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Exchange Transfusion in Neonatal Septicemia

Clinical and Immunological Results in Vivo and in Vitro

Summary: Exchange transfusion of fresh heparinised whole blood was evaluated as a means of supplying "opsonins" and blood cells and lessening the high mortality of bacterial septicaemia in neonates. Pre-transfusion, post-transfusion, donor, and adult control sera were examined for the presence of "opsonic" activity against *Staphylococcus aureus* (A 502 strain) in a standardized bactericidal in vitro assay. In all 23 neonates opsonic activity rose significantly following exchange transfusion. The results are discussed in the light of immuno-therapeutic trials in systemic bacterial infections as a supportive measure of antimicrobial therapy.

Zusammenfassung: Austauschtransfusion zur Behandlung der Neugeborenensepsis. Klinische und immunologische Untersuchungsergebnisse bei in vivo und in vitro Studien. Die Austauschtransfusion mit frischem heparinisiertem Blut wurde als Behandlungsmethode bei der Neugeborenensepsis eingesetzt, um durch die Gabe von „Opsoninen" und Spender-Blutzellen die hohe Letalität der Erkrankung zu senken. Das Serum von Neugeborenen vor und nach der Austauschtransfusion, sowie vom Spender und einer erwachsenen Kontrollperson wurde auf ihre opsonisierenden Eigenschaften gegen des *Staphylococcus aureus*-Stamm A 502 in einem standardisierten Bakterien-Abtötungs-Test in vitro untersucht. Bei 23 untersuchten Neugeborenen stieg die opsonisierende Aktivität nach der Austauschtransfusion signifikant an. Diese Ergebnisse werden im Zusammenhang mit immunotherapeutischen Behandlungsversuchen als unterstützende Maßnahmen der Chemotherapie bei systemischen bakteriellen Infektionen diskutiert.

Introduction

The treatment of neonatal septicemia is still a major problem for the infectious disease pediatrician (1–3).

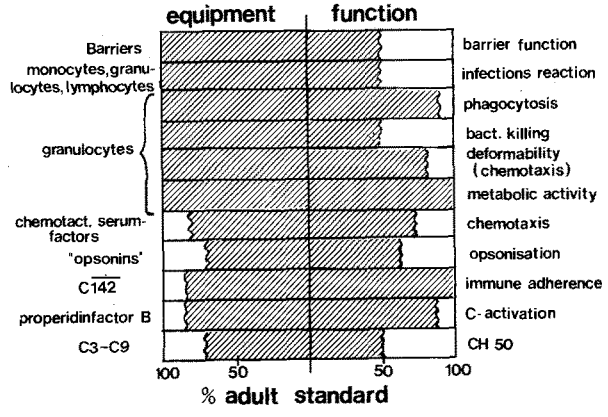

Figure 1: Equipment and function of the neonate's nonspecific anti-infectious immune systems compared to adults.

Since data on the incidence, exposure to infective agents, change in the spectrum of causative agents, and clinical outcome of septicemia in neonates have already been analysed in detail (4, 5), the high susceptibility to bacterial infections in this age group remains to be explained. The neonate, and to a greater extent the premature neonate, is born "immunological virgins" (Figures 1 and 2). Virginity in this respect means that they have almost the complete equipment of nonspecific and specific immune factors to fight infections as compared to adults, with the exception of most of the complement components and specific antibodies, mainly of the IgM and IgA type. However, the

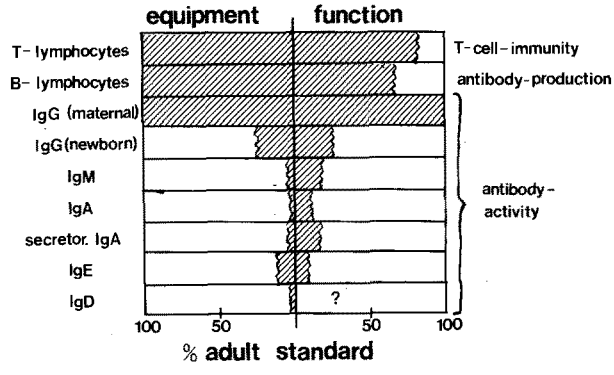

Figure 2: Equipment and function of the neonate's specific anti-infectious immune systems compared to adults.

functional potency of these compartmentally subdivided, but intensively cooperating systems, is deficient. This deficiency is due to lack of antigenic experience, and to postnatal adaptation to an antigenically highly agressive environment (6, 7). The only exception is made by the passively transferred maternal IgG-antibodies that are protective from the very first moment of postnatal life but have a restricted antibacterial spectrum. If, in addition, reanimation and other measures of modern intensive care must be undertaken in high-risk-neonates, the immunological maturation process of the newborn can be significantly disturbed in various ways, thus increasing the disposition to bacterial infections (8).

