Human Prion Diseases (Other than vCJD)

Disease Agent:

- Human prion proteins

Disease Agent Characteristics:

- Current evidence supports the theory that the infectious agent is a prion. However, the existence of accessory factors has not been excluded.
- Prions are proteinacious infectious agents causing transmissible spongiform encephalopathies (TSE): a group of neurodegenerative diseases that include kuru, Creutzfeldt–Jakob Disease (CJD), variant CJD (vCJD; discussed in a separate fact sheet), Gerstmann-Sträussler-Scheinker disease (GSS) and fatal familial insomnia (FFI). Prion diseases are either sporadic, genetic or infectious. The cause of sporadic CJD (sCJD) is unknown. The genetic prion diseases are associated with a germline mutation in the human gene, *PRNP.* The infectious disease occurs in people exposed to food, biologicals or instruments contaminated with prions.
- Prions differ from other infectious agents in that they are formed mostly of abnormally folded prion protein and devoid of detectable nucleic acid.
- Mammalian prions replicate by recruiting the normal cellular prion protein PrP^{C} to form a disease-causing isoform designated PrP^{Sc} (Sc is an abbreviation for scrapie). PrP^{Sc} or PrP^{res} (abbreviation for misfolded core PrP protein resistant to proteinase K) or PrP^{TSE} (a wider definition accepted by WHO) are the designations for the pathogenic forms and are used interchangeably in the literature. Prion diseases represent disorders of protein conformation in which the tertiary structure of the native protein is profoundly altered. The transition occurs when the α-helical PrP^{C} changes into a β-sheet-rich molecule of PrP^{TSE} that is resistant to proteases (proteinase K, lysosomal enzymes).
- Prions are nonimmunogenic as a result of the sharing of epitopes with the normal cellular isoform.
- PrP^{C} is a glycosylated protein attached to the outer-layer of plasma membrane through a glycosylphosphatidylinositol anchor. It is present on variety of cells but also circulates in plasma and has a molecular weight of about 33-35 kDa.
- PrP^{TSE} has a more restricted tissue range than does PrP^{C}; mainly in the CNS.
- PrP^{TSE} forms aggregates that precipitate as diffuse accumulations or as amyloid plaques in the central nervous system; these are a histopathological hallmark of the TSEs. Generally, PrP^{TSE} is identified in a form of PrP^{res} using immunohistological techniques or by immunoblotting after the treatment of tissues by proteinase K.
- Human prion diseases are transmissible to susceptible experimental animals: sCJD mainly to primates, bank voles, guinea pigs and genetically engineered mice.
- Human prions can not be tested for infectivity using cell cultures.
- Physicochemical properties: Resistance of prions to commonly used disinfectants (formaldehyde, glutaraldehyde, ethanol, and iodine [partially]) and other treatments that damage nucleic acids is well recognized. Prions are resistant to ultraviolet light and ionizing radiation, ultrasonication, nucleases, boiling, and heat. Immersion in undiluted bleach (60,000 ppm of available chlorine) for 1 hour can be partially effective. High concentrations of NaOH (1-2 N) or heat in a gravity displacement autoclave at 121ºC or higher or in a porous load autoclave at 134ºC for 1 hour are advocated for disinfection.

Disease Names:

- Sporadic CJD
- Infectious CJD (kuru, iatrogenic CJD [iCJD] and vCJD)
- Familial or genetic or heritable CJD (fCJD); Gerstmann-Sträussler-Scheinker syndrome; fatal familial insomnia
- Human transmissible spongiform encephalopathy

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical; a number of epidemiologic studies do not demonstrate transfusion transmission to humans.
- Public perception and/or regulatory concern regarding blood safety: Very low
- Public concerns regarding disease agent: Absent

Background:

- Human PrP is encoded by a gene (*PRNP*) located on the short arm of chromosome 20.
- Sporadic CJD has been recognized since the 1920s, with a stable incidence in the population at about one case per million population per year. The causative mechanism of sCJD is unknown. A common polymorphism at *PRNP* codon 129 encoding methionine (Met) or valine (Val) influences the susceptibility to sCJD. Most Caucasians with sCJD are homozygous carriers of Met-encoding allele. However, homozygous carriers of Val-encoding allele or heterozygous carriers of both alleles are also known to develop sCJD.
- Iatrogenic CJD results from infection through prion-contaminated human growth hormone or gonadotropin and transplantation of dura mater or cornea from patients who died of CJD. It also occurs following neurosurgical procedures: this happened when brain penetrating electrodes or neurosurgical instruments used on CJD patients were not effectively sterilized and then reused on subsequent patients.
- Familial CJD results from multiple variations of insertion mutations and point mutations of the *PRNP* gene.

