ORIGINAL ARTICLE

# Investigations on the Aetiology and Antibiotic Management of Neonatal Septicemia

*by*

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**Abstract**

*This is a prospective study aimed in identifying the latest aetiological factors of neonatal sepsis in Dr. Cipto General Hospital, Jakarta, and investigating the efficacy of antibiotics treatment especially with ceftriaxone.*

*This study revealed that the present main causative micro organisms are as follows: Pseudomonas, Klebsiella and E. coli. The case fatality rates being: (1) Standard treatment with ampicillin and gentamycin: 80.9%, (2) Standard treatment with consomittant ceftriaxone: 20%, (3) Ceftriaxone: 9,52%.*

*It seems that in facing neonatal septicemia, the initial antibiotic should be the third generation cephalosporine. The second choice is chloramphenicol. However, the causative agent and the sensitivity test should be monitored regularly.*

## Introduction

Neonatal sepsis is a very serious disease with a very high mortality rate. Problems are in the early detection, early and adequate treatment, as well as prevention.

The causative agents changed with time, procedure of nursing, and season. In our unit, in the rainy season the most common cause is Salmonella species. Careful and periodic microbiological monitoring is mandatory to have a rational management.

In our situation where we care neonates from the low socio economic class and where funds and forces are very limited, prevention must be a priority. However this is not always properly done and we always have cases of neonatal sepsis despite antiseptic and aseptic procedures, and rooming-in program.

When we are facing clinical sepsis, the question is how to overcome this condition with available but very effective and reasonable priced antibiotics.

The routine initial treatment against neonatal sepsis in our unit is a combination of ampicillin and gentamycin which is based on the clinical and microbiological monitoring in 1981. The alternative is the administration of third generation cephalosporine such as cefotaxime which has to be given twice daily intravenously or intamuscularly.

Ceftriaxone is a relatively new third generation cephaslosporine developed by ROCHE Research in Basle with a long elimination half-life, good penetration, effective against gram-negative as well as gram-positive bacteria, high beta lactamase stability and without metabolism in the body. It has been tried successfully in man and animal, and being marketed as Rocephin in Indonesia.

*Hypothesis*

The hypothesis are : (1) The current aetiology of neonatal sepsis differs with the previous aetiology. (2) The initial antibiotic administered should be changed accordingly due to the changes in sensitivity of the microorganisms. (3) A new third generation cephalosporine, i.e. ceftriaxone, is effective in the treatment of neonatal sepsis.

The objective of this investigations are : (1) To find out the present aetiological factors of neonatal sepsis in our unit and to have the picture on sensitivity of the microorganisms to various available antibiotics. (2) To describe the clinical experience with the treatment of neonatal sepsis with ceftriaxone compared with the standard antibiotics. (3) To formulate the first line antibiotic that should be given in clinical diagnosis of neonatal septicemia, while waiting for the microbiological examination results.

## Materials and Methods

This is a prospective study covering all infants delivered in the Dr. Cipto Mangunkusumo Hospital during the year 1986. During that year 4112 liveborn babies were nursed in the neonatal unit. Out of these infants 434 cases of infections were detected and from these, 165 were diagnosed as clinical sepsis.

Clinical diagnosis of sepsis is based on criteria adopted by our unit that have been described elswhere (Monintja et al., 1981). Upon the establishment of diagnosis of clinical sepsis, venous blood was withdrawn and cerebrospinal fluid was taken for microbiological examination.

Once the blood and cerebrospinal fluid had been taken the standard usual treatment of ampicillin and gentamycin was given until the result of cultures and sensitivity test were available.

There were three groups of patients according to the methods of treatment, namely: (1) group treated with standard treatment with gentamycin in combination with ampicillin; (2) group with initial treatment with ampicillin and gentamycin then switched to ceftriaxone due to deterioration of the disease within 72 hours; (3) group treated with ceftriaxone only.

Ceftriaxone was administered intravenously with a dose of 50 mg per kg body weight per day given as a single dose for ten consecutive days. Ampicillin was given intravenously with a dose of 200 mg per kg bodyweight per day divided into four doses. Gentamycin was given also intravenously and the dose was 6 mg per kg bodyweight per 24 hours divided into two doses.

*Method of evaluation :*

The evaluation of efficacy of the drugs are as follows: (1) good, if the infant recovered clinically within 7 days of treatment; (2) satisfactory, if the infant is still alive after 14 days of treatment; (3) failed, if the infant died within 7 days after initiation of treatment.

*Laboratory examinations included :*

(1) Peripheral blood examinations on the first day before initation of treatment and on the seventh day of treatment.
(2) Blood and cerebrospinal cultures prior to, and after seven days of treatment.
(3) Other examinations as indicated by clinical conditions, such as SGPT, SGOT, renal functions etc.