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Immunotherapy with Exchange Transfusion

Taking into account the physiological immunodeficiency of the neonate and the additional immunosuppressive effects of intensive care therapy, we started in 1968 performing fresh-blood exchange transfusions (ET) as supportive immunotherapy in the treatment of neonatal septicemia (9, 10).

Table 1: Summary of 167 cases of neonatal septicemia treated by chemotherapy and exchange transfusion (ET) as reported in the literature, compared to a group of 208 neonates with bacterial septicemia treated exclusively by chemotherapy

References	No ET		With ET		Follow-up
	survived	died	survived	died	
(35)	0	11	7	4	1970-71
(11)	11	24	22	7	1972-74
(36)	8	5	5	5	1974
(37)	n. i.	n. i.	11	13	1974-75
(39)	7	10	13	6	-1978
Belohradsky	60	72	34	40	1968-77
TOTAL	86 (41%)	122 (59%)	92 (55%)	75 (45%)	

Table 1 summarizes 167 published cases of neonatal septicemia treated by ET and chemotherapy compared to a group of 208 newborns treated exclusively by chemotherapy. Our own study included patients from both the pediatric surgery clinic and the neonatal intensive care unit. At first sight, treatment by ET does not seem significantly to reduce the high mortality rate (59% in nontransfused versus 45% in transfused patients). *Salle* et al. are the only authors to report an encouraging positive effect in a controlled study (11). Our own results can be interpreted in detail as follows. From 1968 to 1975 ET was the therapeutic measure of ultima ratio in neonates with septicemia in whom chemotherapy had failed. During that period the mortality rate for a total of 41 patients was 63% (26/41). Since 1975 ET has also been adopted for suspected septicemia (before availability of bacteriological results) on the basis of anamnestic, clinical and laboratory data (8). During this observation period only 42% (14 out of 33 patients) died despite treatment by ET, compared to 55% (72 patients out of 132) who did not undergo ET.
However, when comparing two different follow-up intervals a statistical evaluation cannot be performed. We therefore tried to explain the positive effect of ET. Theoretically, two general mechanisms can be considered: a "washout" or dilutionary effect upon offensive agents in the neonatal circulation, and the transfer of cells or cell-products from the donor's blood to the patient (Table 2). These factors may also explain the increasing interest in ET as a therapeutic tool in various clinical situations, such as severe burns, respiratory distress, hepatic coma, Reye's syndrome, inborn metabolic diseases, inborn coagulopathy etc. (8).

Table 2: General mechanisms of exchange transfusion

„Wash out" or dilution:	toxins, bilirubin, bacteria, blood corpuscles, blood-cell-products (e. g. anti-Rh-antibodies), immune complexes, metabolic by-products etc.
Transfer or substitution:	blood-cells, antibodies, complement components, coagulation factors etc.

Immunologically, viable immunocompetent donor T-lymphocytes may transfer cell-mediated immunity via T-cell mediators. The helper effect of T-cells on antibody-forming B-lymphocytes may also constitute one of the therapeutic principles of ET. However, most important and experimentally proven is the substitution of humoral factors, such as antibodies of the IgM-class and complement components, which are responsible for the opsonising serum-activity, neutralisation and binding of bacterial toxins, opsonisation, phagocytosis and thereby intracellular killing of bacterial invaders. The benefit from transferred granulocytes (or thrombocytes) is limited by the small number and the short half-life time of HLA-nonidentical cells. The positive effect of ET in neonates on oxygen transport and release to the tissues has been extensively reported by others (12), likewise the influence on the coagulation system (13, 14) (Table 3).

Table 3: Theoretical and proven benefits of ET in neonatal septicemia, especially regarding the influence on the neonate's immune systems.

