Prions Diseases: Current and Future Challenges

William A. Rutala, Ph.D., M.P.H.
University of North Carolina (UNC) Health Care System and UNC School of Medicine, Chapel Hill, NC, USA

Disclosure

This educational activity is brought to you, in part, by Advanced Sterilization Products (ASP) and Ethicon. It does not constitute recommendations or medical advice of ASP or Ethicon. ASP nor Ethicon provide medical advice. ASP and Ethicon do not have independent knowledge concerning the information contained in this presentation and the studies, findings and conclusions expressed are those reached by the authors. This ASP and Ethicon sponsored presentation is not intended to be used as a training guide. Please read the full Instructions for Use of each device discussed or depicted for more detailed information on the proper use, indications, contraindications, warnings, instructions and steps for use of the devices (s). The speaker receives an honorarium from ASP and Ethicon and must present information in compliance with FDA requirements applicable to ASP.

Prion Diseases: Current and Future Challenges
Topics

- Learning Objectives
  - Define the etiology, epidemiology, and clinical features of prion transmission
  - Review iatrogenic transmission of prion diseases
  - Examine the infectivity of human tissues
  - Review the prion inactivation studies
  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges

Prion Diseases: Current and Future Challenges
Topics

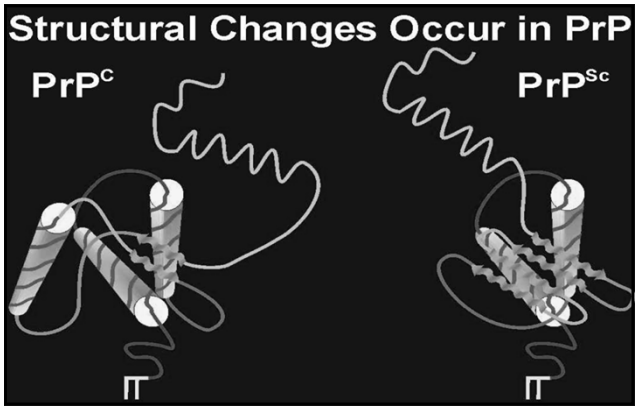
- Learning Objectives
  - Define the etiology, epidemiology, and clinical features of prion transmission
  - Review iatrogenic transmission of prion diseases
  - Examine the infectivity of human tissues
  - Review the prion inactivation studies
  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges

Transmissible Spongiform Encephalopathies (TSEs) of Humans

- Kuru
- Gertsmann-Straussler-Scheinker (GSS)
- Fatal Familial Insomnia (FFI)
- Creutzfeldt-Jakob Disease (CJD)
- Variant CJD (vCJD), 1995 (221 cases, August 2011): 172 UK, 25 France, 4 Ireland, 2 Italy, 3 USA, 2 Canada,1 Saudi Arabia, 1 Japan, 3 Netherlands, 2 Portugal, 5 Spain, 1 Taiwan)

Prion Diseases

- Etiology
  - Prions (proteinaceous infectious agent)
    - ◆No agent-specific nucleic acid
    - ◆Host protein (PrP^{c}) converts to pathologic isoform (PrP^{sc}); PrP gene resides on chromosome 20
    - ◆The function of the normal prion protein is unknown
    - ◆Mutation in this gene may trigger transformation
    - ◆Accumulates in neural cells, disrupts function
    - ◆Resistant to conventional D/S procedures



Epidemiology of CJD in the US

- Degenerative neurologic disorder with progressive dementia
- Incidence
  - One death/million population
  - No seasonal distribution, no geographic aggregation
  - Both genders equally affected
  - Age range 50-80+ years, average 67
- Long incubation disease (months-years)
- Rapid disease progression after onset (death within 6 mo)

Clinical Features of CJD

- Degenerative neurological disorder with progressive dementia (memory, intellect, personality)
- Progressive motor deterioration
  - Unsteadiness and clumsiness
  - Visual deterioration
  - Muscle twitching
  - Severe dementia, mute, immobile
- Death (< 1 year)

Diagnosis of CJD

- Clinical syndrome
  - Progressive intellectual and neurological deterioration
- EEG-classic periodic triphasic wave
- MRI-hyperlucency in the putamen
- CSF testing (surrogate markers-14-3-3 [sensitivity/specificity >90% in the presence of typical clinical picture], tau protein)
- Neuropathology
  - Brain biopsy (dx in 95% of cases confirmed by autopsy)
  - Autopsy, neuropathology confirmation

