A CLINICAL CLASSIFICATION OF THE IDIOPATHIC RESPIRATORY DISTRESS SYNDROME OF THE NEWBORN

H. DE V. HEESE AND A. F. MALAN,* *Department of Child Health, Groote Schuur Hospital, University of Cape Town*

'No condition in recent years has excited the interest of individuals concerned with newborn infants to quite the extent that hyaline membrane disease has.'[1] The term 'idiopathic respiratory distress syndrome' (IRDS) has been used as synonymous with hyaline membrane disease. The syndrome is characterized by signs of respiratory distress in newborn infants in whom specific causes of abnormal breathing, such as pneumothorax, diaphragmatic hernia, congenital heart disease, pneumonia or intracranial haemorrhage, have been excluded by appropriate clinical and special investigations.[2-4] There is, however, no uniform agreement on either diagnostic criteria or terminology for the IRDS.[5] Stahlman[6] prefers to call the condition 'clinical hyaline membrane disease' (CHMD) which is a more correct description of the diagnosis during life. The variable basis for diagnosis also makes it impossible to compare mortality figures reported from different centres.[7] James[8] stated that the diagnosis of the respiratory distress syndrome should rely not on the presence or absence of membranes at necropsy, but rather on the history, symptoms and clinical signs.

The responsibility for the management of this commonest of all causes of premature infant death rests with the practising paediatrician. He has to deal with the problem constantly, often without facilities for serial acid-base and oxygen measurement. He has to make a clinical assessment of the severity of the condition, treat the sick

*Senior Bursar, South African Council for Scientific and Industrial Research.

infant, if need be, empirically with oxygen and sodium-bicarbonate and give a prognosis to anxious parents.

In this article an approach is put forward which should be of value in assisting the clinician with these problems, particularly in those centres where highly technical investigations are not available. A practical classification of IRDS based on the clinical and radiographic signs in 140 infants suffering from the syndrome is presented. The supportive evidence of the correlation between the assessment of severity and the biochemical disturbances and mortality figures is put forward. The prognostic importance of distinguishing between 2 separate conditions within IRDS is emphasized.

Differentiation of the Idiopathic Respiratory Distress Syndrome

It has recently been suggested by Kottler *et al.*[9] and Prod'hom *et al.*[10,11] that the IRDS does not constitute a homogeneous group. Both groups of workers found radiological differences between clinical HMD (referred to as CHMD in this article) and a second group regarded as an aspiration syndrome. We prefer the term 'neonatal disseminated atelectasis' (NDA)[12,13] for this latter group until such time as the aetiological factors and manifestations of the 'aspiration syndrome' have been clarified. NDA and CHMD were indistinguishable on initial clinical examination but had striking differences in mortality. Prod'hom and his co-workers have documented a thorough study of the pathophysiology of the IRDS, differentiating their cases into types I and II.

The radiographic appearance of NDA is characterized by streaky atelectasis in the distribution of the bronchial tree, general emphysema and absence of a marked air bronchogram.[9] This condition should not be confused with the clear-cut entity of meconium aspiration. The characteristic reticulogranular pattern and air-bronchogram of hyaline membrane disease (atelectasis ± hyaline membrane formation) has been fully described and confirmed by numerous authors.[3,7,9,14-16]

Selection of Cases

The IRDS was diagnosed in this series when two or more of the following signs were present in association with a radiographic picture of either HMD or NDA.

(*i*) Respiratory rate of more than 60/min. maintained for more than 3 hours.

(*ii*) Expiratory grunting present after 3 hours of age.

(*iii*) Cyanosis in room air.

(*iv*) Marked costal and sternal recession.

(*v*) Pulmonary crepitations.

A chest radiograph was therefore essential for a diagnosis, dividing the 140 infants into 29 with NDA and 111 with CHMD.

The majority of the infants were born in the 5 maternity hospitals attached to the University of Cape Town Medical School while the remainder were admitted directly, either to Groote Schuur Hospital or the Red Cross War Memorial Children's Hospital. The infants were seen at varying ages after birth and under widely differing conditions. Although most received early attention and specialized treatment, this was not always the case. Many infants admitted from outside were severely affected, hypothermic, and often *in extremis*.

