Managing the risk of nosocomial transmission of prion diseases

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Purpose of review

Prion diseases such as Creutzfeldt–Jakob disease represent a unique infection control problem because prions exhibit an unusual resistance to conventional chemical and physical decontamination methods. This paper reviews the recent literature and provides recommendations for the prevention of nosocomial transmission of prion agents.

Recent findings

Recommendations to prevent the cross-transmission of infection from medical devices potentially contaminated with prions have been based primarily on prion inactivation studies. Newer recommendations consider inactivation data, but also use epidemiological studies of prion transmission, the infectivity of human tissues, and the efficacy of removing microbes by cleaning. Prion-specific disinfection/sterilization is required in only limited settings. Healthcare workers are not at risk of acquiring transmissible spongiform encephalopathies. Blood or blood products have not been demonstrated to be vehicles for transmission.

Summary

On the basis of scientific data, only critical (e.g. surgical instruments) and semicritical devices contaminated with high-risk tissue (i.e. brain, spinal cord, eye) from high-risk patients (e.g. with known or suspected Creutzfeldt–Jakob disease) require special treatment.

Keywords

CJD, disinfection, infection control, sterilization, vCJD

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Abbreviations

BSE	bovine spongiform encephalopathy
CJD	Creutzfeldt–Jakob disease
FDA	Food and Drug Administration
PrP	prion protein
PrP^{sc}	prion protein (Scrapie isoform)
TSE	transmissible spongiform encephalopathy
vCJD	variant Creutzfeldt–Jakob disease

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Introduction

Human transmissible spongiform encephalopathies (TSEs) are degenerative neurological disorders transmitted by a proteinaceous infectious agent or 'prion' [1,2]. They include Creutzfeldt–Jakob disease (CJD; incidence ~1/million), kuru (incidence 0), Gertsmann–Straussler–Sheinker (incidence ~1/billion), fatal familial insomnia syndrome (incidence <1/billion) and sporadic fatal insomnia [2–4]. In recent years, a new variant form of CJD (variant Creutzfeldt–Jakob disease; vCJD) has been recognized [5–8]. Six prion diseases of animals have been described: scrapie in sheep and goats; transmissible mink encephalopathy; exotic ungulate encephalopathy; chronic wasting disease of mule deer and elk; feline spongiform encephalopathy; and bovine spongiform encephalopathy (BSE or 'mad cow disease') [3].

CJD and other TSEs exhibit an unusual resistance to conventional chemical and physical decontamination methods [9,10,11••,12], and are stable in the environment for years. For these reasons, concern has been raised about the possible nosocomial transmission of TSEs. This paper will concisely review the epidemiology of TSEs including vCJD and measures to prevent nosocomial transmission with a focus on recently published papers.

Etiology

Prions are a unique class of pathogens associated with the abnormal isoform of a host cellular protein called prion protein (PrP^{c}) [1]. In humans, the *PrP* gene resides on chromosome 20; mutations in this gene may trigger the transformation of the PrP protein into the pathological isoform. This conversion of the normal cellular protein into the abnormal disease-causing (scrapie) isoform (PrP^{sc}) involves a conformational change whereby the α-helical content diminishes and the amount of β-pleated sheet increases, resulting in profound changes in properties. No prion-specific nucleic acid is known to be required for disease transmission. The pathogenic prions accumulate in neural cells, disrupt function and lead to cell death.

Creutzfeldt–Jakob disease

CJD occurs worldwide as both a sporadic (~90%) and familial disease (~10%); less than 1% of CJD cases have resulted from iatrogenic exposure. There is no seasonal distribution, evidence of changing incidence, sex predilection, or convincing geographical aggregation of cases. Death usually occurs within 6 months from the onset of symptoms (median age at death 68 years).

CJD is not transmitted by direct contact, droplet, airborne, or transplacental spread. CJD can be transmitted from samples obtained from patients to non-human primates [1]. Transmission can occur by peripheral routes of inoculation, but larger doses are required than with intracerebral inoculation. Oral transmission has been demonstrated with even larger doses.

The major clinical signs in CJD have included cognitive deficits, myoclonus, pyramidal tract signs, cerebellar signs, extrapyramidal signs, cortical visual deficits, abnormal extraocular movements, lower motor neuron signs, vestibular dysfunction, seizures, sensory deficits, and autonomic abnormalities [1]. CJD is often misdiagnosed as other neurological diseases, including Alzheimer's disease, Parkinson's disease, and multi-infarct dementia. A definitive diagnosis of CJD requires a histological examination of the affected brain tissue. Increased concentrations of several proteins have been reported in the cerebrospinal fluid of patients with sporadic Creutzfeldt–Jakob disease (sCJD), including protein 14-3-3, neuron-specific enolase, S100b, and tau protein [13].

