LEUCODEPLETION NEWSLETTER 1

This Newsletter is from the NBS Leucodepletion Programme Implementation Board. It is intended to summarise progress so far, further up-dates will be produced as the implementation proceeds.

Introduction

By the late autumn of 1997 it was established beyond reasonable doubt that the transmissible agent of nvCJD is indistinguishable from that of BSE and that nvCJD results from the ingestion of infected food of bovine origin. This gave the possibility that nvCJD might be transmitted by blood transfusion sufficient credence for the search to begin in earnest for practical measures that might be taken as a precaution to reduce that, as yet unproven, possibility.

The biology of certain of the Transmissible Spongiform Encephalopathies (TSEs) of which nvCJD is one, suggests that leucocytes are likely to be the main vehicle in the transmission of the agent if indeed transmission can occur by this route. For this reason leucodepletion of all blood components is viewed as a sensible precaution to reduce that risk.

In brief the pertinent findings are:

- BSE, prions (the putative infectious agents) are found in neural tissue and lymphoid tissue
- In humans with nvCJD there is sufficient accumulation in tonsils for prion to be demonstrated by immunochemical methods
- There is also much evidence from mouse models of CJD for involvement of the lymphoreticular system

Leucodepletion is also an attractive option as it is established practice to reduce the risk of alloimmunisation against HLA antigens, manage certain transfusion reactions and ameliorate potential infection with CMV in immunocompromised patients. Thus Blood Services are familiar with the process of leucodepletion and can develop a realistic programme for its full implementation. Added to this there is interesting if not unequivocal evidence that leucodepletion might reduce the incidence and severity of post-operative infection and clinical relapse of malignancy. If this proves to be true universal leucodepletion will have major advantages additional to the primary objectives of the implementation programme.

Against this background the Spongiform Encephalitis Advisory Committee advised both a systematic risk assessment and that the UK Transfusion Services establish projects to report on the feasibility of universal leucodepletion and develop an outline plan for its implementation. NBS submitted its report to the DoH in March 1998. Subsequently work has continued to prepare for implementation, UK Transfusion Services have collaborated in this work and will continue to do so. Following the Secretary of State's decision on 17th July implementation will proceed over the next twelve to fifteen months.

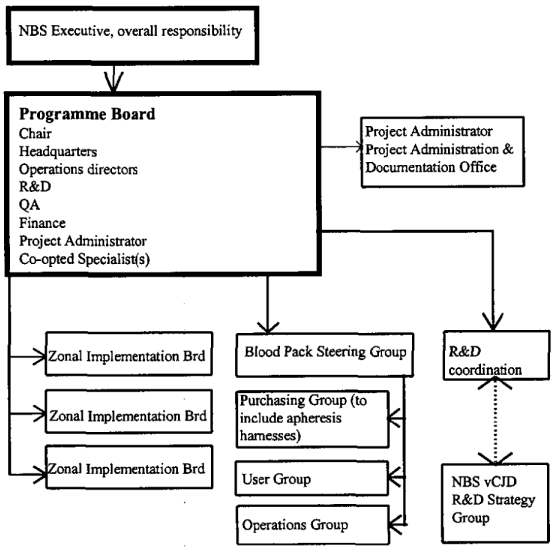
What does the Service plan to implement?

The process we will implement is not yet complete in every detail but its essentials are defined. Components will contain fewer than 5×10^6 leucocytes with 99% confidence limits. Process control testing will be used to assure this result from systems proven in evaluation to be consistently capable of it. A number of steps in the process will need to be controlled to achieve consistent results. The manner of storage of the blood before it is filtered. The ambient temperature in which filtration is carried out. The time filtration takes, the details of how samples will be taken for quality control etc. The Service's present experience of filtration, product information from manufacturers, pilot evaluation of filters and visits to blood centres abroad where universal leucodepletion has been introduced, are all being used to define these specifications. Systems that allow maximum flexibility will be favoured. The loss of red cells through filters must be less than 15%. Filtration of whole blood (from which FFP as well as red cells will be obtained) must not produce significant activation or loss of plasma proteins. The loss of platelets when they are filtered must be no greater than 10%, no more than five buffy coat preparations can be included in a pool to produce an adult therapeutic dose.