Transmissibility of Prions

- Transmission
  - Not spread by contact (direct, indirect, droplet) or airborne
  - Not spread by the environment
  - Experimentally-all TSEs are transmissible to animals, including the inherited forms
  - Epidemiology of CJD: sporadic-85%; familial-15%; iatrogenic-1% (majority after implant of contaminated grafts [dura mater] or receive hormone therapy, ~400 cases worldwide; contaminated medical equipment [6 cases])

General Infection Prevention Precautions

- Standard Precautions should be used for patients with CJD. Gloves worn for handling blood and body fluids.
- Masks, gowns, and eyewear if exposure is anticipated.
- No additional precautions for laundry or handling food utensils.
- Patients with prion diseases should not serve as organ donors
- No special precautions for disposal of body fluids or regulated medical waste.
- No excess precautions needed for burial.

Prion Diseases: Current and Future Challenges
Topics

- Learning Objectives
  - Define the etiology, epidemiology, and clinical features of prion transmission
  - Review iatrogenic transmission of prion diseases
  - Examine the infectivity of human tissues
  - Review the prion inactivation studies
  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges

Iatrogenic Transmission of CJD

- Contaminated medical instruments
  - Electrodes in brain (2)
  - Neurosurgical instruments in brain (4 suspected cases)
- Implantation of contaminated grafts
  - Dura mater grafts (>190)
  - Corneal grafts (3)
- After patients received hormone therapy
  - Use of human growth hormone and gonadotropin (>190 cases)

CJD and Medical Devices

- Six cases of CJD associated with medical devices
  - 2 confirmed cases-depth electrodes; reprocessed by benzene, 70% alcohol and formaldehyde vapor
  - 4 unconfirmed cases-CJD following brain surgery, suspect neurosurgical instruments; index CJD identified-1
- Cases occurred from 1953-1980 in UK, France and Switzerland
- No cases since 1980 and no known failure of steam sterilization

Prion Diseases: Current and Future Challenges
Topics

- Learning Objectives
  - Define the etiology, epidemiology, and clinical features of prion transmission
  - Review iatrogenic transmission of prion diseases
  - Examine the infectivity of human tissues
  - Review the prion inactivation studies
  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges

Risk of CJD Transmission

- Epidemiologic evidence (eye, brain) linking specific body tissue or fluids to CJD transmission
- Experimental evidence in animals demonstrating that body tissues or fluids transmit CJD
  - Infectivity assays a function of the relative concentration of CJD tissue or fluid

Risk of CJD Transmission

Risk of Infection	Tissue
High	Brain (including dura mater), spinal cord, pituitary tissue and posterior eye
Low	CSF, liver, lymph node, kidney, lung, spleen, placenta, olfactory epithelium
No	Peripheral nerve, intestine, bone marrow, whole blood, leukocytes, serum, thyroid gland, adrenal gland, heart, skeletal muscle, adipose tissue, gingiva, prostate, testis, tears, nasal mucus, saliva, sputum, urine, feces, semen, vaginal secretions, sweat and milk

High-transmission to inoc animals >50%; Low-transmission to inoc animals >10-20% but no epid evidence of human inf

Prion Diseases: Current and Future Challenges
Topics

- Learning Objectives
  - Define the etiology, epidemiology, and clinical features of prion transmission
  - Review iatrogenic transmission of prion diseases
  - Examine the infectivity of human tissues
  - Review the prion inactivation studies
  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges

CJD: DISINFECTION AND STERILIZATION

- Effectiveness must consider both removal by cleaning and disinfection/sterilization
  - Probability of a device remaining capable of transmitting disease depends on the initial contamination and effectiveness of cleaning and disinfection/sterilization.
  - Device with 100μg of protein (median protein contamination from 8-91μg per instrument) and CJD brain tissue has a titer of 5 $\log_{10}$ LD_{50}IC/g (mean infectivity calculated from group of 27), an instrument would have 10 potentially infectious units without considering prionicidal activity of process.

