**Creutzfeldt-Jakob Disease (CJD) and the Blood Supply**

CJD is a rare but invariably fatal degenerative brain disease associated with an incompletely understood transmissible agent, although many researchers believe it is a virus-like replicating protein called a prion. CJD may occur sporadically or be acquired by exogenous exposure to infectious material (such as dura mater transplant or human pituitary growth hormone). It may be familial, caused by a genetic mutation of the prion protein gene. CJD has never been determined to be transmissible by blood transfusion; however, blood donor deferral criteria, affecting only rare donors, have been in place for years to guard against the theoretical possibility. This long known disease is now referred to as classical CJD, in contrast to a new related entity that is causing quite a controversy in blood banks around the world.

In 1996, a previously unrecognized new variant of CJD was described, almost exclusively in the United Kingdom, and is referred to as *nvCJD*. There are some epidemiologic and clinical differences between classical CJD and *nvCJD*. Earlier age of onset, predominance of psychiatric and sensory symptoms, absence of diagnostic EEG changes, prolonged duration of illness, and unique neuropathologic features serve to distinguish *nvCJD* from the classical form. Laboratory and epidemiologic studies have linked *nvCJD* to an outbreak of bovine spongiform encephalopathy (BSE) in the United Kingdom. BSE infection in cattle appeared in 1980, peaked in 1992 and fell to low levels in 1996. Many scientists believe the illness has been acquired by eating beef obtained from cattle infected with the disease.

Accumulating epidemiologic and laboratory information indicate transmission of the classical CJD infectious agent by blood products is highly unlikely, and has not been observed. However, the *nvCJD* prion protein can be found in lymphoid tissues, unlike classical CJD, and transmission of *nvCJD* by blood transfusion has been raised as at least a theoretical possibility. Since other clinical and biological differences exist, as mentioned above, transmissibility of *nvCJD* cannot be confidently predicted from studies of classical CJD, and the risk of transfusion transmission is currently considered unknown.

Accordingly, the Food and Drug Administration took the precautionary step of requiring that potential blood donors who have spent six months or more cumulatively in the United Kingdom from 1980 through 1996, and therefore could have been exposed to the *nvCJD* agent, be indefinitely deferred. Recently, the FDA Advisory Committee on Transmissible Spongiform Encephalopathies (TSEs), is considering issuing expanded donor deferral criteria for *nvCJD* to include those living or traveling in certain European countries (France, Portugal, and Republic of Ireland) for a total of 10 years, as reports of *nvCJD* are increasing in these countries. The America's Blood Centers, a consortium of independent regional blood centers which collects about half of the blood in this country, plans to match the FDA policy which would cut the current blood donor pool by one percent. However, the American Red Cross, which collects the other half of the nation's blood supply has announced their intention to voluntarily implement expanded donor deferrals beginning in September 2001 to include donors who have lived in the United Kingdom for a cumulative total of three months since 1980, or who have lived in any other European country for six months since 1980, or donors who have received a blood transfusion in the United Kingdom.

It is difficult to measure the effect of the ARC deferral policy on the nation's blood supply; however, best estimates suggest this will eliminate between 6 and 11 percent of all current donors. Data from the National Blood Data Resource Center (NBDRC) indicate such a drop in donors will adversely affect patient care in the United States. The margin between blood collected and blood transfused has decreased substantially since 1994, causing seasonal and regional blood shortages, postponed surgeries, and postponed transfusions for medical indications. The inventory margin of safety is only one half of the level a decade ago.
Therefore, our national blood system will be severely strained by further loss of blood donors. The American Association of Blood Banks (AABB) advocates caution in implementation of new donor deferral criteria. While the theoretical risk of transfusion transmitted \textit{nvCJD} exists, it is unproved and current scientific data is open to different interpretations. Within this background of uncertainty, regarding the theoretical risk of an extraordinarily rare event, looms the reality of nation wide blood shortages in meeting the very real and present transfusion needs of patients who are actually sick right now. The Rex Blood Plan is following these developments closely, and will remain compliant with all implemented regulations. However, my personal hope is that common sense in balancing risks and benefits of these decisions will prevail. This remains to be seen.