The process of extending leucodepletion to all components will be introduced gradually taking care that blood supplies are not disrupted but must be achieved as quickly as is possible. For that reason after careful option appraisal plans are on the basis of using technologies, blood and platelet filters, blood pack configurations and leucodepleting apheresis which are presently available and in use or undergoing evaluation. Other blood services around the world are also moving to universal leucodepletion. Some have achieved it. Experience is being shared and there is constructive collaboration with the manufacturers of filters, blood packs and apheresis machinery. We expect technologies to develop which simplify and improve the process particularly blood pack filter configurations which reduce the number of sterile docking procedures required. We will work to promote the research and development required and plan in anticipation of a second phase of implementation when procedures are upgraded.

How does the service plan to carry out the implementation?

The figure below shows in diagrammatic form how the programme to achieve implementation is structured.



The Programme Implementation Board (PIB) sets the specification to which the other groups will work, establishes milestones for each element of the programme and monitors the progress of each element with particular attention to tasks which are considered to present the most risk of delay. It reports to the NBS Executive. It is supported by an office established at NBS Bristol to take care of the formal documentation of the Programme as it proceeds. All other elements of the Programme report to it.

This Newsletter was prepared by Dr Tim Wallington on behalf of the Programme Implementation Board. Please address comments and queries to Dr Wallington at NBS Bristol (FeatureNet 2099) or to a member of the NBS Consultant Medical Staff.

Each Zone has established its implementation machinery (coordinated by a Zonal Implementation Board chaired by the Director of Operations) to implement leucodepletion according to specification and to a timetable agreed with the PIB. Implementation is at the end of the day an operational matter and must take note of local circumstances. The success of the Zonal Implementation process is key to this programme delivering. Procedures will require piloting as the programme proceeds and Zones will cooperate in this activity to avoid duplication of effort.

The Blood Bag Steering Group has developed well-tried Protocols for the evaluation and purchase of blood collection packs and blood filters. These Protocols include evaluation of the relevant capabilities of the manufacturer as well as the relevant products. Products are evaluated in the environment in which they will be used. Products on the approved list can be purchased for use in the NBS and it will remain policy that more than one manufacturer's product is used and that there is collaboration across the NBS to ensure that. The purchasing process will be managed at the national level. It has been agreed that harness for apheresis machines be added to the remit of the blood pack purchasing group and a member of NBS staff with special expertise in apheresis matters has joined the group.

Quality Assurance and Research and Development

These vital areas are being taken forward by a single group, led by Dr Lorna Williamson. Various laboratory procedures need to be developed and refined before leucodepletion systems can be properly evaluated and also before adequate quality assurance programmes can be put into place. Low number leucocyte counting will become a much commoner procedure within centres. There is concern that flow-cytometry will not be adequate to cope with the envisaged work load and different approaches are being examined. Particularly with regard to the evaluation of leucodepleting systems it is likely to be necessary to analyze the phenotypic mix of cells remaining in the eluate and assess the eluate for cell fragments and possibly for the presence of prion or a surrogate protein. This all demands a considerable research effort. External quality assurance is needed for these counting methods and will have to be developed. The implementation specification prescribes quality assurance through process control and adequate protocols will have to be developed and evaluated. In addition protocols are under examination for the evaluation of components post filtration although procedure for these is well established.

In addition the R&D activity essential to the practical implementation of the project a further vital priority is that the Service does not loose the opportunity to study other potentially useful effects of leucodepletion as it is introduced. A detailed grant application has been submitted for a project that would examine the impact of leucodepletion on post-operative infection. Leucodepletion only needs to produce a modest reduction in post-operative infection for its cost to be balanced by systems savings within the NHS.

This group also has ties with the NBS committee steering its broad policy of research into nvCJD and related disorders. A high priority is to develop a test for the transmissible agent of nvCJD.

Collection matters

When processes are made more complex the chance of their failure is increased. There will be some loss of collected blood units as a result of universal leucodepletion. Filters are vulnerable to aggregated material, blood clots, precipitated fibrin, platelet aggregates and leucocyte aggregates can all interfere with the function of the filter bed and lead to its failure. The sterile docking of filters following platelet extraction is also subject to some failure. A priority will be work that minimises these losses but nevertheless they may amount to as much as 5% of blood collected and both those responsible for collecting blood and those responsible for using it will have to take steps to compensate for this loss. It is likely that a significantly larger proportion of platelets will be collected by apheresis. A special effort will be required to recruit suitable apheresis donors.

Personnel matters

The planning of implementation is not yet sufficiently advanced for the precise detail of staff needs to be known. New jobs are likely to be created as a result of the introduction of leucodepletion and some current working arrangements may need to be altered. However, these are matters for detailed consultation with the staff groups involved and this will begin as soon as practicable.

