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# The New Standard of Fluids for Hemodialysis in Japan

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**Key Words**
Standard of fluids for hemodialysis · Endotoxin · Bacteria · Central dialysis fluid delivery system

**Abstract**
The standard of fluids for hemodialysis is being evaluated by the International Organization for Standardization (ISO), and will be decided within a few years. In 2008, the Japanese Society for Dialysis Therapy (JSDT) proposed the standard of fluids for hemodialysis by taking the draft ISO standard into consideration and the circumstances in Japan. It was characteristically a standard for Japan, where the central dialysis fluid delivery system (CDDS) is routinely used. In addition, the therapeutic application of each dialysis fluid is clarified. Since high-performance dialyzers are frequently employed in Japan, the standard recommends that ultrapure dialysis fluid be used for all dialysis modalities at all dialysis facilities. It also recommends that the dialysis equipment safety management committee at each facility validate the microbiological qualities of online-prepared substitution fluid, making the responsibility of the dialysis facility clear. This standard is more rigid than those of other countries, and is expected to contribute to improvements in the survival outcome of dialysis patients. 

## Introduction

The necessity of dialysis fluid purification has been discussed since the 1980s, primarily in Europe. The Japanese Society for Dialysis Therapy (JSDT) presented the Quality Standard of Microbiological Contaminants in Dialysis Fluid in 1995 [1] and revised it in 1998 [2] and 2005 [3]. Presently, the International Organization for Standardization (ISO) is preparing an international quality standard for dialysis fluid in which bacterial count is emphasized as the most important parameter for evaluating microbiological qualities of fluids for hemodialysis and related therapies [4]. We proposed a new quality standard for dialysis fluid 2008 that is in harmony with the ISO standards for microbiological management [5]. The purpose of this paper is to introduce the new Japanese standard and discuss the aspects of hemodialysis.

## Microbiological Quality Standard for Dialysis Fluids

*1. Attainment Level*

– Dialysis water (reverse osmosis (RO) water)
Bacteria: <100 CFU/ml
Endotoxin: <0.050 EU/ml

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– Standard dialysis fluid
  Bacteria: <100 CFU/ml
  Endotoxin: <0.050 EU/ml
– Ultrapure dialysis fluid
  Bacteria: <0.1 CFU/ml
  Endotoxin: <0.001 EU/ml (less than detection limit).
  *Note:* Action level shall be set depending on the quality condition of each facility, typically at 50% of the maximum allowable level except for endotoxin of ultrapure dialysis fluid.
– Online-prepared substitution fluid
  Sterile and non-pyrogenic
  Bacteria: $<10^{-6}$ CFU/ml
  Endotoxin: <0.001 EU/ml (less than detection limit).

*2. Frequency of Monitoring*

– *Dialysis water: Every 3 months.* If the quality of each facility is not maintained to allowable levels, the monitoring frequency should be increased to once a month.
– *Standard dialysis fluid: Monthly.* At least two machines are tested each month so that each machine is tested at least once per year.
– *Ultrapure dialysis fluid:* Monthly when used for conventional hemodialysis (including internal filtration-enhanced hemodialysis). At least two machines are tested each month so that each machine is tested at least once per year.
– Ultrapure dialysis fluid for the preparation of online substitution fluid and the dialysis system for active use of back filtrate: Every 2 weeks until the system is validated. After the quality is validated by the dialysis equipment safety management committee, monitor the same frequency as standard dialysis fluid.
– *Online-prepared substitution fluid: Monthly*
  *Endotoxin:* Every 2 weeks until the system is validated. After the quality is validated by the dialysis equipment safety management committee, monitor monthly on every machine of dialysis fluid and substitution fluid.
  *Bacteria:* Sterility of $10^{-6}$ CFU/ml is impossible to detect. Dialysis fluid used for preparation of substitution fluid should be maintained to the quality of ultrapure dialysis fluid. Bacteria culture of dialysis fluid and substitution fluid should be conducted every 2 weeks until the system is validated. After the validation by the dialysis equipment safety management committee, monitor monthly, rotating among machines so that at least two machines are tested each month and each machine is tested at least once per year.