Microbiological examinations were done in the Department of Microbiology and the other laboratory examinations were done by the Department of Clinical Pathology, Medical School, University of Indonesia.

Checklist of vital signs and signs of complications were provided for the nurse to observe periodically.



## Results

The result of the treatment are described on the following tables.

Table 1 : *Incidence of clinical sepsis at the neonatal unit, Dr. Cipto Mangunkusumo General Hospital, Jakarta (1986)*

| | |
|---|---|
| Number of liveborn babies in 1986 | 4112 |
| Number of infection cases | 434 |
| Number of clinical septicemia | 165 |
| Number of blood culture examinations | 106 |
| Number of positive blood culture | 62 |

Table 2 : *Incidence of neonatal sepsis in several wards*

| | number of patients | no of septicemia cases | percentage |
|---|---|---|---|
| Neonatal intensive care unit | 149 | 17 | 11.40 |
| Neonatal special care unit | 1545 | 143 | 9.25 |
| Rooming-in unit | 2418 | 5 | 0.206 |
| Total | 4112 | 165 | 4.01 |

Table 3 : *Results of treatment with ceftriaxone only*

| Number of cases | Number of positive blood culture | Number of negative blood culture | Results of treatment | | |
|---|---|---|---|---|---|
| | | | Good | Fair | Failed |
| 40 | — | 19 | 17 | 1 | 1 |
| — | 21 | — | 15 | 4 | 2 |
| Total 40 | 21 | 19 | 32 | 5 | 3 |

Table 4 : *Results of treatment with ampicillin dan gentamycin*

| Number of clinical sepsis | Number of blood culture | | | Results of treatment | | |
|---|---|---|---|---|---|---|
| | Positive | Negative | Not done | Good | Fair | Failed |
| — | 21 | — | — | 3 | 1 | 17 |
| 94 | — | 15 | — | 3 | 1 | 11 |
| — | — | — | 58 | 13 | 5 | 40 |
| Total 94 | 21 | 15 | 58 | 19 | 7 | 68 |

Table 5 : *Results of treatment with standard + concomittant ceftriaxone*

| Number of cases | Number of blood culture | | Results of the treatment | | |
|---|---|---|---|---|---|
| | Positive | Negative | Good | Fair | Failed |
| — | 20 | — | 10 | 6 | 4 |
| 31 | — | 11 | 5 | 3 | 3 |
| Total 31 | 20 | 11 | 15 | 9 | 7 |



Table 6 : *List of patients with positive blood culture treated with ceftriaxone only*

| Case no | Pathogen | Age (days) | Weight (grams) | Complications | Clinical outcome |
|---|---|---|---|---|---|
| 1. | E. Coli | 4 | A | | Recovered |
| 2. | Pseudomonas SP | 6 | C | | Recovered |
| 3. | Pseudomonas | 13 | B | | Recovered |
| 4. | E. Coli | 2 | C | | Recovered |
| 5. | Stretococcus A | 14 | C | | Recovered |
| 6. | KL. pneumonia | 5 | D | | Recovered |
| 7. | Pseudomonas SP | 9 | B | Meningitis | Recovered |
| 8. | Pseudomonas SP | 15 | A | | Recovered |
| 9. | Pseudomonas SP | 10 | D | | Recovered |
| 10. | Pseudomonas SP | 18 | A | | Recovered |
| 11. | Pseudomonas SP | 15 | A | | Recovered |
| 12. | Pseudomonas SP | 18 | C | | Recovered |
| 13. | Pseudomonas SP | 8 | D | | Recovered |
| 14. | Pseudomonas SP | 3 | C | Meningitis | Recovered |
| 15. | E. coli | 5 | D | | Died |
| 16. | Pseudomonas SP | 8 | C | | Recovered |
| 17. | Pseudomonas SP | 12 | C | | Recovered |
| 18. | Pseudomonas SP | 11 | B | | Recovered |
| 19. | Pseudomonas SP | 5 | C | | Recovered |
| 20. | KL. pneumonia | 23 | C | | Died |
| 21. | S. typhy murium | 5 | C | | Recovered |

A = BW 3000 GM and over
B = BW 2500 - 2999 GM
C = BW 2000 - 2499 GM
D = BW 1500 - 1999 GM