Financial matters

There is no denying that leucodepletion is costly. Much work was done to cost various options during the process of the feasibility study. Until the detail of the implementation process is known any costings are preliminary and inevitably subject to considerable error. However, the annualised revenue costs of the chosen option are estimated at £80 million. Capital expenditure is estimated at £4.8 million. During this financial year it is unlikely that more than half of the annualised revenue amount will be spent. Capital expenditure will be required during this year. Funding for this year will come directly from the DoH based on a monthly account of expenditure. From April 1999 the cost of leucodepletion will be included in the price of blood components. This will coincide with the introduction of a nationally agreed price for these components and is being taken into account in that price.

Medical matters

This programme deliberately excludes the use of bedside leuco-filtration of components. This is not sufficiently reliable to use as a precaution against the transmission of a putative infectious agent. As matters stand now, blood centre leucodepleted platelets should always be available for presently agreed clinical indications. An early consequence of this implementation will be a similar sufficiency of leucodepleted red cells. Quite quickly both leucodepleted platelets and red cells will be available in excess of this requirement. Until implementation is complete standard and leucodepleted components will have to be considered as equivalent other than for cases where guidelines say use leucodepleted components, otherwise the blood inventory will be distorted in a way that will interfere with supplies. No attempt will be made to add to the present list of patient categories for whom leucodepleted components are indicated during implementation.

Virus Inactivated plasma

The NBS remains committed to make a proportion of the FFP it supplies to hospitals available as a virus inactivated product using the methylene blue method which allows the treatment of single donations. On the instruction of the NBS Executive this implementation will be managed alongside leucodepletion as both are demanding of the same facilities and the progress of the one must not be allowed to interfere with the other. Presently this implementation is at the evaluation stage, both an approach which would be based in our blood centres (Baxter Pathinact) and an approach which would contract out the process (the Springer process as offered by Grifols) are under evaluation.

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copy of Sunday one given to David

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For non-medical, non-scientific staff

On 17th July, Frank Dobson, Secretary of State for Health, announced that, on the basis of advice he had received from the Spongiform Encephalopathy Advisory Committee (SEAC), he had decided to ask the National Blood Service to implement its plans for introducing leucodepletion for all blood components. This is purely a precautionary measure designed to reduce any risk there might be that nvCJD could be passed on through blood.

A Leucodepletion Programme has been set up and this newsletter is intended to summarise progress so far. Further updates will be produced as the implementation proceeds.

Background

By the late autumn of 1997, it was established beyond reasonable doubt that the agent thought to cause nvCJD is the same as the agent which causes BSE in cattle. Experts now believe that nvCJD is probably caused by eating BSE-infected beef and there is therefore a danger that the disease could be passed from human to human through blood. There is no evidence that nvCJD has ever been passed on through blood or blood products but there is nevertheless a theoretical risk and the Government is anxious to take all reasonable steps to minimise that risk.

SEAC reviewed the latest research on nvCJD and concluded that, if the disease could be passed on through blood, then it was most likely to be via the leucocytes or white blood cells.

The implementation programme has now begun and is likely to take 12 to 15 months to complete. The NBS already leucodepletes about 5 to 10 per cent of blood for patients where there is a known benefit, eg babies and people receiving bone marrow transplants. So we are already familiar with the process. Leucodepletion may have other benefits, too, including a reduction in infections following operations.

What will the process involve?

The leucodepletion process uses filters which trap and remove 99.9% of white cells within 48 hours of donation. Certain apheresis techniques can also be used for platelets. Rigorous controls will be put in place to ensure that this level of reduction is achieved on a consistent basis. These will include storage arrangements before the blood is filtered; the temperature at which filtration is carried out; the time filtration takes; samples for quality control and so on.

The Service's present experience of filtration, product information from manufacturers, pilot evaluation of filters and visits to blood centres abroad where universal leucodepletion has been introduced, are all being used to define these specifications. Systems that allow maximum flexibility will be favoured. The loss of red cells through filters must be less than 15%. Filtration of whole blood (from which FFP as well as red cells will be obtained) must not significantly alter the red cell or plasma proteins. The loss of platelets when they are filtered must be no greater than 10%. No more than five donations can be included in a pool to produce an adult therapeutic dose.