*3. Indications for Dialysis System Based on the Quality of Dialysis Fluids*

– Standard dialysis fluid
  Minimum requirement for dialysis therapy.
– Ultrapure dialysis fluid*
  Dialysis fluid for the preparation of online substitution fluid.
  Dialysis system for active use of back filtrate (e.g., fully automated dialysis system [6])
  Push & pull HDF system
  Internal filtration-enhanced dialysis (IFEHD)**
– Online-prepared substitution fluid
  Online HDF/online hemofiltration (HF)

  * Ultrapure dialysis fluid is desirable for all dialysis modalities.

  ** Estimated filtration rate in IFEHD ≥35 ml/min [3].

*4. Test for Compliance*

– *Endotoxin: Limulus amoebocyte* lysate (LAL) assay (gel-clot assay, spectrophotometric kinetic assay).
– *Bacteria:* Culture media R2A (Reasoner's Agar No. 2), TGEA (tryptone glucose extract agar) or equivalent.
  Cultivation condition: R2A and TGEA: 17–23°C, 7 days.

*5. Sampling Sites*

– Dialysis water: Outlet of RO equipment
– Dialysis fluid: Inlet line of dialyzer
  *Note:* Push & pull hemodiafiltration (HDF) systems should be tested on the outlet line of dialyzer.
  Online-prepared substitution fluid: extraction site of substitution fluid.

*6. Sampling Day: Before Start of Dialysis and After the Maximal Interval of Dialysis (Commonly Monday)*

*7. Standard of Endotoxin Retentive Filter (ETRF)*

– ETRF should meet the requirement of Japan Medical Devices Manufacturers Association.
– The user should follow the user's manual of each ETRF.
– Exchange time should meet the manufacturer's standard for each ETRF.
– If the manufacturer's standard does not indicate the exchange time, each facility should validate the performance of ETRF. The validated data should be reported to and confirmed by the dialysis equipment safety management committee.

*8. Safety Assurance Programs*

Dialysis fluids and apparatus must be managed according to an appropriate manual. Therefore, the persons responsible for the safety management of medical equipment must validate the dialysis apparatus at their facilities. They should then take the following measures:

(1) Establishment of a curriculum for education and training of dialysis operators.
(2) Preparation and assurance of the availability of a manual for dialysis fluid management.
(3) Management records and measurement records must be prepared and preserved similar to clinical records. The related documents must be preserved for 3 years from the date of preparation.
(4) For the management of the dialysis apparatus and water quality of dialysis fluids, a dialysis equipment safety management committee must be established under the person responsible for the safety management of medical equipment, to perform the following activities:
- A management plan for dialysis equipment and water treatment apparatus must be prepared. Appropriate maintenance work must be performed. Reports must be preserved.
- Seminars for staff members to promote the appropriate use of dialysis equipment must be arranged.
- Related medical information must be collected by a single entity. Delivery of the information to staff members must be assured. Accident-related information must be reported immediately to the committee.

(5) Online-prepared substitution fluids can be used only after validation by the dialysis equipment safety management committee. The committee shall provide written approval prior to use.

## Discussion

There have been various reports and reviews regarding the necessity of dialysis fluid purification. In addition, the adverse effects of microbiological contamination and dissociation between the bacterial count and endotoxin level have become widely recognized. Further, very low levels of contamination have been reported to impair biocompatibility [7–11]. Acceptable endotoxin levels assure the safety of the dialysis fluid. The presence of bacteria suggests a risk for the subsequent spread of contamination. The measurement of endotoxin compensates for the long culture time required for the bacterial test. Therefore, simultaneous evaluation of the bacteria count and endotoxin level is necessary for the assessment of microbiological contamination.

The ISO is a non-governmental, non-profit organization for the establishment of international standards in the industrial field, which holds conferences participated in by various manufacturing companies for the evaluation of international standards for product manufacturing and manufacturing management. In the field of dialysis, 13958 (Concentrates for HD and related therapies), 13959 (Water for HD and related therapies), and 26722 (Water treatment equipment for HD applications and related therapies) have been evaluated as standards for manufacturing companies, and the standards proposed by the organization have been generally understood as ones exclusively for such companies. Standards began to be discussed by physicians conducting dialysis therapy only after the establishment of an international standard for the routine management and purification of dialysis fluids at dialysis facilities (ISO23500; Fluids for HD and related therapies) was planned. ISO23500 was proposed in January 2004, following the revision of the standard for the routine management of dialysis fluids (RD52) by the Association for the Advancement of Medical Instrumentation (AAMI) [12]. Obtaining this information, the JSDT and Japan Association of Clinical Engineering Technologists recognized it as a standard directly related to dialysis therapy, and decided to actively participate in ISO meetings in cooperation with the Japan Medical Devices Manufacturers Association, which is a Japanese liaison organization.