CJD: DISINFECTION AND STERILIZATION

- Cleaning
  - Cleaning results in a 4 to 6 $\log_{10}$ reduction of microbes and ~2 $\log_{10}$ reduction in protein contamination (prions ?)
  - Some alkaline detergents reduce 5 $\log_{10}$ prions; some enzymatic detergents reduce 5 $\log_{10}$ prions
- Sterilization
  - Steam sterilization (121º or 132ºC) results in a 4 to 7 $\log_{10}$ reduction

Decreasing Order of Resistance of Microorganisms to Disinfectants/Sterilants

Prions
Spores
Mycobacteria
Non-Enveloped Viruses
Fungi
Bacteria
Enveloped Viruses

Prion Inactivation Studies

- Problems
  - Studies do not reflect reprocessing procedures in a clinical setting (e.g., no cleaning)
  - Factors that affect results include: brain tissue macerates vs. intact tissue (smearing, drying), weights of tissue (50mg-375mg), strain of prion (22A), prion concentration in brain tissue, animal used, exposure conditions, validation and cycle parameters of sterilizers, resistant subpopulation, different test tissues, different duration of observations, screw cap tubes with tissue (air), etc

Ineffective or Partially-Effective Disinfectants: CJD

- Alcohol
- Ammonia
- Chlorine dioxide
- Formaldehyde
- Glutaraldehyde
- Hydrogen peroxide
- Iodophors/Iodine
- Peracetic acid
- Phenolics

Ineffective or Partially Effective Processes: CJD

- Gases
  - Ethylene oxide
  - Formaldehyde
- Physical
  - Dry heat
  - UV
  - Microwave
  - Ionizing radiation
  - Autoclave at 121ºC, 15m

Effective Disinfectants

($\geq$4 $\log_{10}$ decrease in LD_{50} within 1 hour)

- Sodium hydroxide
  - 1 N for 1h (variable results)
- Sodium hypochorite
  - 5000 ppm for 15m
- Guanidine thiocyanate
  - >3M
- Phenolic (LpH)
  - 0.9% for 30m
- Some alkaline and enzymatic detergents

Effective Processes: CJD

- Autoclave
  - 134ºC for 18m (prevacuum)
  - 132ºC for 60m (gravity)
- Combination (chemical exposure then steam autoclave, potentially deleterious to staff, instruments, sterilizer)
  - Soak in 1N NaOH for 1 hour, remove and rinse in water, then autoclave 121ºC for 60m

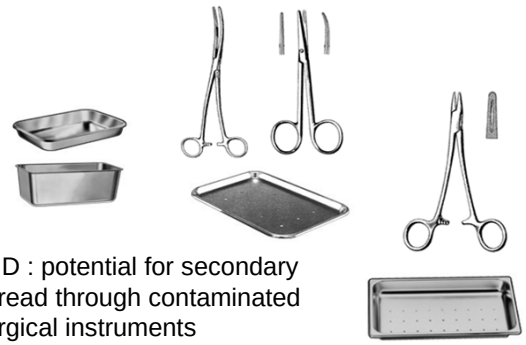
Disinfection and Sterilization

- EH Spaulding believed how an object will be D/S depended on the objects intended use
  - CRITICAL-objects that enter normally sterile tissue or the vascular system should be sterile
  - SEMICRITICAL-objects that touch mucous membranes or skin that is not intact requires a disinfection process (high level disinfection) that kills all but bacterial spores (prions?)
  - NONCRITICAL-objects that touch only intact skin require low-level disinfection

Prion Diseases: Current and Future Challenges

Topics

- Learning Objectives
  - Define the etiology, epidemiology, and clinical features of prion transmission
  - Review iatrogenic transmission of prion diseases
  - Examine the infectivity of human tissues
  - Review the prion inactivation studies
  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges



CJD : potential for secondary spread through contaminated surgical instruments

SHEA Guideline
Infect Control Hosp Epidemiol 2010;31:107

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY FEBRUARY 2010, VOL. 31, NO. 2

SHEA GUIDELINE

Guideline for Disinfection and Sterilization of Prion-Contaminated Medical Instruments

William A. Rutala, PhD, MPH; David J. Weber, MD, MPH

EPIDEMIOLOGY OF THE CREUTZFELDT-JAKOB DISEASE PRION

Creutzfeldt-Jakob disease (CJD) is a degenerative neurologic disorder of humans with an incidence in the United States of approximately 1 case per million population per year.[1-3] tains. To date, no evidence for transmission of chronic wasting disease of deer and elk to humans has been identified.[7-10]