The process of extending leucodepletion to all components will be introduced gradually taking care that blood supplies are not disrupted but must be achieved as quickly as possible. For that reason, after careful option appraisal, plans have been drawn up on the basis of using technologies, blood and platelet filters, blood pack configurations and leucodepleting apheresis techniques which are presently available and in use or undergoing evaluation. Other blood services around the world are also moving to universal leucodepletion. Some have achieved it. Experience is being shared and there is constructive collaboration with the manufacturers of filters, blood packs and apheresis machinery. We expect technologies to develop which simplify and improve the process, particularly blood pack filter configurations which reduce the number of sterile joints that have to be made between filters and blood packs. We will work to promote the research and development required and plan in anticipation of a second phase of implementation when procedures are upgraded.

How does the service plan to carry out the implementation?

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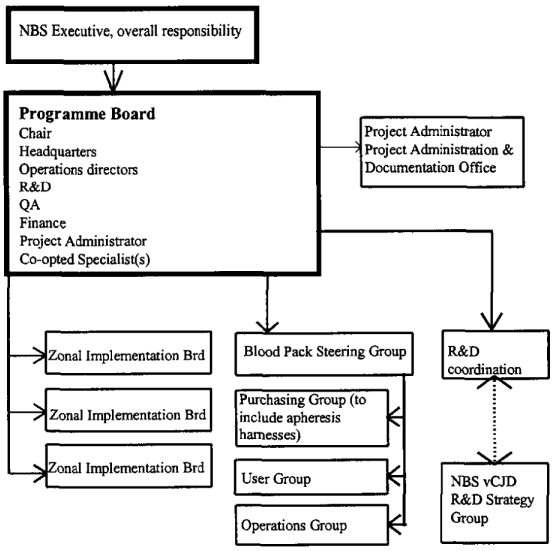

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This newsleter was prepared by Sue Cunningham on behalf of the Programme Implementation Board.
7/31/98

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The Blood Bag Steering Group will be responsible for the evaluation and purchase of blood collection packs and blood filters. It will remain policy that more than one manufacturer's product is used and that there is collaboration across the NBS to ensure that. It has been agreed that harnesses for apheresis machines should be added to the remit of the blood pack purchasing group and a member of NBS staff with special expertise in apheresis matters has joined the group.

Quality Assurance and Research and Development

These vital areas are being taken forward by a single group, led by Dr Lorna Williamson. Various laboratory procedures need to be developed and refined before leucodepletion systems can be properly evaluated and also before adequate quality assurance programmes can be put into place. Low number leucocyte counting will become a much commoner procedure within centres. There is concern that some of the techniques we currently use may not be adequate to cope with the expected workload and different approaches are being examined. For instance, we need to establish how many cell fragments remain after filtration and whether they pose a risk. This all demands a considerable research effort.

We must also be sure that leucocyte counts are accurate and that leucocytes are consistently removed from blood components after processing. We will introduce a system of external check samples (External Quality Assurances) so that we can be sure of the counting. Processing will be controlled for consistency by leucocyte counts in a proportion of leucodepleted components. The operating procedures for this so called process control are complicated and will require a lot of work early in the programme to implement. In addition protocols are under examination for the evaluation of components post filtration although procedure for these is well established.

In addition the R&D activity essential to the practical implementation of the project, a further vital priority is that the Service does not lose the opportunity to study other potentially useful effects of leucodepletion as it is introduced. We are seeking financial support for a project that would examine the impact of leucodepletion on post-operative infection. Leucodepletion only needs to produce a modest reduction in post-operative infection for its cost to be balanced by savings within the NHS.

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Medical matters

The implementation programme deliberately excludes the use of filtration at the patient's bedside. This process is not considered reliable enough to prevent the transmission of nvCJD. Guidelines for the use of leucodepleted components for specific groups of patients already exist. The NBS can already supply enough platelets to meet the likely demand for these patients and we should soon be in a position to supply sufficient red blood cells. The whole implementation programme is likely to take about 12 to 15 months and, until it is complete, no distinction will be drawn between standard and leucodepleted components as far as routine supplies to hospitals are concerned. Hospitals will be able to request leucodepleted components only for those patients specified in the existing guidelines. Otherwise it would make the management of blood stocks extremely difficult and lead to unnecessary shortages.

Virus inactivated plasma

The NBS remains committed to treat a proportion of the FFP it supplies to hospitals to virus inactivate using the methylene blue method. On the instruction of the NBS Executive, this implementation will be managed alongside leucodepletion as both involve the use of the same facilities and the progress of the one must not be allowed to interfere with the other.