, and R Perera did the main analysis. M Thompson, R Mayon-White, D Mant, M Levin, N Ninis, and A Harnden drafted and revised the manuscript, and all authors commented on the text. M Thompson and N Ninis are guarantors for the report. M Thompson had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest statement

We declare that we have no conflict of interest.

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Changing the diagnostic framework of meningococcal disease

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In today's *Lancet*, Matthew Thompson and colleagues show that leg pain, cold extremities, and abnormal skin colour, which are symptoms and signs of sepsis and shock, are seen in the first 12 h of meningococcal disease, whereas the classic features of haemorrhagic rash—meningism, and impaired consciousness—are relatively late signs with a median onset of 13–22 h.[1] The authors recommend that the diagnostic framework is changed to emphasise recognition of the early symptoms of sepsis (panel). Thompson and colleagues' study pioneers the description of the presentation and time course of meningococcal disease in children and adolescents before admission to hospital.[2]

Few infections can cause the tremendous stress that occurs when meningococcal disease enters a community.[3] The rapid onset of disease, the fulminant course of some infected patients, and the mortality and morbidity are all reasons why this infection is so dreaded.[3] Meningococcal disease continues to be a major worldwide health problem and is the most common infectious cause of death in children in many developed countries.[4] Studies have shown improved outcomes in children who receive aggressive treatment in paediatric intensive care units,[5] but initial misdiagnosis often delays appropriate treatment.[6] A multivariate analysis showed that not receiving care from a paediatrician, insufficient supervision of junior staff, and failure of staff to administer adequate inotropes were all independently associated with an increased risk of death.[7] Those authors concluded that suboptimum health-care delivery significantly reduces survival in children with meningococcal disease. Also, it is important that parents recognise when to seek medical assistance for their children so that appropriate treatment can be started as quickly as possible.

Early diagnosis can be challenging because the initial features of the patients in Thompson and colleagues' study are similar to many common, self-limiting viral illnesses seen in primary care. These include the misleading features of coryza and sore throat, and this non-specific phase lasted about 4 h in younger children and 8 h in adolescents. Nonetheless, most of the sepsis symptoms arose before the first contact with a physician.[1] Changing the diagnostic framework is crucially important to enable doctors to recognise serious illness. However, two important items are missing: the ability to determine positive and negative predictive values of leg pain, cold extremities, and abnormal skin colour for the diagnosis of meningococcal disease. This information could be provided by a study of children presenting with the common viral illness signs and symptoms whether or not they are subsequently diagnosed as having meningococcal disease.[8] Until this information is available, doctors should be encouraged to schedule clinical review within 4–6 h if early meningococcal disease cannot be ruled out at the first contact. Our experience is that delay in providing appropriate treatment is common in children who die of meningococcal disease. This delay is sometimes caused by parents' unawareness of their child's condition.[9] To wait for the late signs of meningitis, such as neck stiffness, photophobia, and bulging fontanelle, is a glaring mistake if meningococcal disease is to be promptly diagnosed, because those signs usually arise as late as 12–15 h after onset of illness.[1] In our experience, this is an important factor in the delay in the diagnosis of meningococcal disease. The recognition of early signs of meningococcal disease could reduce subsequent mortality.

***Panel*: Diagnostic framework of meningococcal disease**

Classic signs
Haemorrhagic rash, meningism, impaired consciousness
Median onset 13–22 h

Newly identified signs and symptoms
Leg pain, cold extremities, abnormal skin colour
Median onset 7–12 hours

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Statins: a preventive strike against sepsis in patients with cardiovascular disease?

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In today's *Lancet*, Daniel Hackam and co-authors[1] report that statin therapy in patients with cardiovascular disease is associated with a reduced rate of sepsis, severe sepsis, and fatal sepsis. Statins are well established as lipid-lowering drugs. Cardiovascular morbidity and mortality are significantly reduced by primary and secondary prevention with statins, as well as by acute therapy with a statin.[2–5]

While lipid lowering itself was initially thought to be responsible for the beneficial effects of statins in cardiovascular disease, more recent findings have suggested that pleiotropic effects of statins—eg, anti-inflammatory and antioxidative properties, modulation of cellular immunity, improvement of endothelial function, or increased bioavailability of nitric oxide—might contribute. Notably, most of these effects are independent of lipid lowering, and seem to be mediated by interference with isoprenoid synthesis and subsequent geranylation of membrane proteins. For instance, blockade of the isoprenoid pathway modulates immune-cell responses by inhibiting the expression of coagulation factors, chemokines, MHC II, and adhesion molecules. Some statins directly antagonise adhesion receptors independently of isoprenoid metabolism.[6,7] Statins have also been shown to exert direct antichlamydial effects during pulmonary infection with *Chlamydia pneumoniae* in mice.[8] The benefit of the drugs might also extend to fungal and viral pathogens.[9] They might even hold promise against the potential threat of an influenza pandemic.[10]

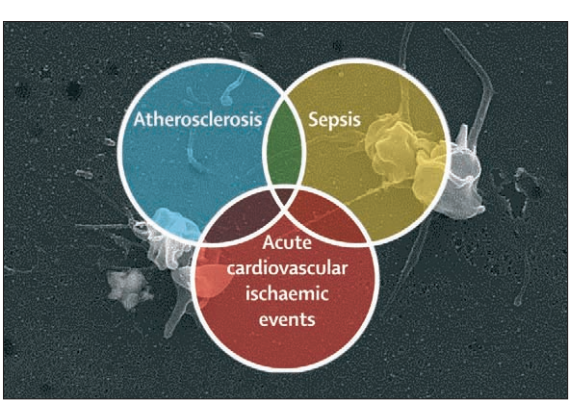

Figure: **Overlapping benefit of statins in patients with atherosclerosis at risk for recurrent acute cardiovascular events, severe sepsis, or both**
Cells in background are activated platelets.

Among many clinical and experimental approaches undertaken to curb the lethal toll of sepsis, activated protein C and low-dose hydrocortisone have, to date, emerged as the only inflammation-modulating substances to benefit patients with severe sepsis.[11,12] In view of their strong effect on inflammation, statins may represent a desirable enforcement in the battle against the increasing incidence and morbidity of severe sepsis and septic shock in developed countries. Indeed, studies in animals[13] and observational reports[14,15] provide evidence in support of this notion. In a prospective cohort study[16] in 361 patients with acute bacterial infections, previous treatment with statins was associated with a substantially reduced rate of severe sepsis and admission to the intensive care unit. However, this study was not powered to detect differences in mortality.

Benefiting from the unique medical infrastructure with linked administrative databases in Ontario, Hackam and colleagues have produced an impressive observational study by initial evaluation of 141 487 patients with cardiovascular disease, resulting in a well-paired and homogeneous study cohort of 69 168 patients after propensity-based matching. To minimise the risk inherent to any observational study of the conclusion being based on selection bias in the treatment group, the investigators carefully scrutinised and adjusted the data for several possible confounders. Furthermore, to exclude significant bias favouring statin users, they have analysed tracer outcomes (eg, the association between statin therapy and cataract extraction was assessed to check for the lack of