Common Human Exposure Routes:

- Sporadic: 85% of cases
- Familial: 10-15% of cases
- Iatrogenic: Majority of cases are related to dura mater transplants and treatments with human pituitary-derived growth hormone. A few cases developed after treatments with

human pituitary-derived gonadotropin, corneal transplants and after neurosurgery.
- Kuru: Historic interest as it was associated with ritual cannibalism in Papua New Guinea.

Likelihood of Secondary Transmission:

- Transmission by surgical instruments and tissue implants, and pituitary hormones.

At-Risk Populations:

- Those with known genetic susceptibility
- Those exposed to ineffectively sterilized surgical instruments during neurosurgery (e.g., intraoperative EEG electrodes) or who received a contaminated dura mater transplant or cornea or who received injections of human pituitary growth hormone derived from deceased infected donors

Vector and Reservoir Involved:

- Human reservoir
- Ineffectively sterilized surgical instruments, intraoperative EEG electrodes, tissue implants, and human-tissue–derived hormones

Blood Phase:

- Identified in some experimentally infected animal models prior to clinical disease
- Not specifically identified in humans

Survival/Persistence in Blood Products:

- Unknown: probably stable if present

Transmission by Blood Transfusion:

- Demonstrated in animal models (other than sCJD: hamsters, mice, sheep, deer)
- Transfusion transmission in humans has not been demonstrated despite multiple epidemiological studies.
    - No cases of CJD have been observed among 461 recipients of blood components from 40 donors subsequently diagnosed with CJD, as of December 31, 2008.
        - Among them are 359 deceased recipients, 85 living recipients and 17 that are lost to follow up.
        - In total 157 recipients survived 5 years or longer following transfusion: they include 71 recipients (38 alive, 32 deceased and 1 lost to follow up) who received blood components donated by the donors 60 months or less prior to the onset of CJD.
    - No cases of CJD were observed following autopsies of hemophilia patients over the past 20 years.
    - An Italian study among patients with CJD and controls found the odds ratio for receipt of blood transfusion more than 10 years before CJD onset to be 5.05 (95% CI: 1.37-18.63) after adjustment for confounding. The authors were appropriately conservative in their conclusions, recognizing their results may represent biases from the method used for selection of the control population and/or recall of remote behavioral and clinical events by the relatives of incapacitated or deceased CJD patients.

Cases/Frequency in Population:

- Global incidence is one per million annually.
- Prevalence is unknown but is likely to be at least 10-fold higher, considering the very long presumed incubation period.

Incubation Period:

- Unknown in sporadic cases
- Incubation periods for iatrogenic CJD secondary to human pituitary-derived growth hormone range between 5 and 30 years (median of 12 years) being similar to what was seen with kuru, although in some kuru cases the incubation periods exceed 40 years.

Likelihood of Clinical Disease:

- Unknown in sCJD as presymptomatic infection is not readily detectable; high in familial and iatrogenic diseases

Primary Disease Symptoms:

- Neurodegenerative disease (behavioral changes, dementia, ataxia, progressive sleep disorder in case of FFI).

Severity of Clinical Disease:

- High (progressive, invariably fatal)

Mortality:

- 100% for symptomatic disease

Chronic Carriage:

- Lengthy incubation period for many years; abnormal prions presumed present throughout, but not necessarily in the blood

Treatment Available/Efficacious:

- The few proposed treatments have not been effective in halting or reversing the neurodegenerative disease.

