Clinical profile and predictors of severe illness in young South African infants (<60 days)

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Background. Most childhood deaths occur within the first 2 months of life. Simple symptoms and signs that reliably indicate the presence of severe illness that would warrant urgent hospital management are of major public health importance.

Objectives. To describe the disease profile of sick young infants aged 0 - 59 days presenting at King Edward VIII Hospital, Durban, and to assess the association between clinical features assessed by primary health workers and the presence of severe illness.

Methods. Specific clinical signs were evaluated in young infants by a health worker (nurse), using a standardised list. These signs were compared with an assessment by an experienced paediatrician for the need for urgent hospital- or clinic-based care.

Results. Nine hundred and twenty-five young infants were enrolled; 61 were <7 days old, 477 were 7 - 27 days old, and 387 were 28 - 59 days old. Illnesses needing urgent hospital management in the age group <7 days were hyperbilirubinaemia (43%) and sepsis (43%); in the age group 7 - 27 days they were pneumonia (26%), sepsis (17%) and hyperbilirubinaemia (15%), and in the age group 28 - 59 days they were pneumonia (54%) and sepsis (15%). The clinical sign most consistently predictive of needing urgent hospital care across all groups was not feeding well. Among those over 7 days old, a history of difficult feeding, temperature ≥37.5°C and respiratory rate ≥60 per minute were also important.

Conclusions. The simple features of feeding difficulties, pyrexia, tachypnoea and lower chest in-drawing are useful predictors of severity of illness as well as effective and safe tools for triaging of young infants for urgent hospital management at primary care centres. Neonatal hyperbilirubinaemia, pneumonia and sepsis are the common conditions for which young infants require urgent hospital-based management.

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Perinatal and young infant deaths account for most deaths of children <5 years old (U5MR) globally.[1,2] Of the 9.7 million deaths annually worldwide of children <5 years of age, approximately two-thirds occur in infancy, with two-thirds of these (about 4 million) occurring during the neonatal period.[3,4] More than half of neonatal deaths occur in the first week of life. In South Africa, nearly two-thirds of infant mortalities and one-third of <5 mortalities occur in the neonatal period.[5,6] Despite a commitment to achieving Millennium Development Goal 4 of reducing U5MR by 2015 from that recorded in 1990 by two-thirds, childhood mortality in South Africa is increasing.[5] Severe infections, especially sepsis and pneumonia, account for 36% of these deaths,[6] prematurity for 28% and asphyxia for 23%.[1]

To reduce infant mortality rates substantially, it is necessary to address the burden of diseases occurring in the first 2 months of life. As little information is available on the potential value of clinical features that might identify severe illness requiring urgent hospital management, it is important to have a simple algorithm that could predict severity of illness so as to refer these children promptly.

The Integrated Management of Childhood Illnesses (IMCI) guidelines for managing young infants were developed from a Young Infant Study (YIS).[7,8] The latter included few neonates aged 0 - 6 days, focused predominantly on infectious diseases without sufficient consideration of non-infectious conditions, and were not validated in other settings. While many sick young infants needing referral have serious bacterial illnesses, many need referral for increased surveillance and/or management of conditions not addressed by the YIS, such as jaundice, congenital malformations, asphyxia, low birth weight and poor feeding.[9-11]

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The present study was part of a multicentre study to validate the utility of previously proposed clinical signs and symptoms for identifying severe illness in young infants of 0 - 59 days old.[13] It provides details of the South Africa site (1 of 6 participating centres), including the spectrum of presenting illnesses and the prevalence and association with the need for hospitalisation for all clinical signs assessed by a primary health care worker.

Methods

The study was conducted at King Edward VIII Hospital, Durban, from February 2003 to February 2004. Young infants presenting to the Outpatient Department (OPD) because of caregiver-perceived illness were screened by a triage nursing sister for inclusion. Inclusion criteria were: age <60 days, residence within 50 km of the hospital (to ensure follow-up), and the caregiver providing informed consent. Exclusion criteria included having been enrolled in the study for an earlier episode, hospitalisation in the previous 2 weeks (except for delivery), referral from another health care facility/physician with therapy instituted before referral, obvious lethal malformation, and requiring immediate cardiopulmonary resuscitation. Informed consent was obtained. Excluded infants were referred to the emergency ward or OPD for further evaluation and treatment. Enrolment took place on Monday to Friday between 08h00 and 16h00. Children admitted were followed up daily until discharge, while all children managed as outpatients were seen between 48 and 72 hours after the initial visit. Children not presenting for hospital follow-up were visited at home within a week.