Compartment	Principle	Effect
T-lymphocytes	T-cell-mediators	T-cell-information?
B-lymphocytes	IgG-,IgA-,IgM-antibodies	toxin-binding, complement activation, opsonisation
Complement	chemotactic factors, "opsonins"	chemotaxis, phagocytosis, opsonisation
Granulocytes	phagocytes	phagocytosis, intracellular killing
Monocytes	T-B-cell-contact?	initiation of antibody response?
Thrombocytes	hemostasis	substitution during intravascular coagulation
Erythrocytes	ATP; HbA, 2, 3-DPG	oxygen-transport and tissue-release
Coagulation system	coagulation factors	substitution

Serum-Dependent Opsonic Activity Before and After Exchange Transfusion in Septicemic Neonates

In order to find out whether one of the therapeutical mechanisms mentioned could be demonstrated in vitro we conducted the following experiments.
In a bactericidal assay (15) we cultured "indicator"-granulocytes from normal adults together with sera from different neonates (taken before and after ET), from healthy control persons and from the blood donor for the ET, together with a constant amount of a defined strain of *Staphylococcus aureus* (A 502). After one and two hours respectively, we determined by a bacteriological technique the amount of bacteria that were phagocytosed and killed within the granulocytes under the opsonising influence of the different sera (Figure 3). The results for 16 neonates, treated by ET for bacterial septicemia are demonstrated in Table 4.
Serum levels of IgG, IgM, IgA and C3 were determined by radial immunodiffusion and the results are given in Table 5.

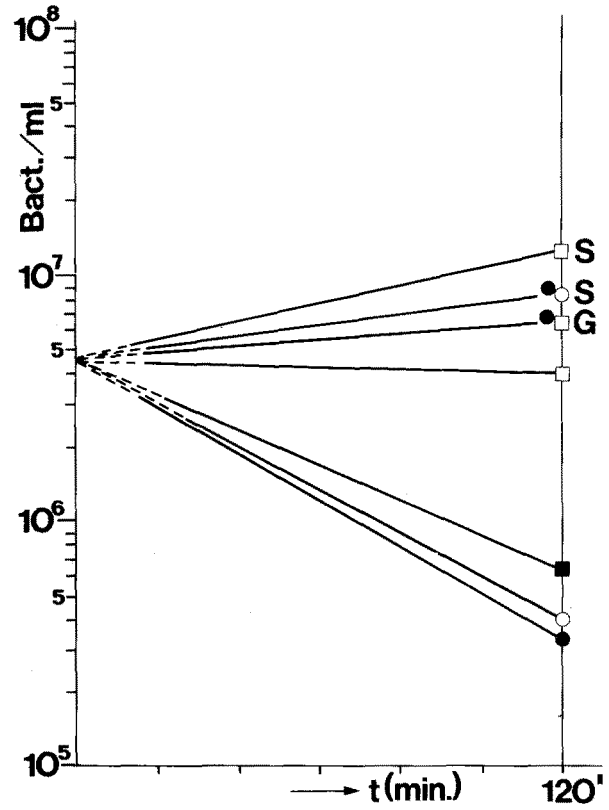

Figure 3: Intracellular killing of bacteria (S. *aureus* A 502) in vitro after a 120 minute incubation period.

experimental controls
- □ S = serum from neonate *before* ET, without granulocytes
- ● S = serum from healthy adult without granulocytes
- ○ S = serum from blood donor for ET, without granulocytes
- □ G = granulocytes from blood donor, without serum
- ● G = granulocytes from adult, without serum
- □ = serum from neonate *before* ET, with granulocytes from healthy adult (indicator granulocytes)
- ● = serum from adult with autologous granulocytes
- ○ = serum from blood donor with adult granulocytes
- ■ = serum from neonate *after* ET, with adult granulocytes

Discussion

It is known that bacterial endotoxin may activate the alternate pathway of complement through properdin → C3 → Factor D (=GBGase) → Factor B (16), but until now we have had no data demonstrating any influence of ET on this process.
Possible hazards emerging from the immuno-manipulating ET should, of course, be neither overlooked nor overemphasised. In general, the known side-effects of blood transfusion or exchange transfusion in neonates can be considered as minimal. The overall mortality of ET in 1785 neonates, mostly performed for Rhesus-incompatibility with hyperbilirubinemia, hemolysis, and anemia, was 1.3% (8, 17–21) (Table 6).
Immunological hazards are also exceptional (Table 7). Graft-versus-host reactions have been reported in the literature in 11 neonates following exchange transfusions, three of whom had severe combined immunodeficiency, thus explaining the pathomechanism of this rare complication (8, 22–30).