TRANSMISSION OF CJD VIA MEDICAL DEVICES

Risk Assessment for Special Prion Reprocessing: Patient, Tissue, Device

- High-Risk Patient
  - Known or suspected CJD or other TSEs
  - Rapidly progressive dementia
  - Familial history of CJD, GSS, FFI
  - History of dura mater transplant, cadaver-derived pituitary hormone injection
- High-Risk Tissue
  - Brain, spinal cord, eyes
- High-Risk Device
  - Critical or semicritical

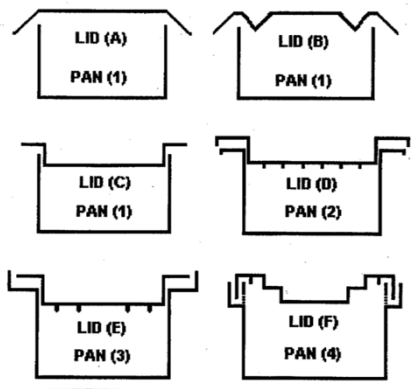
CJD: Disinfection and Sterilization
Conclusions

- Critical/Semicritical-devices contaminated with high-risk tissue from high-risk patients requires special prion reprocessing
  - 134ºC for 18m (prevacuum)
  - 132ºC for 60m (gravity)
  - NaOH and steam sterilization (e.g., 1N NaOH 1h, then 121ºC 1h)
- Discard instruments that are impossible to clean
- No low temperature sterilization technology currently recommended*
- Noncritical-four disinfectants (e.g., chlorine, Environ LpH) effective (4 log decrease in LD_{50} within 1h)

*VHP and HP gas plasma (Sterrad NX) reduced prion infectivity but not cleared by FDA

CJD: Instrument Reprocessing

- Special prion reprocessing by combination of NaOH and steam sterilization
  - Immerse in 1N NaOH for 1 hour; remove and rinse in water, then transfer to an open pan and autoclave at 121ºC for 1 hour
  - Immerse in 1N NaOH for 1 hour and heat in a gravity displacement sterilizer at 121ºC for 30 minutes
- Combined use of autoclaving in sodium hydroxide has raised concerns of possible damage to autoclaves, and hazards to operators due to the caustic fumes.
- Risk can be minimized by the use of polypropylene containment pans and lids (AJIC 2003; 31:257-60).



Examples: CJD D/S

- High risk patient, high risk tissue, critical/semicritical device-special prion reprocessing
- High risk patient, low risk tissue (defined as CSF, kidney, liver, spleen, lung, etc) critical/semicritical device-no recommendation, use either conventional D/S or special prion reprocessing
- High risk patient, no risk tissue, C/SC device-conventional D/S
- Low risk patient, high risk tissue, critical/semicritical device-conventional D/S
- High risk patient, high risk tissue, noncritical device-conventional disinfection

D/S of Medical Devices

- Issues
  - Do not allow tissue/body fluids to dry on instruments (e.g., place in liquid)
  - Some decontamination procedures (e.g., aldehydes) fix protein and this may impede effectiveness of processes
  - Clean instruments but prevent exposure
  - Assess risk of patient, tissue, device
  - Choose effective process

Prevent Patient Exposure to CJD Contaminated Instruments

How do you prevent patient exposure to neurosurgical instruments from a patient who is latter given a diagnosis of CJD?

Hospitals should use the special prion reprocessing precautions for instruments from patients undergoing brain biopsy when a specific lesion has not been demonstrated (e.g., CT, MRI). Alternatively, neurosurgical instruments used in such cases could be disposable.

Prion Diseases: Current and Future Challenges

Topics

- Learning Objectives
  - Define the etiology, epidemiology, and clinical features of prion transmission
  - Review iatrogenic transmission of prion diseases
  - Examine the infectivity of human tissues
  - Review the prion inactivation studies
  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges and changes

Critical/semicritical instruments contaminated with high-risk tissue from a high-risk patient require “special prion reprocessing”. New technologies may alter the need for “special prion reprocessing” in the future.