Postmortem confirmation of the diagnosis was obtained in all the CHMD cases that went to autopsy. Two infants were labelled NDA during life, but autopsy showed that one had, in fact, HMD while the other died of a pseudomonas peritonitis and septicaemia with focal areas of atelectasis.

RESULTS

The clinical findings in both NDA and CHMD are summarized in Tables I and II.

NEONATAL DISSEMINATED ATELECTASIS

NDA comprises 21% of the total and differs from CHMD in several aspects. The most striking difference is the rapid improvement and low mortality. In both infants who died, a specific cause for death was demonstrable. Prod'hom *et al.*[11] had no deaths in their type II, the corresponding group of their series.

TABLE I. IDIOPATHIC RESPIRATORY DISTRESS SYNDROME—CLINICAL CLASSIFICATION

	Neonatal disseminated atelectasis	*Clinical hyaline membrane disease*			
Chest radiograph	Streaky atelectasis and emphysema	Reticulogranular pattern + air bronchogram			
Grading of severity	Mild–Moderate	*Mild*	*Moderate*	*Severe I*	*Severe II*
Oxygen requirement	<40%	<40%	<40%	>40% usually 50–70%	100%
Respiratory rate >60/min.	93%	77%	95%	83%	46%
Grunting	65%	67%	93%	97%	65%
Recession	65%	77%	95%	100%	77%
Cyanosis (room air)	48%	33%	88%	100%	100%
Oedema	21%	—	83%	89%	92%
Crepitations	10%	—	39%	71%	88%
Sternal bulge	28%	—	68%	71%	65%
Apnoeic attacks	7%	11%	22%	52%	92%
Mortality	6·9%	0%	14·5%	57·1%	92·3%
		←	55·5%	→	
	←		36·5%	→	
Number of cases		9	41	35	26
(Total 140)	29		111		

TABLE II. IRDS—CLINICAL DATA

		Neonatal disseminated atelectasis	*Clinical hyaline membrane disease*			
			Mild	*Moderate*	*Severe I*	*Severe II*
Number of cases		29	9	41	35	26
Age at first observation (hours)	Average	5·5	9·6	9·9	8·9	3·8
	Range	0–18	1–16	1–47	1–36	¾–31
Weight (kg.)	Average	2·69	2·06	1·98	2·03	2·25
	Range	1·50–4·09	1·10–3·92	1·19–3·18	1·13–3·12	1·08–3·63
Maturity (weeks)	Average	36·7	33·0	34·9	33·4	34·0
	Range	28–40	29–36	29–38	28–39	30–38
Apgar (1 min.)	Average	5·2	6·7	6·7	7·0	4·7
	Range	1–9	2–9	1–10	1–10	1–10
Sex ratio		Male: 1·9 Female: 1		Male 1·75 : Female 1		
Mortality		6·9%	0%	14·5%	57·1%	92·3%
Age death (hours)	Average	57	—	58	42	32
	Range	36–78	—	21–108*	11–153*	4–179*

* Life prolonged on respirator.

Half of the infants were cyanosed in room air, but the environmental oxygen required was more than 40% in only one of them. The respiratory rate was well over 60/min. in the majority of cases. The incidence of oedema, crepitations, sternal bulging and apnoeic attacks was notably lower than in CHMD. Prod'hom *et al.*[11] also recorded less oedema and no rales. Both series showed the gestational maturity and weight to be greater in NDA. A comparison between the infants in the 2 series is given in Table III. It is interesting to note that there were more

TABLE III. COMPARISON OF NDA WITH IRDS TYPE II

Authors	*Prod'hom et al.*	*Heese and Malan*
Terminology	IRDS type II	Neonatal disseminated atelectasis
No. of infants	8	29
Mortality	0%	6·9%
Radiology	7/8 Aspiration syndrome	Aspiration syndrome
Average gestational age (weeks)	34·9	36·7
Average birth weight (kg.)	2·16	2·69
Male : Female	0·6 : 1·0	1·9 : 1·0
Rales	0%	10%
Oedema	Less than type I	21%
Average pH	7·22	7·26
Q_S/Q_T	27–34%	29% (1 case only)
$NaHCO_3$ treatment	0	1

females in the series of Prod'hom *et al.*[11] while the present series follows the usual male preponderance in neonatal respiratory distress.