Study procedures

The training of study persons A (intensive care nursing sister) and B (paediatrician) was by didactic sessions and demonstration of clinical signs, using cases and video. A pilot phase was conducted during the first month of patient recruitment in which procedures were standardised and tested. The paediatrician had 10 years' experience and served as a gold standard to determine whether urgent hospital- or clinic-based care was needed.

Infants enrolled by triage were sent to A for recording history and selected predetermined clinical signs (Table I)

Table I. Baseline clinical characteristics of study group according to age group*

	0 - 6 days		7 - 27 days		28 - 59 days		Combined	
Number of infants	61		477		387		925	
Female gender	39		47		45		46	
Exclusive breastfeeding	64		57		43		52	
Vital signs								
Respiratory rate >60 (person A)	16		9		16		12	
Respiratory rate >60 (person B)	16		9		16		12	
Fever (temperature >37.5^{0}C) (person A)	5		5		7		6	
Fever (temperature >37.5^{0}C) (person B)	3		5		8		6	
Tachycardia (pulse >160)	11		17		23		19	
Hypoxaemia (SaO_2 <95)	15		14		11		13	
Anthropometric measurements								
Weight (kg): mean *z* score (SD)	-0.9	(0.7)	-0.9	(1.1)	-0.7	(1.4)	-0.8	(1.2)
Length (cm): mean *z* score (SD)	-0.5	(1.0)	-0.7	(1.2)	-0.7	(1.3)	-0.7	(1.3)
Head circumference (cm): mean *z* score (SD)	-0.6	(0.8)	-0.6	(1.0)	-0.6	(1.2)	-0.6	(1.1)
Obstetric history								
Home delivery	13		3		4		4	
Delivered by skilled attendant	87		98		96		96	
Birth weight (kg): mean (SD)	3.0	(0.4)	3.0	(0.5)	2.9	(0.7)	2.9	(0.6)
Low birth weight (<2 500 g)	10		15		21		17	
Parity >0	48		45		42		44	
Gestational age <37 weeks	8		12		19		15	
Maternal tetanus toxoid	95		96		95		96	
Antenatal care (3 visits or more)	95		96		93		95	
Diabetes during pregnancy	0		0		2		1	
Anaemia during pregnancy	5		1		2		2	
Urinary tract infection during pregnancy	3		4		3		3	
Fever at time of delivery	0		0		2		1	
Prolonged labour	3		8		7		7	
Prolonged rupture of membranes	0		2		2		2	
Vaginal delivery	89		70		61		68	

*Values are expressed as percentages of group with characteristic except where indicated otherwise.

and then referred to B who was blinded to A's findings. B (principal investigating paediatrician PMJ) categorised primary and secondary diagnoses using standard operating manual definitions, and decided on urgent hospital admission or outpatient management. Non-urgent cases were regarded as those that could be managed at the clinic or by non-urgent hospital care. Children admitted were followed up daily until discharge, while all children managed as outpatients were seen between 48 and 72 hours after the initial visit.

Enrolled patients had pulse oximetry performed after clinical examination (Nedcor 500A pulse oximeter, Ohmeda, Basel, Switzerland). Patients requiring urgent hospital-based therapy had blood cultures, bilirubin, full blood count, electrolytes and serum glucose estimates. A lumbar puncture and/or chest X-ray was performed if clinically indicated. Based on these tests and the clinical evaluations, patients were admitted or sent home on appropriate management. The clinical course and final diagnosis of admitted patients were recorded. Patients deemed not to require urgent hospital care were treated as outpatients and advised to return for re-evaluation within 48 - 72 hours for follow-up assessment. Home visits were arranged within 7 days of the initial visit if the patient did not return. If the patient was admitted to another hospital, hospital outcome details were recorded. The completed forms A and B were reviewed by a senior investigator at King Edward VIII Hospital.

Data entry, cleaning and management

Case record forms were checked and entered into an EpiData data base (version 2.1, EpiData Association, Odense, Denmark). The Data Coordination Centre in Melbourne, Australia, checked data files for consistency and monitored the quality of submitted data. Subjects at the review site (King Edward VIII Hospital) were classified according to the primary outcome category of needing urgent hospital-based care only if they needed immediate hospitalisation. Therefore, infants who required urgent investigations initially as outpatients were not included in this category. Subsequently, as the study focus was to identify all patients requiring urgent hospital-based management, a comprehensive review on subjects who had investigations performed as part of their care, but who were not admitted, were re-assigned to the primary outcome category of requiring urgent hospital-based outpatient care.