Inactivation of Prions

Recent Studies

- Yan et al. Infect Control Hosp Epidemiol 2004;25:280. Enzymatic cleaner (EC)-no effect
- Fichet et al. Lancet 2004;364:521. Phenolic (Environ LpH), alkaline cleaner (AC), EC+VHP-effective
- Baier et al. J Hosp Infect 2004;57:80. AC-effective
- Lemmer et al. J Gen Virol 2004;85:3805. SDS/NaOH, AC, 0.2% PA, 5% SDS-effective (in vitro)
- Jackson et al. J Gen Virol 2005;86:869. E (Pronase, PK)-effective
- Race R and Raymond G. J Virol 2004;78:2164. Environ LpH-effective
- Peretz et al. J Virol 2006;80:1. Acidic SDS and SDS+SS-effective
- Fichet et al. JHI 2007;67:278. Gaseous HP-effective
- Yan et al. Zentr Steril 2008;16:26-34. HP Gas Plasma effective (Sterrad NX)
- Rogez-Kreuz C. ICHE 2009;30:769. HP Gas Plasma effective (Sterrad NX)

Variant CJD

- Strongly associated with epidemiology of BSE (1983) in UK
- BSE amplified by feeding cattle meat and bone meal infected with BSE (bovine spongiform encephalopathy)
- August 2011, (221 cases: 172 UK, 25 France, 4 Ireland, 2 Italy, 3 USA, 2 Canada,1 Saudi Arabia, 1 Japan, 3 Netherlands, 2 Portugal, 5 Spain, 1 Taiwan)
- Affects young persons (range 13-48y, median 28y)
- Clinical course is longer (14 mo vs <6 mo)
- BSE not reported in the United States
- vCJD and BSE are believed caused by the same prion agent

vCJD: Disinfection and Sterilization

- To date no reports of human-to-human transmission of vCJD by tissue but 4 possible cases by blood transfusion reported
- Unlike CJD, vCJD detectable in lymphoid tissues (e.g., spleen, tonsils, thymus, appendix) and prior to onset of clinical illness
- Special prion reprocessing (or single use instruments) proposed in the UK in dental, eye, or tonsillar surgery on high risk patients for CJD or vCJD
- If epidemiological and infectivity data show these tissues represent a transmission risk then special prion reprocessing could be extended to these procedures

Conclusions

- Epidemiologic evidence suggests nosocomial CJD transmission via medical devices is very rare
- Guidelines based on epidemiologic evidence, tissue infectivity, risk of disease via medical devices, and inactivation data
- Risk assessment based on patient, tissue and device
- Only critical/semicritical devices contacting high risk tissue from high risk patients require special prion reprocessing

CJD: Disinfection and Sterilization
Conclusions

- Critical/Semicritical-devices contaminated with high-risk tissue from high-risk patients requires special prion reprocessing
  - 134ºC for 18m (prevacuum)
  - 132ºC for 60m (gravity)
  - NaOH and steam sterilization (e.g., 1N NaOH 1h, then 121ºC 1h)

Prion Diseases: Current and Future Challenges
Topics

- Learning Objectives
  - Define the etiology, epidemiology, and clinical features of prion transmission
  - Review iatrogenic transmission of prion diseases
  - Examine the infectivity of human tissues
  - Review the prion inactivation studies
  - Provide the recommendations to prevent cross-transmission from medical devices contaminated with prions
  - Discuss future challenges

Thank you

disinfectionandsterilization.org

Disinfection and Sterilization for Prion Diseases
References

- Rutala WA, Weber DJ. Creutzfeldt-Jakob Disease: Recommendations for Disinfection and Sterilization. Clin Inf Dis 2001;32:1348-1356.
- Rutala WA, Weber DJ, and HICPAC. CDC Guideline for Disinfection and Sterilization (draft). www.cdc.gov/ncidod/hip/dsguide.htm
- Prusiner SB. Prion Biology and Diseases. 1999. Cold Spring Harbor Laboratory Press, New York.
- Rutala WA, Weber DJ. Guideline for disinfection and sterilization of prion-contaminated medical instruments. In press.
- Weber DJ, Rutala WA. 2002. Managing the risks of nosocomial transmission of prion diseases. Current Opinions in Infectious Diseases. 15:421-426.

CJD and Medical Devices

- World Health Organization, 2000
  - When instruments contact high infectivity tissue, single-use instruments recommended.
  - If single-use instruments not available, maximum safety attained by destruction of re-usable instruments.
  - Where destruction is not practical, reusable instruments must be decontaminated by immerse in 1N NaOH and autoclaved (121ºC/30m), cleaned, rinsed and steam sterilized.
  - After decontamination by steam and NaOH, instruments can be cleaned in automated mechanical reprocessor.

