SEPTICAEMIA OF THE NEWBORN

A CLINICAL STUDY OF FIFTEEN CASES

BY

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Analysis of the causes of death in the neonatal period shows that infection is frequently responsible. In different series (Cruikshank, 1930; d'Esopo and Marchetti, 1942; Parsons, 1944; Macgregor, 1946; Scottish Scientific Advisory Committee, 1947) the incidence has varied between 8 per cent. and 42 per cent. The incidence of infective conditions in the neonatal period, other than those causing death, is also high. Corner (1946) reported 6,534 consecutive live births in two maternity units in Bristol, and found that 25.3 per cent. of all babies in one hospital and 29.7 per cent. in another had evidence of infection.

Recognition of the symptoms and signs of neonatal septicaemia at an early stage, followed by adequate treatment, would greatly reduce neonatal mortality. The object of this paper, dealing with fifteen cases of neonatal septicaemia admitted to the Queen Elizabeth Hospital for Children, London, during 1946, is to point out the paucity of signs and symptoms in the majority of these cases, to stress the difficulty of diagnosis unless routine blood cultures are taken in all obscure illnesses of the newborn, and to describe the results of treatment.

Criteria of Diagnosis

Although the crucial test of the septicaemic nature of an illness is the isolation of the causative organism from the blood stream, there is no reason why a positive blood culture should invariably be required before the diagnosis of septicaemia is made. Strong presumptive evidence of septicaemia may be afforded by osteomyelitis, meningitis, or by multiple abscesses in the subcutaneous or deep tissues.

Etiology and Pathogenesis

The organisms commonly responsible for septicaemia in the newborn are staphylococcus, streptococcus, and *B. coli*; less frequently pneumococcus, meningococcus, pyocyaneus, proteus, paratyphoid, Gaertner, Klebs-Löffler bacilli, and monilia are encountered. In Dunham's (1933) series of thirty-nine cases, septicaemia was due to streptococcus in

fifteen cases, staphylococcus in eleven cases, *B. coli* in ten, pneumococcus in two, and pyocyaneus in one.

Infection may occur before birth, during delivery, or after birth.

(a) **Before birth.** Clifford (1947) recently reported three cases of maternal septicaemia in which positive blood cultures were obtained from the babies at birth. The organisms were β -haemolytic streptococcus, *B. coli*, and *B. Suipestifer*. Laffont and Mele (1926) reported a similar case.

(b) **During delivery.** Browne (1921) stressed the importance of inhalation of bacteria in the production of neonatal infections and stated that *B. coli* are frequently found in infection of the lungs. Gonorrhoeal ophthalmia and monilia infection may also be acquired during the infant's passage down the birth canal. Dodd (1947) has recently shown that the virus of epidemic diarrhoea of the newborn may be acquired in a similar manner. Infected maternal passages may thus be a potent focus from which organisms are transferred from mother to child.

(c) **After birth.** Obviously there is a risk of transference of organisms to the newly born from the nose, throat, and hands of the attendants, and through infected fluids given by feeding bottles. Entry of the organisms into the baby may occur via skin, umbilicus, mouth, and respiratory tract.

Clinical Features

Fifteen cases of septicaemia are reported, but two do not fall strictly into the neonatal period—their ages being forty-nine days and sixty-seven days on admission; they are included because the symptoms and signs were similar to those of babies admitted during the first four weeks of life. The cases are considered in groups, based upon the probable mode of entry of the organisms into the child's body.

Group A: Umbilical infection. There were six cases in this group, four were male and two female. The umbilicus appeared normal in two cases; in one case the cord was still attached at the age of three weeks and appeared puffy and inflamed; in the remaining three cases the umbilicus was sticky and surrounded by exudate, which in one case was blood-stained. All six cases had frequent fluid

stools, and in three vomiting also occurred. There was marked loss of weight in the absence of dehydration. In four cases the appetite was normal. Haemorrhages occurred in three cases, and jaundice in two. The liver was enlarged in only one case, and in no case was the spleen palpable. Pyrexia over 100° F. occurred in only one case. The white blood counts showed a wide variation, from 10,000 to 31,000 per c.mm., but a high proportion of primitive white cells was present in every case.