Table 7 : *List of patients with initial standard treatment and concommittant ceftriaxone with positive blood culture*

| Case no | Pathogen | Age (days) | Weight (grams) | Complications | Clinical outcome |
|---|---|---|---|---|---|
| 1. | Pseudomonas SP | 8 | C | | Recovered |
| 2. | Pseudomonas SP | 14 | A | Meningitis | Recovered |
| 3. | Pseudomonas SP | 12 | C | | Recovered |
| 4. | Pseudomonas SP | 8 | C | | Recovered |
| 5. | KL. pneumonia | 14 | C | | Recovered |
| 6. | KL. pneumonia | 17 | C | Meningitis | Recovered |
| 7. | Pseudomonas SP | 3 | C | | Died |
| 8. | Pseudomonas SP | 10 | C | | Recovered |
| 9. | Pseudomonas SP | 10 | A | | Recovered |
| 10. | Pseudomonas SP | 8 | C | | Recovered |
| 11. | Pseudomonas SP | 2 | C | | Recovered |
| 12. | Pseudomonas SP | 15 | C | | Recovered |
| 13. | Pseudomonas SP | 8 | C | | Recovered |
| 14. | Enterobacter | 12 | C | | Recovered |
| 15. | Pseudomonas SP | 8 | C | | Recovered |
| 16. | Serratia M | 5 | C | | Died |
| 17. | Pseudomonas SP | 13 | C | | Recovered |
| 18. | Serratia M | 9 | C | | Recovered |
| 19. | Pseudomonas SP | 5 | D | | Died |
| 20. | Pseudomonas SP | 3 | C | | Died |

A = BW 3000 GM and over
B = BW 2500 - 2999 GM
C = BW 2000 - 2499 GM
D = BW 1500 - 1999 GM



Table 8 : *Percentage of sensitivity of the recovered microorganisms to available antibiotics*

| Antibiotics | Microorganisms | | |
|---|---|---|---|
| | Pseudomonas species | E. coli | Klabsiella species |
| | % | % | % |
| 1. Gentamycin | 10.71 | 66.66 | 40 |
| 2. Ampicilline | 7.14 | 33.33 | — |
| 3. Tetracycline | 10.71 | 66.66 | 40 |
| 4. Chloramphenicol | 92.86 | 66.66 | 40 |
| 5. Erythromycin | 10.71 | 66.66 | — |
| 6. Streptomycin | — | 66.66 | 20 |
| 7. Cotrimoxazole | 92.86 | 66.66 | 40 |
| 8. Cloxacillin | 32.14 | — | — |
| 9. Sulbenicilline | 85.71 | 66.66 | — |
| 10. Penicilline G | — | — | — |
| 11. Netromycine | 14.29 | 66.66 | 80 |
| 12. Cefotaxime | 100. | 100. | 100. |
| 13. Lincomycin | — | — | — |
| 14. Clindamycine | — | — | — |
| 15. Ceftadine | 100. | 100, | 100. |
| 16. Ceftriaxone | 100. | 100. | 100. |
| 17. Tobramycin | 21.42 | 100. | 80 |
| 18. Cefoperazole | 100. | 100. | 100. |
| 19. Cefmetazole | 100. | 100. | 100. |

Table 9 : *List of possible side effects on patients treated with ceftriaxone*

| | |
|---|---|
| Oral thrush | 18 cases |
| Jaundice/exageration of jaundice | 2 cases |
| Skin rash | 2 cases |
| Thrombocytopenia | 3 cases |
| Leukopenia | 1 cases |

The observation showed that infection still played a great role in neonatal morbidity in our unit. The incidence of septicemia was 3.98% and the incidence of overall infection was 10.55%. The highest incidence of septicemia was in the neonatal intensive care unit followed by in special care unit while the lowest was in the rooming-in unit, being 0.16% only.

The most important problem in managing septicemia in our unit was the establishment of microbiological diagnosis due to limited funds available. Without the trial of using ceftriaxone, only 38% of clinical sepsis was subjected to microbiological examination. Most of the cases were diagnosed clinically using our clinical criteria.

The result of standard treatment which was based on 1982 informations was not satisfactory. This was due to the changing of microorganisms pattern, and also to the changing of efficacy of the antibiotics. The mortality rate of the group with standard treatment was 72.34%, while the mortality rate of cases treated with ceftriaxone was 7.5% and the group treated initially with standard treatment later on switched to ceftriaxone was 22.58%. It is ethically not proper to analyze the difference statistically but clinically we are sure that ceftriaxone gave a very good results in lowering mortality rate in our septicemia cases. The results of sensitivity tests as described in table 9 showed that in vitro the effect of ceftriaxone was the same as other third generation cephalosporines. The only difference was the other cephalosporines were not as effective as ceftriaxone to Salmonella species (Monintja, to be published).

Pseudomonas species emerged as the main causative agent followed by Klebsiella. It is also interesting that there was a comeback of E.coli, while Salmonella species which had been the main causative agents in previous years only discovered in one case.