Statistical methods

Analyses were primarily descriptive. We obtained prevalence of diagnoses on whether or not the infant was classified as requiring urgent hospital management in age groups 0 - 6, 7 - 27 and 28 - 59 days. Prevalence of clinical signs assessed by the primary health care worker was calculated, and the association of each sign with the primary outcome ('severe illness' classification by B) was examined by calculating sensitivity and specificity.[12] Different age groups were used to assess whether their disease burden and the physical signs denoting severity of illness differed.

Ethical clearance

The study was approved by the Ethics Committee of the University of KwaZulu-Natal and the Boston University Institutional Review Board.

Results

A total of 957 young infants was triaged, of whom 925 satisfied the study enrolment criteria and reasons for exclusion (Fig. 1); 61 (6.6%) were <7 days, 477 (51.6%) 7 - 27 days, and 387 (41.8%) 28 - 59 days of age. Most babies were born in health facilities (96%), received antenatal care (96%) and were born at term (84%) (Table I). Forty-six per cent were female, 52% were exclusively breast-fed, 44% of mothers were primigravidas, and 68% had normal vaginal deliveries. Of the 925 infants enrolled, the most common presenting complaints included cough (42.6%), skin problems (37.5%), blocked nose or upper respiratory tract infection (URTI) (29.9%), fever (24.8%), jaundice (24%), and eye problems (19.9%). Oral problems, respiratory distress, abdominal distension, not feeding well, and diarrhoea occurred in <10% overall. Infants often had more than one presenting complaint.

Urgent hospital-based management was required by 232 (25.1%) (Table II); 81 (34.9%) were admitted and 151 (65.1%) were managed as outpatients. Urgent hospital-based management was required by 21 of 61 0 - 6-day-old neonates (34.4%), mainly for neonatal hyperbilirubinaemia and sepsis; by 78 of 477 (16.4%) infants 7 - 27 days of age, mainly for pneumonia, sepsis and hyperbilirubinaemia; and by 133 of 387 (34.4%) infants 28 - 59 days of age, mainly for pneumonia and sepsis. Children considered suitable for management at a primary health care facility numbered 693 (74.9%).

Common conditions for which infants 0 - 6 days old required care were neonatal hyperbilirubinaemia (52.5%), skin conditions (36.1%) and conjunctivitis (29.5%); for the 7 - 27 days old group, skin conditions (50.3%), URTIs (28.3%) and hyperbilirubinaemia (15.9%); and for those 28 - 59 days old, skin conditions (47.8%), URTIs (36.4%) and pneumonia (23.0%). Several children had more than one secondary diagnosis, including feeding problems such as gastrocolic reflex, constipation and regurgitation; oral and disseminated candidiasis; diarrhoea; and minor congenital malformations. Tuberculosis exposure and low birth weight and/or prematurity rates were high while rates of birth asphyxia, hypoglycaemia, hypothermia and anaemia were low.

There were 4 deaths (0.4% of all infants and 1.7% of those requiring urgent hospital-based care (*N*=232)); 3 of these were admitted at study enrolment – 2 with bronchopneumonia with disseminated candidiasis and 1 with neonatal sepsis and disseminated intravascular coagulation. A child with trisomy

18 was treated as an outpatient initially but required admission for a worsening congenital heart lesion. Of the 693 infants who were considered suitable for primary care management, all recovered at follow-up, although 7 required a second follow-up visit. From the entire cohort, 20 (2.2%) were lost to follow-up.

The prevalence, sensitivity and specificity of each of the reported history and clinical signs for prediction of serious illness requiring urgent hospital management are shown in Table III. Cases requiring hospital care for hyperbilirubinaemia were included as non-urgent because the clinical signs were not intended to identify jaundiced babies. For the age group <0 - 6 days, a history of not feeding well was the most significant symptom or sign predicting the need for hospital-based care. In neonates aged 7 - 59 days, a number of individual signs clustered as general (history of difficult feeding, not feeding well, and temperature >37.5°C) and respiratory (respiratory rate ≥60/min, severe chest in-drawing) significantly predicted the need for hospital-based management.

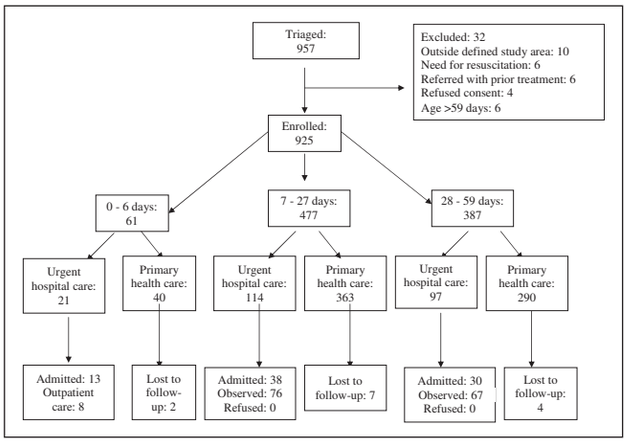

Fig. 1. Study profile.