The low Apgar score at 1 min. (Table II) suggests depression with possible aspiration of material.

CLINICAL HYALINE MEMBRANE DISEASE—ASSESSMENT OF SEVERITY

It is extremely difficult to estimate the prognosis in hyaline membrane disease. The disease often runs a rapid course so that the early condition of the infant may not be an indication of later events.

We have divided the 111 infants with CHMD into 4 categories according to their oxygen requirements (Table I). The assessment was made on the initial examination, irrespective of the age or subsequent course. In mild and moderate illness the inspired oxygen requirements were less than 40%, while in severe cases they were over 40%. The mild cases were distinguished from moderate illness by the absence of oedema, crepitations and a sternal bulge. Severe illness was further subdivided into Severe I and Severe II. All infants requiring 100% oxygen to maintain normal arterial saturation (or PaO_2 of about 100 mm.Hg) were placed in the Severe II category.

The major defect in hyaline membrane disease is one of gaseous exchange in the lungs. This is most strikingly reflected in the oxygen desaturation of the blood. The advent of severe respiratory acidosis is a late indication of imminent death.[17] It would be reasonable, therefore, to grade the severity according to the arterial oxygen tension.[6,18] In the absence of facilities for measuring oxygen tension and saturation, one could rely on the amount of supplementary oxygen required to relieve cyanosis.[19] The drawback to this method is that the PaO_2 drops to fairly low levels before clinical cyanosis becomes apparent.[20] Gairdner[21] regards the pH as the most useful single measure of respiratory insufficiency while Stahlman[6] found a high blood lactic acid the best single criterion for non-survival. The lactic acid correlated poorly with the PaO_2.[22]

CLINICAL CORRELATION

The relationship between the 4 categories and the clinical data are shown in Tables I and II.

The infants with mild illness had transient respiratory distress. The respiratory rate was usually raised but grunting, recession and cyanosis were short-lived. The infants required no treatment other than some additional oxygen, and all survived.

In the more severe cases the clinical signs compared well with our grading of severity.

(*a*) *Respiratory rates.* The highest rates were recorded in moderate illness, often over 100/min. Slow rates (under 60/min.), associated with a high oxygen requirement, had a poor prognosis.

(*b*) *Grunting and recession.* There was little difference between the moderate and Severe I groups, but the incidence of grunting and recession actually decreased in the Severe II cases.

(*c*) *Oedema and crepitations.* The incidence of these 2 findings rose with the severity and were adverse

prognostic signs, particularly if present soon after birth.

(*d*) *Apnoeic attacks*. As would be expected these occurred more frequently in the more severely affected infants.

(*e*) *Mortality*. This ranged from 0 to 92% and followed the grading of severity. The average age of death was also earlier in the more severe illness.

(*f*) *Birthweight and maturity*. The Severe II group had a slightly higher birthweight but no difference was found in the average gestational ages. The increased weight appeared to be due to infants of diabetic mothers and a higher percentage of caesarean section deliveries.

(*g*) *Apgar rating and age of onset*. The most severely affected infants had the lowest Apgar ratings and were in difficulties earlier.

Acid-Base Balance

The average acid-base values for NDA and CHMD are given in Table IV. There was good correlation between the acid-base status and the clinical severity of CHMD. The NDA group occupied an intermediary position between mild and moderate CHMD. The values for mild illness lay outside the average values for healthy premature infants but within the acceptable range of normality.[23] The ages of initial biochemical assessment (Tables IV and V) are the same as shown in Table II.