Agent-Specific Screening Question(s):

- Several current questions are required by FDA and AABB Standards:
    - Diagnosis of CJD
    - Potential iatrogenic exposure (dura transplant, human pituitary growth hormone)
    - Family history (blood relatives) of CJD, unless shown free of mutation in the *PRNP* gene
        - Additional information is found in footnote 71of the 2010 FDA guidance for industry (see Suggested Reading list), "For the purposes of this document, FDA considers the less common TSEs, Gerstmann-Sträussler-Scheinker syndrome and fatal insomnia syndromes, to be equivalent in risk to familial

and sporadic CJD. The blood establishment need not name these rare syndromes in the questionnaire but might consider them as equivalent in risk to CJD if, in response to a question about CJD, the donor offers information that a family member has been diagnosed with one of them."

Laboratory Test(s) Available:

- No FDA-licensed blood donor screening test exists.
- No readily accessible presymptomatic test is available.
- Genetic tests to detect pathogenic mutations that are indicative of heritable disease may be performed in a limited number of research laboratories.

Currently Recommended Donor Deferral Period:

- Permanent per FDA Guidance and AABB Standard

Impact on Blood Availability:

- Agent-specific screening question(s): Minimal
- Laboratory test(s) available: Not applicable

Impact on Blood Safety:

- Agent-specific screening question(s): Unknown
- Laboratory test(s) available: Not applicable

Leukoreduction Efficacy:

- Leukoreduction was introduced as a potential control measure for vCJD in the UK in 1999 due to preliminary data supporting infection of lymphocytes. Subsequently, in hamster scrapie models, a 42-72% reduction in prion content (two different studies) was observed. Recently, in a BSE-sheep model, leukoreduction of blood components did not prevent disease transmission.

Pathogen Reduction Efficacy for Plasma Derivatives:

- Inactivation data are not available for human plasma. Highly significant dilution and/or partitioning of infectivity away from final derivatives by fractionation process suggested in animal models.
- The FDA does not require recall of pooled plasma or final products upon inadvertent inclusion of plasma from an at-risk donor.
- To date, there is no epidemiologic evidence of transmission of sCJD by pooled plasma derivatives.
- Nanofiltration is effective in model systems.

Other Prevention Measures:

- Affinity-based removal filters (for red blood cell products) under development; primarily considered for vCJD, but should be efficacious for other human TSEs if they are transmissible via this route.

Suggested Reading:

1. Beck JA, Poulter M, Campbell TA, Adamson G, Uphill JB, Guerreiro R, Jackson GS, Stevens JC, Manji H, Collinge J, Mead S. PRNP allelic series from 19 years of prion protein gene sequencing at the MRC Prion Unit. Hum Mutat 2010;31:E1551-63.
2. Belay ED, Schonberger LB. The public health impact of prion diseases. Annu Rev Public Health 2005;26:191-212.
3. Brown P. Creutzfeldt–Jakob disease: reflections on the risk from blood product therapy. Haemophilia 2007 Dec;13 Suppl 5:33-40. Review.
4. Brown P, Brandel JP, Preece M, Sato T. Iatrogenic Creutzfeldt–Jakob disease: the waning of an era. Neurology 2006 Aug 8;67(3):389-93. Epub 2006 Jul 19. Erratum in: Neurology 2006 Oct 24;67(8):1528. Preese, Michael [corrected to Preece, Michael].
5. Center for Blood Evaluation and Research. FDA Guidance, May 2010: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Cretuzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt–Jakob Disease (vCJD) by Blood and Blood Products. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf.
6. Collinge J, Whitfield J, McKintosh E, Beck J, Mead S, Thomas DJ, Alpers MP. Kuru in the 21st century–an acquired human prion disease with very long incubation periods. Lancet 2006;367:2068-74.
7. Creutzfeldt–Jakob disease. Ed. Turner MC, AABB Press, Bethesda, Maryland, 2006.
8. Dorsey K, Zou S, Schonberger LB, Sullivan M, Kessler D, Notari E 4th, Fang CT, Dodd RY. Lack of evidence of transfusion transmission of Creutzfeldt–Jakob disease in a US surveillance study. Transfusion 2009;49:977-84.
9. Evatt B, Austin H, Barnhart E, Schonberger L, Sharer L, Jones R, DeArmond S. Surveillance for Creutzfeldt–Jakob disease among persons with hemophilia. Transfusion 1998;38:817-20.
10. Gregori L, Gurgel PV, Lathrop JT, Edwardson P, Lambert BC, Carbonell RG, Burton SJ, Hammond DJ, Rohwer RG. Reduction in infectivity of endogeneous transmissible spongiform encephalopathies present in blood by adsorption to selective affinity resins. The Lancet 2006;368:2226-30.
11. Gregori L, McCombie N, Palmer D, Birch P, Sowemimo-Coker SO, Giulivi A, Rohwer RG. Effectiveness of leucoreduction for removal of infectivity of transmissible spongiform encephalopathies from blood. The Lancet 2004;364:529-31.
12. Hamaguchi T, Noguchi-Shinohara M, Nozaki I, Nakamura Y, Sato T, Kitamoto T, Mizusawa H, Yamada M. The risk of iatrogenic Creutzfeldt–Jakob disease through medical and surgical procedures. Neuropathology 2009 Oct;29(5):625-31. Epub 2009 Jul 29. Review.
13. Hewitt PE, Llewelyn CA, Mackenzie J, Will RG. Creutzfeldt–Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiologic Review study. Vox Sang 2006;91:221-30.
14. Holman RC, Belay ED, Christensen KY, Maddox RA, Minino AM, Folkema AM, Haberling DL, Hammett TA, Kochanek