Blood culture was successfully undertaken in four cases, and resulted in the isolation of staphylococcus aureus (coagulase positive) in three cases and of staphylococcus albus in one.

Three cases recovered and three died. Post-mortem examinations confirmed the septicaemic nature of the disease process.

The umbilicus of the newborn used to be considered an important portal of entry for organisms capable of producing generalized sepsis (Cullen, 1916; Ritter von Reuss, 1920; Allen, 1930). The older literature describes only the advanced cases of septicaemia, showing jaundice, haemorrhages, and rigors, with obvious local evidence of the source of infection. Friedlaender (1927) showed that local lesions of the umbilicus may be absent, but inflammatory reaction and necrosis of the liver may be present in these cases. Morison (1944) described nine cases of umbilical sepsis and acute interstitial hepatitis.

The common clinical features in my six cases were frequent fluid motions, loss of weight, and primitive white cells in large numbers even when the total white count was normal. Enlargement of the liver and spleen was not observed.

Group B: Skin sepsis. The skin lesions in the three cases in this group were marked. One child had a brawny swelling about three inches in diameter in the left clavicular and pectoral region; the second showed an area of redness and desquamation in the scrotal area which spread rapidly on to the abdominal wall, and the right thigh was swollen as far as the knee; in the third case, multiple septic spots were present on the thigh, legs, buttocks, and scalp; the eyes showed purulent discharge.

Feeds were taken badly in all three cases, and two had frequent, fluid motions. There was loss of weight in two cases. The temperatures were higher than in group A, recordings of 100°, 103°, and 104° F. being obtained. Again no enlargement of liver or spleen was noted. Blood culture was positive in all three cases, staphylococcus aureus (coagulase positive) in two cases, and staphylococcus albus (coagulase positive) in the other case. Two cases died. Castle (1925), Campbell (1931), and Mount (1935) have reported similar cases.

Group C: Respiratory tract. Only two cases in this group were observed, and evidence of septicaemia was not conclusive. One child showed very few clinical signs of respiratory infection, the cry was vigorous, cyanosis was absent, and in the early

stages the respiration rate was normal. Fine crepitations were present at both lung bases. In the other child respiratory signs were obvious. There was cyanosis, the respirations were rapid, and pneumonic signs were present in both lungs. In both cases loose, offensive motions were present, and both had lost weight in spite of good appetite. Liver and spleen were not enlarged. Blood culture was unfortunately not performed. The organism responsible was staphylococcus aureus (coagulase positive).

Group D: Unknown portal of entry. There were four cases in this group. One case had a septic arthritis of the left knee, and 15 ml. of thick pus (staphylococcus aureus) were aspirated. Twenty-four hours after the onset of the swelling of the left knee, septic spots appeared on the skin of the left thigh and paronychia were present on the right index finger and left thumb. A radiograph of the left knee joint showed no abnormality. Blood culture was not performed because the organism had already been obtained from the left knee joint.

Two cases had osteomyelitis of the maxilla accompanied by severe oedema and cellulitis of the cheek. A radiograph showed no abnormality. Blood culture was not performed because the diagnosis was not in doubt. Clinically these three cases showed no general systemic disturbance, appetite was not impaired, and there was no loss of weight. All three cases responded quickly to treatment with penicillin.

The fourth case in this group was puzzling from the etiological viewpoint, for although the blood culture was positive for *B. coli*, no source of infection was found. The child was well until the sixth day of life, when she developed a temperature of 104° F. The following day a squint was noticed, but there was no vomiting or twitching. Lumbar puncture showed a sterile fluid. The mother had a temperature of 102° F. after delivery, and this returned to normal with sulphonamides. It is possible that the baby was infected from the mother. This child recovered following penicillin and sulphathiazole therapy.

Discussion

The clinical picture produced by septicaemia of the newborn differs considerably from that seen in older children or in adults. High temperature, rigors, and convulsions are exceptional. As Parsons (1944) has said, 'It is so entirely different from that usually associated with an acute infective illness that it may pass unrecognized by doctors, nurses and paediatricians without special experience.'