There were two cases of Serratia marcescens; one case died and one survived with the initial standard treatment and later on changed to ceftriaxone. The agent was a newcomer in our unit and had never been recovered before even though we had looked for it.

It is strange that we found no beta Streptococcus in our series. It might be due to the rigid prophylactic treatment with ampicillin in our suspected cases with infection.

The side effects are described in table 9 which shows that there were no notable side effects except jaundice and thrombocytopenia which could be caused by the disease itself.



## Discussion

Neonatal septicemia is a severe disease in the newborn with a very high mortality rate. Naturally we tried hard to prevent it by all means. From table 2 we can clearly conclude that rooming-in is one of the best method to prevent infection espècially neonatal sepsis. With rooming-in the infants are exposed to their natural environment and also breast feeding is promoted.
In the neonatal intensive care unit neonatal sepsis is mostly due to nosocomial infections. It is very sad indeed to observe those babies died not from their primary disease but from nosocomial infections. The use of potent antibiotics is justified because without it the patient will surely die. The problem is how to use the antibiotics rationally.

Besides prevention, the problems of neonatal sepsis are :

(1) How to detect it in the early stage.
(2) What kind of antibiotic to be given initially.
(3) What diagnostic procedures could be done.
(4) Are there any complications.
(5) The epidemiology.

To detect it we have adopted the clinical criteria which were described elswhere. Amongst the bedside laboratory criteria which could support the diagnosis, thrombocytopenia, positive CRP and change in leucocyte morphology are statistically significant. Our experience with our clinical criteria does help us very much in screening neonatal sepsis; the percentage of positive blood culture being 60%. Of course there are many factors which may influence the result of blood culture; the figure we offered is from average daily condition. This is rather low compared to the figure of Ranuh et al. (1982) with 83% of positive blood culture.

Facing a very severe infection, one would like to use a very potent, save and reasonable priced antibiotic. Ceftriaxone does not meet all of those criteria, but through coopertion with Roche we were able to use it on the group II and group III patients. The mortality rates of both groups are far below the mortality rate of those with standard antibiotics.

Ceftriaxone is a new third generation cephalosporine with a high degree of beta lactamase stability. Antibacterial activity of ceftriaxone according to our observation, is more or less the same as other third generation cephalosporines, except to Salmonella species. Previous studies in animal and human being using ceftriaxone has shown that the drug was exceedingly active against major pathogens in bacterial sepsis and meningitis in neonates, infants and children (Mc Cracken et al., 1982; Schaad et al., 1981; Martin, 1983). Ceftriaxone has a considerable penetration into cerebrospinal fluid in experimental animals (Marchou et al., 1980; Schaad et al., 1981). Ceftriaxone has a long elimination half-life good cerebrospinal penetration and tissue distribution, and in addition, the drug is completely absorbed from tissues (Chadwick et al., 1983; Mc Cracken et al., 1982; Steele et al., 1983; Patel et al., 1981). This drug has been tried succesfully with a dose of 50 mg per kg bw/24 hours in severe infections in children and neonate with good results by Congeni et al. (1985) and Martin (1983). Contrary to the report of Congeni et al. (1985) our results with Psedomonas species were excellent.

Looking back at the results of ceftriaxone treatment in our series, there was a mortality of 7.5% in clinical sepsis and 9.5% in proven sepsis. In patients with initial standard treatment and then switch-

ed to ceftriaxone, the mortality rate in clinical sepsis was 22.58% and mortality rate in proven septicemia was 20%. Those observations showed that ceftriaxone indeed has an outstanding effect against neonatal sepsis and the sooner it is given the better the results.

There were no significant side effects except 2 cases with exageration of jaundice on the third day of administration. Another possible side effect is thrombocytopenia or rather deterioration of thrombocytopenia. There were two cases with mild skin rash that disappeared without discontinuation of the drug. There were 2 cases with leukopenia but we are not sure whether it was due to the treatment or due to the infection. Oral thrush developed is 18 cases requiring treatment with nystatin and recovered during hospitalization.

Our experience with ceftriaxone showed that this antibiotic, like other third generation cephalosporines, is one of the drug of choice in treating neonatal septicemia with the present microbiological spectrum. Ceftriaxone offers more convenience because it is administered once a day with a dose of 50 mg per kg body weight parenterally. The other advantage is that ceftriaxone has a considerable cerebrospinal fluid penetration. There were 4 cases with meningitis at the start of the treatment and all of them recovered.

## Conclusion

The results of this investigations are :

(1) The present aetiology of neonatal sepsis in our unit is quite different compared with the aetiology found in 1981.
(2) Ceftriaxone is a potent drug in treating neonatal sepsis.
(3) The first initial antibiotics used when we are facing clinical sepsis while waiting for microbiological examination results should be third generation cephalosporines.

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