Variant Creutzfeldt–Jakob disease

BSE was first identified in 1986 in the UK, and by 2001 approximately 180 000 cattle had been infected [14]. The number of cases peaked in 1992, with 1537 cases reported in 2000. BSE has been reported from native cattle in many European countries and Japan [14]. BSE appeared to have resulted from the exposure of cattle to meat and bone meal contaminated with scrapie (or unrecognized endemic BSE), which was produced by a new rendering process in which the temperature was reduced and the hydrocarbon solvent extraction step omitted [15]. The World Health Organization has published a guideline designed to control the transmission of BSE and other similar diseases in animals [16]. A total of 115 human cases had been diagnosed (109 in the United Kingdom, five in France, and one in Ireland) by March 2002 [6,14]. Although the absolute number of cases has been low, the number of deaths per year increased by 33% from 1995 to 2000 [17]. Both epidemiological and molecular biological evidence support a casual link between BSE and vCJD [7,8,18,19]. BSE has not been reported in the United States but one case of vCJD has been identified in a UK citizen residing in the United States. The CDC believes this patient acquired the disease while living in the UK.

The epidemiology, clinical and pathological profile differs from that of sCJD. The mean age of onset is 29 years (range 16–48 years) compared with 65 years for sCJD. The duration of illness is 14 months for vCJD and 4.5 months for sCJD. Patients with vCJD frequently present with sensory and psychiatric symptoms that are uncommon with sCJD [1,2]. All patients with vCJD have been potentially exposed to contaminated beef during the 1980s, before measures to control human exposure were taken.

The sensitivity and specificity of protein 14-3-3 for the diagnosis of vCJD is less than that for sCJD [13]. Unlike sCJD, abnormal PrP (PrP^{sc}) immunostaining has been reported in the lymphoid tissues of individuals infected with vCJD, including the tonsil [20,21], the appendix [22], the spleen [23], and lymph nodes [23]. Importantly, such studies have reported detecting PrP^{sc} before the onset of clinical vCJD.

Infectivity of tissue

To date all known cases of iatrogenic CJD have resulted from exposure to infectious brain, dura mater, pituitary, or eye tissue. Although prions may be present in many body tissues, they are present in lower numbers than in the brain and therefore transmission is less likely (Table 1). Transmission to primates has never been documented with any body fluid other than cerebrospinal fluid [1]. Prions have been isolated from the blood of infected animals and patients with CJD. However, there are no known cases of CJD attributable to the reuse of devices contaminated with blood or via the transfusion of blood products. The transmission of CJD from human blood to laboratory animals has occasionally been reported, but the methods used in these experiments and hence the conclusions have been criticized [24].

PrP^{sc} has been detected in the spleen, lymph nodes, tonsils, retina and proximal optic nerve of patients with vCJD [23,25]. Research has found that the spleen and tonsils have similar levels of infectivity in vCJD and that these levels are 100–1000 times lower than infectivity levels in the brain [25].

Table 1. Comparative frequency of infectivity in organs/tissue/body fluids of humans with transmissible spongiform encephalopathies

Infectious risks	Tissue
High	Brain (including dura mater), spinal cord, eye (e.g. (corneas)
Low	Cerebrospinal fluid, liver, lymph node, kidney, lung, spleen
None	Peripheral nerve, intestine, bone marrow, whole blood, leukocytes, serum, thyroid gland, adrenal gland, heart, skeletal muscle, adipose tissue, gingiva, prostate, testis, placenta, tears, nasal mucus, saliva, sputum, urine, feces, semen, vaginal secretions, milk

Adapted from Rutala and Weber [11••]. Infectivity: high transmission to inoculated animals $\geqslant$50%; low transmission to inoculated animals $\geqslant$10–20% (except lung 50%) but no epidemiological evidence of human infection via these tissues; non-transmission to inoculated animals 0%.

Iatrogenic Creutzfeldt–Jakob disease

Iatrogenic CJD has been described in humans in three circumstances: after the use of contaminated medical equipment (two confirmed cases); after the use of extracted pituitary hormones (over 130 cases) or gonadotrophin (four cases); and after the implant of contaminated grafts from humans (cornea three cases, dura mater over 110 cases) [26]. Transmission via stereotactic electrodes is the only convincing example of transmission via a medical device, but the method used to 'sterilize' these electrodes would not currently be considered an adequate method for sterilizing medical devices. The infrequent transmission of CJD via contaminated medical devices probably reflects the inefficiency of transmission, unless dealing with neural tissue and the effectiveness of conventional cleaning and current disinfection and sterilization procedures. Retrospective studies suggest that five other cases may have resulted from the use of contaminated instruments in neurosurgical operations [26].