KD, Sejvar JJ, Schonberger LB. Human prion diseases in the United States. PLoS One 2010;5:e8521.
15. Hoots WK, Abrams C, Tankersley D. The impact of Creutzfeldt–Jakob disease and variant Creutzfeldt–Jakob disease on plasma safety. Transfus Med Rev 2001;15: 45-59.
16. Houston F, McCutcheon S, Goldmann W, Chong A, Foster J, Sisó S, González L, Jeffrey M, Hunter N. Prion diseases are efficiently transmitted by blood transfusion in sheep. Blood 2008 Dec 1;112(12):4739-45. Epub 2008 Jul 22.
17. Knight R. Prion diseases. Vox Sang 2004;87 Suppl 1:S104-6.
18. Knight R. The risk of transmitting prion disease by blood or plasma products. Transfus Apher Sci 2010;43:387-91. Epub 2010 Nov 11.
19. Ludlam CA, Turner ML. Managing the risk of transmission of variant Creutzfeldt–Jakob disease by blood products. Br J Haematol 2005;132:13-24.
20. McCutcheon S, Alejo Blanco AR, Houston EF, de Wolf C, Tan BC, Smith A, Groschup MH, Hunter N, Hornsey VS, MacGregor IR, Prowse CV, Turner M, Manson JC. All clinically-relevant blood components transmit prion disease following a single blood transfusion: a sheep model of vCJD. PLoS One. 2011;6:e23169. Epub 2011 Aug 17.
21. Prusiner SB. Prions. In: Knipe DM, Howley PM, editors. Fields virology, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 3059-91.
22. Puopolo M, Ladogana A, Vetrugno V, Pocchiari M. Transmission of sporadic Creutzfeldt–Jakob disease by blood transfusion: risk factor or possible biases. Transfusion 2011 Jan 7. doi: 10.1111/j.1537-2995.2010.03004.x. [Epub ahead of print]
23. Tyshenko MG, El Saadany S, Oraby T, Darshan S, Aspinall W, Cooke R, Catford A, Krewski D. Expert elicitation for the judgment of prion disease risk uncertainties. J Toxicol Environ Health Part A 2011;74:261-85.
24. Wilson K, Hébert PC, Laupacis A, Dornan C, Ricketts M, Ahmad N, Graham I. A policy analysis of major decisions relating to Creutzfeldt–Jakob disease and the blood supply. Can Med Assoc J 2001;165:59-65.
25. WHO Manual for surveillance of human transmissible spongiform encephalopathies including variant Creutzfeldt–Jakob disease, Geneva, Switzerland, 2003. http://www.who.int/bloodproducts/publications/en/.