Biochemistry

R-L shunts were calculated using the standard equation[24] in one case of NDA and in 39 of CHMD (Table V). Prod'hom *et al.*[11] recorded a striking difference in R-L shunts between their type I and type II infants. The relative infrequency of oxygen studies is an obvious weakness, as the crucial test of our clinical assessment of severity would be the respective alveolar-arterial oxygen gradients. Facilities for the direct estimation of PO_2 with an electrode were, however, not available during the early part of this study. Initial PaO_2 levels were high in a few of the moderate and Severe I cases but all fell subsequently. Boston *et al.*[18] obtained a good correlation between PaO_2 and subsequent outcome. More estimations are needed in mild CHMD to verify the apparently minor R-L shunt.

The other figures in Table V show no relation to the severity of the condition. Potassium levels over 6·5 mEq./l.[25] were sometimes present in both moderate and severe illness. The highest recorded was 12 mEq./l. in a Severe II

TABLE IV. IRDS—ACID-BASE VALUES

		Neonatal disseminated atelectasis (18)*	*Clinical hyaline membrane disease*			
			Mild (4)	*Moderate* (36)	*Severe I* (35)	*Severe II* (21)
pH	Average	7·264	7·348	7·253	7·146	7·022
	Range	7·090–7·367	7·250–7·400	7·100–7·400	6·990–7·305	6·620–7·250
PCO_2 mm./Hg	Average	46·6	37·7	49·5	52·9	88·0
	Range	31·3–72·0	24·5–49·5	25·0–80·0	31·5–91·0	23·5–150
Base excess	Average	−5·8	−5·3	−6·3	−9·3	−14·8
mEq./l.	Range	−2·6 to −10·5	−2·7 to −7·0	+3 to −15·2	−2 to −19·5	−5 to −30
Buffer base	Average	40·2	42·9	41·5	38·1	31·6
mEq./l.	Range	33·6–47·0	41·5–43·8	31·2–52·0	28·7–46·2	20·0–44·5
Standard HCO_3^-	Average	18·2	19·8	19·2	17·1	13·9
m.Eq/l.	Range	15·1–23·0	18·8–21·7	13·1–26·4	11·1–22·0	7·2–20·5
Actual HCO_3^-	Average	19·6	19·4	21·1	19·4	17·8
mEq./l.	Range	15·1–29·0	15·2–21·5	10·5–30·5	9·7–26·7	6·0–28·5

* No. of estimations.

TABLE V. IRDS—BIOCHEMICAL FINDINGS

		Neonatal disseminated atelectasis	*Clinical hyaline membrane disease*			
			Mild	*Moderate*	*Severe I*	*Severe II*
K+	Average	5·8(9)*	4·5(1)	6·0(21)	5·7(26)	6·1(22)
	Range	4·5–10·0	—	4·3–9·8	3·5–10·0	4·1–12·0
Na+	Average	137(9)	130(1)	136(20)	137(18)	134(22)
	Range	119–142	—	125–142	125–145	122–144
Cl−	Average	103(4)	—	99(8)	96(12)	98(8)
	Range	98–106	—	91–105	85–109	88–102
Urea	Average	21(4)	84(1)	38(9)	45(10)	47(10)
	Range	15–45	—	12–49	10–110	19–73
Sugar	Average	53(7)	37(1)	79(18)	66(24)	72(17)
	Range	30–88	—	14–308	20–137	11–227
Total proteins	Average	5·3(5)	5·0(1)	4·3(14)	4·4(18)	4·4(15)
	Range	4·2–5·6	—	2·6–5·7	3·2–6·3	3·1–6·3
Albumin	Average	3·7(5)	3·4(1)	3·1(14)	3·2(18)	3·3(15)
	Range	3·6–4·1	—	2·0–4·2	2 1–4·1	2·3–4·6
Globulin	Average	1·7(5)	1·6(1)	1·1(14)	1·0(18)	1·1(15)
	Range	1·0–2·0	—	0·6–1·7	0·3–2·2	0·2–1·8
R–L shunt	Average	29%(1)	30%(2)	43%(11)	47%(14)	62%(12)
	Range	—	28–32	37–60	28–78	41–84

* No. of estimations.

infant who recovered following respirator therapy. Usher[26] found rising values with increasing age.