Infection in the newborn tends to be generalized, it is often not accompanied by fever, and it may be rapidly fatal within twenty-four hours. Spence (1941) states that the variety of pathogenic organisms is great, but they all tend to produce septicaemia,

with symptoms of drowsiness and disinclination for food, developing sometimes within twenty-four hours of birth, and with localization of the infection as a neonatal pneumonia; or, more typically, an infant may thrive well for a few days, then refuse foods, become drowsy or peevish, and develop a little diarrhoea. Cameron (1929) states that an estimate of the efficiency of the circulatory, respiratory and suction apparatus of the child will serve directly as a measure of the child's general well-being and vitality. Almost all forms of neonatal disorder show themselves as disturbances of one or more of these vital functions: and loss of appetite, with consequent loss of weight in the neonatal period, is probably the most constant sign of neonatal septicaemia. Paterson and Bodian (1946) state that the manifestations of septicaemia may be masked, and clinically may be slight, the infant merely being listless, apyrexial, or failing to take its feeds or thrive.

Since any infection in the newly born, however trivial, must be taken seriously if a high neonatal mortality rate is to be avoided, an evaluation of the clinical features is important.

Diarrhoea occurred in seven of Morison's (1944) nine cases of umbilical sepsis; Leopold (1944) and Brennemann (1945) consider it a constant feature, but in Dunham's (1933) thirty-nine cases no mention is made of it. Diarrhoea was a marked feature in ten cases of the present series, and was present in all six babies suffering from umbilical sepsis.

Loss of weight is an important sign. In Morison's (1944) series all cases showed an abnormal initial fall in weight, with no increase after the fourth day. Leopold (1944) states that the infant loses weight rapidly as a result of loss of appetite, vomiting, and loose stools. Of my fifteen cases, loss of weight occurred in ten, two were not weighed, and in three a gain in weight was recorded.

Jaundice is considered a very prominent finding by Leopold (1944), and Brennemann (1945) states that it is frequently present. It was present in fourteen out of thirty-nine cases recorded by Dunham (1933), including seven of eleven cases of staphylococcal infection and six out of ten cases of *B. coli* infection. In none of the thirteen cases of streptococcal septicaemia was jaundice present.

It occurred in only two cases of the present series; both had umbilical sepsis and the organism was a staphylococcus.

Bleeding occurred in ten of Dunham's (1933) series; in five of the six cases of staphylococcal infection, and in three of the seven infected by *B. coli*. It occurred in none of the fourteen streptococcal cases. Three of my patients showed a bleeding tendency, all were examples of umbilical sepsis and had a prolonged prothrombin time.

Fever was a feature of thirty-three of the thirty-nine cases recorded by Dunham (1933). In nine cases of the present series temperatures above 99° F. were recorded, and in six cases the temperature rose to over 100° F. Leopold (1944) stated that pyrexia may be absent, slight, or high. Brennemann (1945) considered that the temperature is not characteristic but that fever is usually present at some stage of the illness.

The spleen was felt in only one case of my series. It was palpable in nineteen of Dunham's (1933) thirty-nine cases, and Brennemann (1945) considered that it was nearly always enlarged.

The leucocyte count in nine of the eleven cases of the present series in which this examination was performed showed a range from 10,000 to 20,000 with an average count of 17,000 per c.mm. The other two cases had a leucocytosis of 31,000 and 32,000 per c.mm. A striking feature of all the counts was the high percentage of immature cells. Dunham (1933) recorded figures ranging from 4,000 to 50,000, and the cases with a leucopenia or a leucocytosis above 30,000 carried a poor prognosis. Both my cases with high white cell counts recovered. A differential white cell count to determine the number of immature cells is of more value than the total white cell count, for the absence of leucocytosis does not rule out infection, especially in the neonatal period.

Treatment

Penicillin was given to all the fifteen cases of my series, and seven received sulphonamides in addition. Treatment was started before the nature of the infection or the sensitivity of the organism to the drugs was known.

The dose of penicillin was 3,000 units per pound of expected body weight in twenty-four hours, given in divided doses intramuscularly, but this dose was increased if the organism proved relatively insensitive—for example one case was given 15,000 units per pound per day.

The sulphonamide dosage was approximately 0.25 g. per pound per day.

Bodian (1945) and Couper (1946) have advocated the combined use of penicillin and sulphonamide, and this is of particular value if the organism is *B. coli*.

The table records the details of therapy.