\textit{Timothy R. Carter, MD}

\textbf{Reactive Cellular Changes In Pap Smears}

The Bethesda System for reporting of cervical/vaginal cytologic diagnoses was introduced in 1988 as a means to standardize Pap Smear reporting and to encourage the use of specific, descriptive diagnoses. Within the Bethesda System, there are three broad diagnostic categories: 1) Within Normal Limits, 2) Benign Cellular Changes, and 3) Epithelial Cell Abnormalities. With the exception of “Within Normal Limits”, each of these broad categories is then subdivided into specific diagnostic categories. The diagnostic category of “Benign Cellular Changes” includes specific Infections such as Trichomoniasis, Herpes, and Candida but also includes the nonspecific category "Reactive Cellular Changes”

Reactive Cellular Changes can be secondary to atrophic vaginitis, radiation/chemotherapy or Intrauterine Contraceptive Devices (IUD’s) but are usually of nonspecific etiology and presumed to be secondary to chronic cervicitis or other inflammatory process. Because this diagnosis is neither normal nor abnormal enough to warrant treatment, it can be a source of confusion for both patients and their caregivers. Another source of confusion is that this subjective diagnosis can vary from laboratory to laboratory. At some laboratories, including Rex Healthcare, mild examples of “Reactive Cellular Changes” are reported out as “Within Normal Limits”. There are other laboratories which include many cases of “Reactive Cellular Changes” in their “Atypical Squamous Cells of Uncertain Significance (ASCUS)” category. According to established national guidelines, the “Reactive Cellular Changes” rate at a laboratory should be less than 5% of cases. At Rex Healthcare, our “Reactive Cellular Changes” rate has historically ranged from 1.5 – 3.0%.

Follow-up studies of women with “Reactive” Pap tests have shown that a small percentage (less than 5%) will eventually be diagnosed with dysplasia (usually low-grade). For this reason, special attention to annual follow-up Pap testing is warranted in these patients. Thin layer (monolayer) Pap tests may be helpful in following or further evaluating these patients. In high-risk patients earlier repeat Pap testing at six months may be warranted.

For further information please contact Dr. Keith Nance, Medical Director of Cytology at Rex Healthcare, at 784-3286.

\textit{Keith V. Nance, MD}

\textbf{Apheresis Platelets: Are They Really Better?}

Patients requiring platelet transfusions may receive pooled platelet concentrates (PCs) or platelets collected from a single donor by apheresis (apheresis platelets). An apheresis platelet product contains the same platelet dose as about 6 PCs. Over the years, apheresis platelets have been considered superior for several reasons. However, many of the purported advantages of apheresis platelets have disappeared, been disproved or are now recognized as minimal. For example, at one time, apheresis platelets were considered "fresher" than PCs. However, with current testing requirements and inventory management, apheresis platelets are routinely transfused on day 4 or 5 of storage, as are PCs. More significantly, apheresis platelets were thought to provide a better platelet increment, even when non-HLA-matched, to an alloimmunized recipient. Now, with leukocyte reduction techniques and further observation, it is generally accepted that the expected corrected platelet count increment is identical for the
two components. Apheresis platelets were thought to cause less alloimmunization. However, the multicenter Trial to Reduce Alloimmunization to Platelets (TRAP study) clearly showed this is not the case.\(^1\) The same study showed that WBC reduction was important in preventing alloimmunization, and WBC reduction is now available for both components.

Today, there remain two presumed advantages of apheresis platelets. First, there is reduced donor exposure. Second, a therapeutic dose can be collected from a single donor with unique characteristics, such as HLA-matched, PLA1 negative, or IgA-deficient. This second advantage is real, but only applies to a small percentage of patients at Rex. The first advantage becomes a bit tenuous as the risk of transfusion transmitted disease continues its remarkable plummet. Risk of platelet septic reactions remains, but preliminary data from an ongoing study fail to identify a difference between apheresis platelets and PCs in this regard.

Therefore, it is becoming increasingly difficult to identify a significant patient advantage for apheresis platelets in many clinical settings. Apheresis platelets are significantly more expensive than pooled platelet concentrates (currently $1500 charge to patient for apheresis platelets versus $860 charge for PCs), and may be more difficult to obtain. When ordering platelets for your patient, it would be appropriate to reconsider whether they really need the apheresis product at the exclusion of the pooled platelet concentrates.

Timothy R. Carter, MD

---

**Rh Immune Globulin Dosage Guidelines**

The Blood Bank receives periodic requests for assistance with determining postpartum Rh Immune Globulin (RhIG) dosing. Here are some recommendations.