Infants with CHMD had low total protein concentrations in the serum. Subsequent estimations have demonstrated that the gammaglobulin fractions are particularly low.[27] The NDA group had higher values than CHMD.

COMMENT

(i) *Neonatal Disseminated Atelectasis*

There is an obvious clinical overlap between this condition and the milder forms of CHMD. Radiology is most helpful, but occasionally one finds a coarse reticulogranular pattern that could be either NDA or CHMD. Smith[28] has suggested that these might be mild cases of hyaline membrane disease. It is hardly necessary to stress the value of serial roentgenograms in doubtful cases. Prod'hom *et al.*[11] found that one of their type II infants had an 'HMD' roentgenogram. Similarly, one 'NDA' infant in this series had hyaline membranes at autopsy. Hutchison *et al.*[7] found that not all of their mild cases had significant radiographic changes. It is interesting to speculate that in some cases the respiratory distress could have been due to NDA.

The single, most helpful investigation, in these infants is the calculation of the R-L shunt on 100% oxygen. Few centres will be able to emulate the careful studies of Prod'hom *et al.*[11]

Much more difficulty is experienced in formulating a clear concept of the pathology. Schaffer[29] stated that the massive aspiration syndrome covers a whole range of pathology. One may get either segmental or disseminated atelectasis. Avery,[1] discussing the role of aspiration of clear fluid in the causation of respiratory distress, came to no definite conclusion. In the case of the infant who died from pseudomonas septicaemia at 78 hours, the upper lobes were expanded but there were areas of atelectasis in the middle and lower lobes. The alveolar ducts were normal and no particulate matter, squames or hyaline membranes were seen.

(ii) *Clinical Hyaline Membrane Disease*

Although the division of CHMD into 4 categories would seem unnecessary at first, we believe there is justification for this. The mild group is the most doubtful separate entity. Smith[2] has pointed out that there are very mild grades of the IRDS. One cannot be sure some even have the disease. Most of those with mild illness would probably be missed unless a chest radiograph was taken.

The work of other authors support the present grading. Stahlman used 3 categories, mild, severe-lived and severe-died,[25] later changing 'mild' to 'moderate' illness.[6] Hutchison *et al.*[7] studied 2 groups, mild and severe. Forty percent ambient oxygen was also found to divide the mild from the severe cases. In their study, they included only infants with respiratory rates over 60/min., thus excluding most of our Severe II group. The requirement of 100% oxygen clearly separates some infants into a special category with predictable death in the vast majority.[6]

The serious prognostic import of a slower respiratory rate in the face of severe illness has been well documented.[8,16,25,30,31] At the other end of the spectrum, some of the mild cases never had a respiratory rate over 60/min.

Usher[26] found a high mortality with early rales and oedema. All the severe cases in the series reported by Hutchison *et al.*[7] had oedema.

Severe retraction is also listed by Usher[26] as being associated with a high mortality. Our experience rather confirms the opposite views of James[8] and Tizard[32] that in very severe illness the infant may be too feeble to have either retractions or grunting.

Unlike Stahlman[6] who stated that it was rare for one group suddenly to go into another, we had several infants who deteriorated rapidly from moderate to severe illness. The complications of pneumothorax and intracranial haemorrhage were frequently the cause of sudden progression of the illness and death. On the other hand, recovery was invariably a gradual process over a period of 2 - 4 days.

SUMMARY

A study of 140 infants suffering from the 'idiopathic respiratory distress syndrome of the newborn' is reported. On radiological evidence the infants were divided into 'clinical hyaline membrane disease' and an aspiration syndrome labelled 'neonatal disseminated atelectasis'. Prod'hom *et al.*[11] have reported an identical division on radiological and ventilation studies.

A grading of severity dividing clinical hyaline membrane disease into 4 categories is put forward. The supportive evidence of clinical signs, acid-base balance, biochemical data and mortality figures is presented. Related literature on the subject is reviewed and discussed.

The proposed classification would appear to be of value in the clinical assessment of the 'idiopathic respiratory distress syndrome of the newborn'.

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