Table 4: Results of the serum-dependent intragranulocytic bactericidal activity in 16 cases of neonatal septicemia treated by fresh-blood ET. After ET the ability of the neonate's sera significantly to kill higher numbers of bacteria (*S. aureus* A 502) can be demonstrated.

	Bacterial colonies t_0	colonies t_1 (120 min)	△ Bacterial colonies (120 min)	% Bactericidal effect (120 min)
Before ET (n=16)	210 (±152)	244 (±152)	+ 34 (±47)	+ 21 (±89)
After ET (n=16)	200 (±71)	75 (±43)	−125 (±62)	− 41 (±67)
Blood donor (n=16)	212 (±86)	36 (±25)	−176 (±88)	− 80 (±12)
Control (n=16)	201 (±58)	21 (± 9)	−180 (±56)	− 89 (± 4)

$p < 0{,}001$

Table 5: Serum levels of IgG, IgM, IgA and C3 in 16 neonates before and after ET for bacterial septicemia, compared with blood donor for the ET. Serum protein levels determined by radial immunodiffusion and expressed in mg/dl (mean and standard deviation).

	IgG	IgM	IgA	C3
Before ET (n=16)	455 (±390)	34 (±39)	21 (±21)	21 (±19)
After ET (n=16)	652 (±198)	100 (±39)	134 (±35)	40 (±19)
Blood donor (n=16)	752 (±271)	129 (±60)	181 (±57)	48 (±18)

Table 6: Possible side-effects of blood transfusion or exchange transfusion.

Hemolysis
Leukocyte agglutinins
Posttransfusion syndrome
Posttransfusion purpura
"Allergic" reactions
(anti-IgA- and anti-Gm-antibodies)
Pyrohenic reactions
Transfer of infections
(e. g. hepatitis, CMV, syphilis)
Air embolism
Venous and arterial catheter complications
Electrolyte imbalances (ACD-blood)
Retrolental fibroplasia

Table 7: Potential immunological hazards following exchange transfusion in neonates.

Compartment	Principle	Effect
T-cells	non-self-recognition	gvh-disease
B-cells	feed-back-suppression	impaired antibody synthesis
Granulocytes	HLA-sensitisation	shortened life-time
Monocytes	unknown	unknown
Complement	unknown	unknown

A feed-back suppression of the infant's antibody production (e. g. following active immunisation during the first year of life) has been demonstrated in some of our long-term follow-up studies on 25 patients, one to six years after ET (31), as well as by others (32). But this transitory deficient antibody formation was not correlated with an increased susceptibility to infections.

When asked about therapeutic alternatives to the ET, one must be aware that fresh-frozen plasma of fresh blood in adequate amounts (33) carries the risk of circulatory overload; that commercially available immunoglobulin preparations for intravenous use do not contain sufficient amounts of IgM or complement components; and that IgM-enriched immunoglobulins for intramuscular use do not reach a peak in the circulation until the second to third day after the injection.

Table 8: Speculative suggestions on improvement of prevention and treatment of neonatal bacterial infections.

- antenatal antibacterial vaccination of the mother, transplacental passage of IgG-antibodies to the fetus;
- antibacterial hyperimmune serum against bacteria responsible for nosocomial infections;
- bacterial decontamination of neonate and isolation under gnotobiotic conditions (40);
- "prophylactic" exchange transfusion (e.g. prematures with major congenital malformations and high risk for infections);
- immunostimulation (e.g. levamisole, thymosin, transfer factor)
- immunosubstitution ("opsonin-concentrate", T-cell-mediators?, helper-T-cells?)
- genetic manipulation of bacterial R-factors

Conclusion and Speculations

The positive effect of ET in neonatal septicemia is based on a fortunate clinical observation. In 1957, *Betke* and *Keller* performed ET in two severely ill neonates suffering from hyperbilirubinemia which was not caused by a detectable incompatibility in the ABO- or Rh-system (34). Bacteriological findings later demonstrated bacterial systemic infection which was successfully treated by chemotherapy and possibly by ET in addition.