Florey (1944) originally suggested a standard adult dose of 1,000 units per pound in twenty-four hours, and Bodian (1945) employed the same dose in infants from four days to eleven and a half months old when treating twenty-one cases of bacteraemia due to staphylococcus aureus (14), β -haemolytic streptococcus (3), staphylococcus aureus, and β -haemolytic streptococcus (1), and staphylococcus albus (2). Fifteen cases (71 per cent.) recovered. Bodian (1946) found that the above dosage gave adequate blood levels of circulating penicillin when divided into four-hourly intramuscular injections in

TABLE
DETAILS OF THERAPY IN FIFTEEN CASES OF NEONATAL SEPTICAEMIA

Number of case	Penicillin		Sulphonamide			Organism	Result
	Units/lb./24 hrs.	Total (Units)	Preparation	G./lb./24 hrs.	Total (g.)		
1	1,000	30,000	Sulphathiazole	0.25	6.5	Staph. aureus	Died
2	3,000	189,000	Sulphamezathine	0.25	6.5	Staph. aureus	Recovered
3	15,000	320,000	Sulphamerazine	0.25	1.25	Staph. aureus	Died
4	6,000	30,000	—	—	—	Haem. strep.	Recovered
5	3,000	50,000	Sulphamezathine	0.5	6.0	Staph. aureus	Died
6	3,000	120,000	Sulphathiazole	0.5	9.5	Staph. albus	Recovered
7	1,000	108,000	Sulphadiazine	0.25	8.0	Staph. aureus	Died
8	3,000	216,000	—	—	—	Staph. albus	Recovered
9	2,000	10,000	—	—	—	Staph. aureus	Died
10	3,000	20,000	—	—	—	Staph. aureus	Died
11	3,000	30,000	—	—	—	Staph. aureus	Died
12	3,000	390,000	—	—	—	—	—
		and 100,000 into joint.	—	—	—	Staph. aureus	Recovered
13	3,000	720,000	—	—	—	Staph. aureus	Recovered
14	3,000	324,000	—	—	—	Staph. aureus	Recovered
15	3,000	243,000	Sulphathiazole	0.25	20.0	B. coli	Recovered

full-term babies and six-hourly in premature infants. Allen (1946) suggested a dose of 1,500 units per pound in twenty-four hours in cases of neonatal sepsis; no penicillin blood levels were undertaken. Couper (1946) suggested a total of 25,000 units in twenty-four hours in divided doses irrespective of weight.

Buchanan (1946) found that 1,000 units per pound in twenty-four hours was an inadequate dose, but that 2,000 units per pound in twenty-four hours was adequate. However, to allow for variable sensitivity and a margin of safety she advocated a dose of 4,000 units per pound in twenty-four hours given by intramuscular injections three-hourly. By employing still higher doses (5,000 units per pound in twenty-four hours) at six-hourly intervals an adequate blood level and satisfactory response to treatment was observed.

It is doubtful whether the blood level of penicillin commonly accepted as desirable must be maintained throughout the entire twenty-four hours, and I suggest that 3,000 units per pound in twenty-four hours given by six-hourly intramuscular injections will be found effective. Sulphonamides should always be given in addition, at least until the nature of the organism and its sensitivity has been determined.

The results of treatment of these fifteen cases are not impressive, only eight cases surviving. In most cases chemotherapy was started within an hour of admission to hospital, and in dosage which, by accepted standards, could be regarded as adequate.

Summary

1. Fifteen cases of neonatal septicaemia seen at a children's hospital in London during 1946 are

reported, with clinical findings and pathological investigations.

2. The infrequency of diagnostic clinical findings is stressed. Loss of appetite, failure to gain weight (or weight loss), and diarrhoea are common findings. The temperature is rarely raised above 100° F., jaundice is infrequent, and a palpable spleen is rare. The level of the white blood count is not of value in diagnosis, but the high percentage of immature cells is of considerable importance.

3. Blood culture is an important investigation in a newborn baby who fails to gain weight but in whom abnormal clinical signs are minimal or absent.

4. The treatment suggested is a minimum dosage of 3,000 units of penicillin per pound expected body weight every twenty-four hours, in six-hourly doses intramuscularly; together with 0.25 g. of a sulphonamide per pound per twenty-four hours. This combined treatment should be started before the results of investigations are known.

5. The results of treatment were disappointing. There were eight deaths.

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