Discussion

This study provides new and informative descriptive epidemiological information on illness in infants reporting to a secondary health facility. As the policy to provide health care to all young infants in South Africa requires referral to a hospital, the disease spectrum identified reflects the epidemiology of illness of this age group. Infants were brought to health care facilities by parents with nonspecific symptoms of cough, skin lesions, nasal obstruction, fever, jaundice and eye problems. Conditions commonly diagnosed by a paediatrician as requiring urgent hospital management included neonatal hyperbilirubinaemia, pneumonia and sepsis. Physiological jaundice, infectious and chemical conjunctivitis, oral thrush, infectious (including umbilical) and non-infectious skin conditions and URTI were frequently encountered and considered safe to manage as outpatients at primary health centres. These findings may be helpful to primary health care

Table II. Frequency of primary diagnoses according to age and need for urgent hospital management

	Required urgent hospital management						Did not require urgent management					
	0 - 6 days		7 - 27 days		28 - 59 days		0 - 6 days		7 - 27 days		28 - 59 days	
Disease categories	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Prematurity, low birth weight	0	(0)	1	(1)	1	(1)	1	(3)	20	(5)	9	(4)
Birth asphyxia	0	(0)	0	(0)	2	(2)	0	(0)	1	(0)	0	(0)
Birth injury	0	(0)	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)
Early neonatal hyperbilirubinaemia	9	(43)	12	(15)	1	(1)	14	(35)	42	(11)	1	(0)
Sepsis	9	(43)	13	(17)	20	(15)	0	(0)	0	(0)	0	(0)
Meningitis	0	(0)	2	(3)	3	(2)	0	(0)	0	(0)	0	(0)
Pneumonia, ALRI	0	(0)	20	(26)	72	(54)	0	(0)	3	(1)	7	(3)
URTI, mild ARI	0	(0)	1	(1)	2	(2)	1	(3)	86	(22)	94	(37)
Skin infection	1	(5)	4	(5)	2	(2)	2	(5)	31	(8)	31	(12)
Skin condition (non-infectious)	0	(0)	0	(0)	1	(1)	4	(10)	28	(7)	24	(9)
Eye infection	1	(5)	1	(1)	1	(1)	7	(18)	37	(9)	5	(2)
Oral thrush	0	(0)	0	(0)	2	(2)	1	(3)	20	(5)	17	(7)
Umbilical infection and other problems	1	(5)	0	(0)	0	(0)	0	(0)	5	(1)	5	(2)
Diarrhoea, dysentery, persistent diarrhoea	0	(0)	4	(5)	6	(5)	1	(3)	22	(6)	13	(5)
Colic	0	(0)	0	(0)	0	(0)	0	(0)	13	(3)	7	(3)
Feeding problem	0	(0)	0	(0)	0	(0)	1	(3)	16	(4)	12	(5)
Non-infectious conjunctivitis	0	(0)	0	(0)	0	(0)	0	(0)	6	(2)	3	(1)
Prolonged neonatal jaundice	0	(0)	0	(0)	0	(0)	0	(0)	27	(7)	7	(3)
Other	0	(0)	19	(23)	20	(15)	6	(15)	38	(10)	18	(7)
Well baby	0	(0)	0	(0)	0	(0)	2	(5)	4	(1)	1	(0)
Total	21	(100)	78	(100)	133	(100)	40	(100)	399	(100)	254	(100)

ALRI = acute lower respiratory tract infection; ARI = acute respiratory infection; URTI = upper respiratory tract infection.

workers seeking to triage patients optimally in overcrowded health care systems in developing countries. Triage improvements would also obviate the need to transport to hospital many young infants who could be effectively managed at a primary health clinic. This would reduce costs and limit the risk of nosocomial infections.

We also found that sick infants 0 - 59 days old requiring urgent hospital management could be effectively identified using simple features that predict severity of illness such as feeding difficulty, not feeding well, pyrexia, and respiratory features including tachypnoea and lower chest in-drawing, which were common among them. Other infrequent respiratory features (cyanosis) and neurological features (inability to suck, history of convulsions, failure to arouse with minimal stimulation, history of change in activity) also suggested severe illness. A simpler algorithm, with easily recognisable signs and without the need for laboratory testing, will assist educators in a training programme for the recognition and urgent referral of sick children by primary care health personnel. Detailed modelling of signs predicting admission has been reported.[13] Implementing this algorithm will contribute to achieving Millennium Development Goal 4 of reducing infant mortality rates.