A D-negative woman with a D-positive infant should receive one full dose of RhIG within 72 hours of delivery, unless she is known to be alloimmunized to D previously (in which case the RhIG will not help). If 72 hours pass without administration, it is better to give the treatment late than not at all. Note that the presence of residual anti-D from antepartum RhIG does not indicate ongoing protection. Correlation with the office records of RhIG administration is usually helpful; however, always give RhIG when doubt about antepartum administration cannot be easily resolved. It should also be given if there is any problem determining Rh type of the infant.

Postpartum administration of RhIG may not prevent immunization if the quantity of D-positive fetal red blood cells entering the maternal circulation exceeds the immunosuppressive capacity of RhIG. One 300 ug dose protects against 15 ml of D-positive red cells or 30 ml of fetal blood. Quantification of fetal maternal hemorrhage (FMH) is performed by the Kleihauer-Betke acid-elution test. Results are reported as ml of fetal blood. [It should be noted that the precision and accuracy of the Kleihauer-Betke test may be poor, particularly as the volume of FMH increases; however, it remains the best available method. If the calculated FMH is > 75 ml, the following steps will be taken: result will be reported as >75 ml, the patient's physician or nurse will be called, and the pathologist on-call will be notified in order to discuss the findings with the obstetrician as indicated. Although precision and accuracy are suspect for values > 75ml, a general estimate can often be made with review of the clinical circumstances and test results.]

**Since 300 ug of RhIG protects against FMH of 30 ml of fetal blood, the number of RhIG doses is determined by dividing the estimated volume of fetal blood by 30.** For example:

1. Kleihauer-Betke reported as 65 ml.
2. 65/30 = 2.2 doses of RhIG required.

Because quantification is inherently imprecise and the consequences of underdosing can be serious, it is desirable to provide a safety margin in calculating RhIG dose. One recommended approach is as follows:

1. When the number to the right of the decimal point is less than 5, round down and add one dose of RhIG. Ex. If calculation comes to 2.2 doses as above, give 3 doses.
2. When the number to the right of the decimal point is 5 or greater, round up to the
next number and add one dose of RhIG. Ex. If the calculation is 2.8, give 4 doses.
No more than five doses of RhIG should be injected intramuscularly at one time. For larger quantities, injections can be spaced over a 72-hour period for patient comfort.

**Timothy R. Carter, MD**

Outreach Specimen Labels and Requisitions

To assure efficient processing and analysis of Outreach specimens, proper labeling of each sample is required. Minimum information necessary includes the following: complete patient name, date/time of collection, initials of collector. For your convenience, each Rex OutReach request form has pre-numbered, bar-coded specimen labels which provide a unique patient ID # for that encounter, as well as prompts for the required information. Proper specimen labeling is important to verify the source of the specimen and assure accuracy of results. The accompanying requisition should have the following minimum information: complete patient name, D.O.B., SS#, ICD-9 code(s), specimen source (if applicable), complete name of ordering physician, complete billing information.

Improperly labeled specimens or incomplete requisitions require additional time and effort to process on the part of the Laboratory and the physician office staff. They may also delay analysis; an inconvenience to patients and physicians. Questions or concerns about specimen labels or requisitions may be directed to Debbie Lompa at 784-3355.

**Deborah Lompa**

Client Service Representative

Rex OutReach Laboratory Services

Amino-glycosides Interfere with CSF protein

We recently learned from the manufacturer of our CSF protein method that aminoglycoside antibiotics (including gentamicin, tobramycin, amikacin, and kanamycin) interfere with measurement. The pyrogallol red dye used in the method may bind to basic amino groups in the antibiotics, causing a spurious elevation. The nature of the interference is still under investigation, and the manufacturer hopes it can be resolved. As aminoglycosides penetrate the blood brain barrier very poorly in most clinical settings, the degree of elevation is minimal (< 3-4%) and not clinically significant. However, in neonates (with immaturity of the blood-brain barrier) or patients receiving intrathecal or intraventricular aminoglycoside therapy, the degree of spurious elevation may be significant. If you have a patient who falls into the latter categories, contact the Core Laboratory (ext. 2159) to arrange for CSF protein analysis to be performed by an alternate method.

**John D. Benson, MD**


For further information, call the Laboratory (784-3040). Telephone extensions are: Pathologists’ Direct Line (3201), Sharon Logue (Lab Director 2400), Robin Ivosic (Core Lab Manager 3053), Elaine Patterson (Core Lab Manager 3054), Jackie Okoth (Core Lab PM Manager 4248), Diane Young (Anatomic Pathology Manager 3888), Nga Moore (Customer Service Manager 3396), Kori Horsley (Customer Service PM Manager 4340).