TABLE 3. Efficacy of Chemicals in Inactivating Prions

Ineffective (⩽3 $\log_{10}$ reduction within 1 hour)	Effective (>3 $\log_{10}$ reduction within 1 hour at temperatures of 20°C–55°C)
Acetone	Alkaline detergent (specific formulations)
Alcohol, 50%–100%	Chlorine, >1,000 ppm
Alkaline detergent (specific formulations)	Copper, 0.5 mmol/L, and hydrogen peroxide, 100 mmol/L
Ammonia, 1.0 M	Enzymatic detergent (specific formulations)
Chlorine dioxide, 50 ppm	Guanidine thiocyanate, >3 M
Enzymatic detergent (specific formulations)	Hydrogen peroxide, 59%
Formaldehyde, 3.7%	Peracetic acid, 0.2%
Glutaraldehyde, 5%	Phenolic disinfectant (specific formulation), >0.9%
Hydrochloric acid, 1.0 N	Quaternary ammonium compound (specific formulation)
Hydrogen peroxide, 0.2%, 3%, 6%, 30%, 60%	Sodium dodecyl sulfate, 2%, and acetic acid, 1%
Iodine, 2%	Sodium hydroxide, ⩾1 N
Ortho-phthalaldehyde, 0.55%	Sodium metaperiodate, 0.01 M
Peracetic acid, 0.2%–19%	
Phenol/phenolics (concentration variable)	
Potassium permanganate, 0.1%–0.8%	
Quaternary ammonium compound (specific formulation)	
Sodium dodecyl sulfate, 1%–5%	
Sodium deoxycholate 5%	
Tego (dodecyl-di[aminoethyl]-glycine), 5%	
Triton X-100, 1%	
Urea, 4–8 M	

NOTE. The same process may be listed as both effective and ineffective because of differences in chemical concentration, exposure time, temperature, pH, etc, or differences in testing methods. All of these experiments were done without cleaning. Modified from Rutala and Weber,[14] with information from other studies.[illegible]

TABLE 2. Efficacy of Sterilization Processes in Inactivating Prions

Ineffective (⩽3 $\log_{10}$ reduction within 1 hour)	Effective (>3 $\log_{10}$ reduction from 18 minutes to 3 hours)
Autoclave at standard exposure conditions (121°C for 15 minutes)	Autoclave at 121°C–132°C for 1 hour (gravity displacement sterilizer) or 121°C for 30 minutes (prevacuum sterilizer)
Boiling	Autoclave at 134°C for 18 minutes (prevacuum sterilizer)
Dry heat	Autoclave at 134°C for 18 minutes immersed in water
Ethylene oxide	Hydrogen peroxide gas plasma (Sterrad NX)
Formaldehyde	Radiofrequency gas plasma
Hydrogen peroxide gas plasma, Sterrad 100S (ASP)	Sodium dodecyl sulfate, 2%, plus acetic acid, 1%, plus autoclave at 121°C for 15–30 minutes
Ionizing radiation	
Microwave	Sodium hydroxide (NaOH), 0.09 N or 0.9 N, for 2 hours plus autoclave at 121°C for 1 hour (gravity displacement sterilizer)
UV light	
	Vaporized hydrogen peroxide, 1.5–2 mg/L

NOTE. The same process may be listed as both effective and ineffective because of differences in sterilant concentration, exposure time, temperature, etc, or differences in testing methods. All of these experiments were performed without cleaning. Modified from Rutala and Weber,[14] with information from other studies.[27-62]

TABLE 1. Comparative Frequency of Infectivity in Organs, Tissue, and Body Fluids of Humans with Transmissible Spongiform Encephalopathies (Creutzfeldt-Jakob Disease)

Infectious risk[a]	Tissue
High	Brain (including dura mater), spinal cord, posterior eye, pituitary tissue
Low	Cerebrospinal fluid, liver, lymph node, kidney, lung, spleen, placenta, olfactory epithelium
No risk	Peripheral nerve, intestine, bone marrow, whole blood, leukocytes, serum, thyroid gland, adrenal gland, heart, skeletal muscle, adipose tissue, gingiva, prostate, testis, tears, saliva, sputum, urine, feces, semen, vaginal secretions, milk, sweat

NOTE. Modified from Brown[14] and Brown et al,[15] with information from other studies.[16-23]

[a] High risk indicates a rate of transmission to inoculated animals of >50%; low risk indicates a rate of transmission to inoculated animals of ⩾10%–20% (except for lung tissue, for which transmission is 50%); no risk indicates a rate of transmission to inoculated animals of 0% (several tissues in this category had few tested specimens).