Evidence-based case management is important for the development of health care policies globally. The previous YIS identified fever >37.7°C, hypothermia (temperature <35.5°C), inability to suck, crackles, cyanosis, history of convulsions, lower chest in-drawing, failure to arouse with minimal stimulation, history of change in activity and respiratory rate (RR) ≥60/min as predictive of severe infection.[14] The current IMCI algorithm uses an additional 5 clinical signs to identify a serious bacterial illness: bulging fontanelle, pus draining from ear, redness around umbilicus extending to skin, lethargy or unconsciousness, and reduced movements.[15-17] Using only the 9 signs as proposed by the previous YIS analysis indicates a slightly lower sensitivity but greater specificity to predict severe infection than the IMCI guidelines, although neither was optimal. A Kenyan study failed to find valid clinical signs to consistently predict severe bacterial infections.[18,19] Others suggest that only the addition of laboratory testing could improve the prediction of serious bacterial infection to 95%,[20-22] which is not feasible in resource-restricted countries. This study identified similar features to the Baby Check scoring system, which used 23 characteristics. Since the latter is more complex and was devised to identify sick infants <6 months of age in developed countries with a different spectrum of diseases, our study's findings are more relevant for developing countries.[24,25]

There are limitations to this study. Because it is a site-specific report, the sample size is insufficient to make firm recommendations, especially in the age group 0 - 6 days where small numbers were enrolled. It is reassuring that our findings at the King Edward VIII Hospital site reflect the overall conclusions of the main multicentre trial, whose results were published in the *Lancet*.[13] Furthermore, the high rate of babies born by skilled attendants at health care facilities, low rates of birth asphyxia and low-birth-weight infants, and low incidence of hypoglycaemia make them relevant to a population where a similar level of health care is provided. This is unlike the home-based trial where a combination of birth weight <2 000 g,

Table III. Prevalence, sensitivity and specificity of individual signs for prediction of 'serious illness requiring urgent hospital management' (excluding jaundice) for infants in three age groups

	0 - 6 days			7 - 27 days			28 - 59 days		
	Prev. (%)	Sens. (%)	Spec. (%)	Prev. (%)	Sens. (%)	Spec. (%)	Prev. (%)	Sens. (%)	Spec. (%)
Number of infants	61	12	49	477	66	411	387	132	255
General signs and symptoms									
History of fever	33.3	41.7	68.8	39.6	47.0	61.6	53.0	67.2	54.3
History of difficulty feeding	9.8	41.7	98.0	14.3	24.2	87.3	19.0	26.0	84.6
Not feeding well	3.3	16.7	100.0	7.8	13.6	93.2	9.0	15.2	94.1
Movement only when stimulated				0.2	1.5	100.0			
Lethargic	4.9	8.3	95.9	0.2	1.5	100.0	0.5	1.5	100.0
Restless and irritable	-	-	-	0.4	3.0	100.0	1.0	2.3	99.6
Temp. <35.5°C	-	-	-	0.6	3.0	99.8	0.3	0.0	99.6
Temp. ≥37.5°C	4.9	8.3	95.9	4.6	15.2	97.1	7.0	14.4	96.9
Prolonged capillary refill	-	-	-	-	-	-	0.3	0.8	100.0
Respiratory signs									
Respiratory rate ≥60	18.0	16.7	81.6	8.2	19.7	93.7	13.5	27.3	93.7
Nasal flaring	-	-	-	1.5	6.1	99.3	3.4	8.3	99.2
Grunting	-	-	-	1.5	6.1	99.3	2.6	7.6	100.0
Cyanosis	-	-	-	0.2	1.5	100.0	-	-	-
Severe chest indrawing	-	-	-	4.6	12.3	96.6	16.1	31.1	91.7
Neurological signs									
History of no cry at birth	11.5	8.3	87.8	18.2	24.2	82.8	14.9	13.0	84.1
History of convulsions	3.3	0.0	95.9	3.6	9.1	97.3	7.5	11.4	94.5

preterm birth (<37 weeks) or the baby not taking feeds was associated with an increased risk of death on the first day of life.[23] Caution must therefore be exercised in extrapolating these results to settings where most deliveries take place at home with unskilled birth attendants. Despite these limitations, our data have relevance to areas with a similar patient population, as in many middle-income countries.

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