The risks associated with blood products have been reviewed and it was concluded that CJD had not been transmitted by the transfusion of human blood products [27,28]. Evidence supporting this conclusion includes studies in patients with CJD [29], hemophilia [30,31]; intravenous drug use [1]; and humans [32] and animals [29] receiving blood from CJD patients.

There is no evidence of the occupational transmission of CJD to healthcare workers. In the context of occupational exposure, the highest potential risk is from exposure to high infectivity tissue through needlestick injuries with inoculation. Exposure by splashing of the mucous membranes or unintentional ingestion may be considered a hypothetical risk.

Control measures

Currently the Food and Drug Administration (FDA) requirements for dura mater transplantation include screening and eliminating donors with neurological diseases, the avoidance of any opportunity for cross-contamination between grafts, treating grafts with 1.0 N sodium hydroxide or other procedures with a comparable degree of safety, a full autopsy of each donor's brain with a histological examination to exclude prion diseases, and keeping records of both the donor and recipient of each graft [33]. However, the transmission of CJD by dura mater graft has been reported despite treatment with 0.1 N sodium hydroxide [34].

Concern has been raised by the presence in certain vaccines of bovine-derived materials obtained from countries in which BSE or a substantial risk of BSE exists [35]. The FDA recommends that vaccines manufactured with bovine-derived materials from countries on the USA list be replaced with bovine-derived materials from other countries.

The FDA currently recommends the exclusion of blood donors who had lived in the United Kingdom for 3 months or more between 1980 and 1996, and included the exclusion of donors who have lived in other European countries [36].

Because CJD has been transmitted via corneal transplantation, the FDA proposed in 1999 that TSE screening (history and physical examination) be undertaken for all cell and tissue donors, including cornea donors [37]. However, a committee of the Eye Bank Association of America concluded that screening for symptoms of CJD would have a minimal impact on safety, but would reduce the donor supply and probably result in many patients not receiving the necessary treatment [38].

Healthcare workers when caring for patients with CJD should use standard precautions. Added personal protective equipment such as gowns or masks are unnecessary in view of the lack of communicability to healthcare workers.

Guidelines for the reprocessing of CJD-contaminated medical devices have been published by the Centers for Disease Control and Prevention [39], the World Health Organization [9], and healthcare professionals [10–12,40–42]. To minimize the possibility of the use of potentially contaminated neurosurgical instruments from patients later diagnosed with CJD, hospitals should consider using the sterilization guidelines below for neurosurgical instruments used on patients undergoing brain biopsy when a specific lesion (e.g. suspected tumor) has not been demonstrated (e.g. magnetic resonance imaging, computed tomography) [11,40]. Alternatively, the neurosurgical instruments used in such cases could be disposable.

Disinfection and sterilization

The inactivation of prions by germicides and sterilization processes has been studied by several investigators, but such studies do not reflect the reprocessing procedures in a clinical setting. Variables in these disinfection studies include the prion strain, prion concentration, test tissue, test animal, duration of follow-up, method of calculating the log decrease of the prion with disinfection, and exposure conditions. On the basis of the disinfection studies, many but not all processes fail to inactivate clinically significant numbers of prions (Table 2). Similarly, many but not all sterilization processes fail to inactivate prions (Table 3).

Concerns with variant Creutzfeldt–Jakob disease

Most of the data that form the basis of our recommendations have been generated from studies of the prions

Table 2. Efficacy of chemical disinfectants in inactivating prions

Ineffective chemical disinfectants (<3 $\log_{10}$ reduction in 1 h)	Effective chemical disinfectants ($\geqslant 3$ $\log_{10}$ reduction in 1 h)
Alcohol 50%	Chlorine >1000 ppm
Ammonia 1.0 M	Sodium hydroxide $\geqslant 1$ N
Chlorine dioxide 50 ppm	Phenolic $>0.9\%$
Formaldehyde 3.7%	Guanidine thiocyanate 4 M
Glutaraldehyde 5%	
Hydrochloric acid 1.0 N	
Hydrogen peroxide 3%	
Iodine 2%	
Peracetic acid	
Phenol/phenolics 0.6%	

Adapted from Rutala and Weber [10].