Since eradication of bacteria and infections would be unrealistic (and harmful in some respects) some more futuristic therapeutic speculations may be allowed (Table 8).

The ultimate solution of the problem of iatrogenic-induced or nosocomially acquired neonatal infections will hopefully be derived from information emerging on host defense mechanisms in the neonate.

Acknowledgements

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Discussion

Allison: Do you separate cells very efficiently or irradiate?

Belohradsky: No, we do not irradiate because there are so few cases where graft-versus-host reaction has been observed[1]).

Simon: On which day of the disease did you perform the exchange transfusion, and was the clinical outcome dependent on the timing?

Belohradsky: During the last two years we usually performed exchange transfusion before we had the bacteriologic diagnosis of septicaemia. Sometimes the course of the disease can be so fulminant in a few hours that we really did not have the choice of waiting for the bacteriological results. When the suspicion of a systemic infection is sufficiently based on clinical and haematological data, we then treat by exchange transfusion, which means for most of the cases within the first hours or the first day of suspected septicaemia.

Acar: Have you used antibiotics?

Belohradsky: Given the fact that we have had over the past four years in our intensive care unit a great increase in *Klebsiella* causing the neonatal septicaemia cases, we now use a combination of cephalosporins (e. g. cefamandole, cefuroxim, cefoxitin) with an aminoglycoside (e. g. tobramycin, amikacin). During the last 12 to 14 months, we have seen an increase in streptococcus B infections in the newborns, so we decided to add penicillin as well, in cases with respiratory distress or other known risk factors.

Acar: I would be interested in studying the mortality rates in the well-adapted and in those not well adapted to primary treatment with antibiotics.

Belohradsky: We ourselves have no controlled study. The only controlled study was performed by *Salle* in Lyon, together with *Relier* in Paris with encouraging results[2]).

Raeburn: Could you tell us more about the spectrum of bacteria in the three hundred patients with septicaemia?

Belohradsky: We still have about 60–70% gram negative bacteria causing neonatal septicaemia. Among these are 60% *E. coli*, and about 15–20% *Klebsiella*. Minor differences also depend on the different intensive care units, as the surgical unit is separated from the premature intensive ward.

Baehner: The endpoint measured here is death and obviously is the one we should be evaluating. However, multiple factors may influence death rates. Newborns are vulnerable to infection often with associated bleeding. Platelet levels and coagulation factors are easily depressed in newborns. Could the beneficial effects of exchange transfusions be due to improvement of the coagulation factors by the fresh blood used for the transfusion? Do you also give platelet transfusion in addition to performing exchange transfusions?

Belohradsky: You might have seen on one of the slides a remark on the influence on the coagulation factors. We, together with *Klose* et al.[3]) have done some studies from which we deduced that we should use fresh heparinized blood and not ACD blood. We were able to show that we could influence DIC in some cases. These studies are still going on. We do not, however, give thrombocyte transfusions.

Acar: Concerning the indications for exchange transfusion, do you think that there is a need for quantitative blood culture? How do you decide whether a patient should be given an exchange transfusion or not?

Belohradsky: That is the most difficult question for the clinician. We have set up a kind of score for the indications for exchange transfusion. We do not want to publish it just yet, because we are still working on it. This score depends on clinical data, the subjective feeling about the patient's situation, haematologic parameters like the drop of neutrophils under 10 000/ml, and the rise of neutrophils over 30 000/ml, within the first days of life. So we sometimes perform an exchange transfusion arbitrarily. But we feel that the potential hazards of this treatment are negligible compared to the potential therapeutic benefits.

Acar: You haven't tried bacterial colony counts?

Belohradsky: No, we haven't done quantitative counts.

Guggenbichler: Have you seen patients with necrotising enterocolitis after exchange transfusion? Exchange transfusion seems to be a predisposing factor for necrotising enterocolitis.

Belohradsky: No, fortunately we have not seen any cases of this.

Guggenbichler: That is very interesting. An exchange transfusion might even prevent necrotising enterocolitis by restoring some of the immune mechanisms.

Belohradsky: Nobody really knows what causes necrotising enterocolitis, but if it is thought to be due to hypoxia then we feel that this exchange transfusion might even be a treatment for necrotising enterocolitis since the patient is being provided with erythrocytes which are rich in 2.3 DPG and ATP and are thus able to transport oxygen much more easily to tissues.

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