Table 3. Efficacy of chemical disinfectants in inactivating prions

Ineffective sterilization processes (<3 $\log_{10}$ reduction)	Effective sterilization processes ($\geqslant 3$ $\log_{10}$ reduction)
Steam sterilization at conventional exposure conditions (121°C for 15 min)	Autoclaving at 134°C for 18 min (prevacuum sterilizer)
Ethylene oxide for 1 h	Autoclaving at 121–132°C for 1 h (gravity displacement sterilizer)
	0.09 or 0.9 N sodium hydroxide for 2 h plus 121°C for 1 h (gravity displacement sterilizer)

Adapted from Rutala and Weber [10].

responsible for sCJD or animal TSE diseases (e.g. scrapie). Limited data are available on which to base recommendations for the prevention of vCJD. To date, there have been no reports of human-to-human transmission of vCJD by blood or tissue. Unlike sCJD, patients with vCJD have PrP^{sc} detectable in the lymphoid tissue. Furthermore, PrP^{sc} proteins may be detectable before the onset of clinical illness. This has raised concerns about the possible human-to-human transmission of vCJD by medical instruments contaminated with such tissues. On the basis of these concerns, the use of prion disinfection and sterilization guidelines (or single-use instruments) has been proposed in the UK for instruments used in dental procedures [43], eye procedures [44], or tonsillar surgery [45] on patients at high risk of sCJD or vCJD. If epidemiological and infectivity data show that these tissues represent a transmission risk then CJD sterilization precautions (or the use of disposable equipment) could be extended to equipment used for these procedures.

Conclusion

Prion diseases are rare and therefore do not constitute a major infection control risk. Nevertheless, prions represent an exception to conventional disinfection and sterilization practices. Our guidelines for CJD disinfection and sterilization are based on the consideration of epidemiological data, infectivity data, and cleaning and inactivation studies (Table 4). Guidelines for the management of CJD-infected patients and patient equipment should be modified as scientific information becomes available.

Table 4. Key infection control precautions for patients with known or suspected Creutzfeldt–Jakob disease

General precautions

1. Precautions are used on all patients with known or suspected prion disease, including patients with rapidly progressive dementia and dura mater transplants or human growth hormone injection.
2. Standard precautions should be used on all patients with known or suspected CJD. Gloves (and when indicated gowns, masks, protective eyeware) should be worn if exposure to blood or other potentially infectious material is anticipated.

Decontamination of contaminated medical devices

1. High-risk tissues from high-risk patients (e.g. known or suspected CJD) and critical/semicritical items.
   (a) Those devices that are constructed such that cleaning procedures result in effective tissue removal (e.g. surgical instruments) can be cleaned and then sterilized by autoclaving at 134°C for $\geqslant 18$ min in a prevacuum sterilizer, or 132°C for 1 h in a gravity displacement sterilizer.
   (b) Those devices that are impossible or difficult to clean could be discarded. Alternatively, one should place the contaminated items in a container filled with a liquid (e.g. saline, water or phenolic solution) to retard adherence of material to the medical device; followed by initial decontamination by autoclaving at 134°C for 18 min in a prevacuum sterilizer (liquids must be removed before sterilization), or 132°C for 1 h in a gravity displacement sterilizer, or soaking in 1 N NaOH for 1 h; and finally, terminal cleaning, wrapping and sterilization by conventional means.
   (c) Environmental surfaces contaminated with high-risk tissues should be cleaned and then spot decontaminated with a 1 : 10 dilution of sodium hypochlorite (i.e. bleach). To minimize environmental contamination, disposable cover sheets could be used on work surfaces.
   (d) Non-critical equipment contaminated with high-risk tissue should be cleaned and then disinfected with a 1 : 10 dilution of sodium hypochlorite or 1 N NaOH depending on material compatibility.
2. Low-risk tissues from high-risk patient and critical/semicritical medical device. These devices can be cleaned and disinfected or sterilized using conventional protocols of heat or chemical sterilization, or high-level disinfection.
3. No-risk tissue from high-risk patient and critical/semicritical medical device.
   (a) These devices can be cleaned and disinfected or sterilized using conventional protocols of heat or chemical sterilization, or high-level disinfection.
   (b) Endoscopes would be contaminated only with no-risk materials (except neurosurgical endoscopes) and thus standard cleaning and high-level disinfection protocols would be adequate for reprocessing.

CJD, Creutzfeldt–Jakob disease; NaOH, sodium hydroxide. Adapted from Rutala and Weber [11••] (see reference for comprehensive guideline).

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