A characteristic of the microbiological quality standard proposed by the ISO is that the standard is divided into 3 levels. Importantly, the fact that the standard clearly recognizes the presence of online-prepared substitution fluids indicates that online HDF has become an internationally accepted standard treatment.

Initially, only TGEA was used as the medium for bacterial detection, but Reasoner's Agar No. 2 (R2A) was also recommended as an equivalent medium due to pressure from Japan. In addition, the fact that the central dialysis fluid delivery system (CDDS) is mentioned many times in the standard is considered to be a reflection of Japanese opinion.

ISO11663 (Quality of dialysis fluid for HD and related therapies), which states numerical targets, was separated from ISO23500, which was initially entitled 'Fluid for hemodialysis and related therapies', and the latter was newly entitled 'Guidance for the preparation and quality management of fluids for hemodialysis and related ther-

apies', clarifying that it is a standard for software. It provides detailed provisions concerning the frequencies of microbiological measurements, conditions of culture media, and culturing methods. This standard directly affects the clinical practice of dialysis therapy, and further evaluation is necessary to ensure that Japanese views are reflected.

The ISO standard presents criteria for various dialysis fluids and those for instruments to achieve them, but includes no provisions concerning their clinical application because of the nature of the ISO. It is left to the standards of each country. For this reason, the JSDT proposed a new dialysis fluid quality standard based on the ISO standard [5]. Its characteristic is that it considers the site of application. Particularly, it requires a standard dialysis fluid to have a bacterial count of <100 CFU/ml and an ET of <0.050 UE/ml, which are stricter requirements than the ISO standard, in consideration of the situation whereby high-performance dialyzers account for more than 95% of all dialyzers used in Japan [13]. These values are considered to be appropriate, because they are met by 86% of the facilities according to the results of a statistical survey by the JSDT [14]. Most importantly, it recommends an ultrapure dialysis fluid level (bacterial count <0.1 CFU/ml, ET <0.001 EU/ml) for all dialysis modalities at all dialysis facilities. While the ISO standard regards the ultrapure dialysis fluid level as a criterion applied to dialysis fluid for online-prepared substitution fluid, the European Best Practice Guidelines recommend it for all dialysis modalities similarly to the JSDT standard, stating: 'Use of ultrapure water is strongly recommended for conventional and high-flux dialysis' [15].

Online-prepared substitution fluid is defined as sterile and non-pyrogenic, and the bacterial count, $10^{-6}$, is a theoretical value and undetectable [16]. Therefore, the draft ISO standard considers that this level can be realized only through the use of a dialyzer validated by its manufacturer. In Japan, the CDDS is used in many dialysis facilities, and dialysis fluids are prepared through multiple processes performed by various apparatuses connected in series. A dialysis facility functions as a dialysis fluid manufacturing facility, and is responsible for the final quality of the dialysis fluid. Therefore, a person responsible for manufacturing and managers of various processes must be appointed for dialysis fluid purification in the same manner as at manufacturing facilities. According to the JSDT standard, the dialysis equipment safety management committee is appointed under the safety management of medical equipment committee, the establishment of which is required by the Japanese Ministry of Health, Labour and Welfare for the quality management of dialysis apparatus and fluids, and the entire procedure for dialysis fluid preparation is controlled in an integrated manner by this committee as the organization responsible for the manufacturing of dialysis fluids. It particularly requires that online HDF be used only in a state validated by this committee and with its approval and guarantee. If, in the future, dialyzers exclusively for online HDF are approved, users must abide by the conditions of approval, and their manufacturers must guarantee the water quality. Each dialysis facility was thus held responsible for the management, because, in Japan, government-licensed clinical engineering technologists manage dialysis equipment in cooperation with physicians, unlike in other countries.

A problem unique to Japan is how the CDDS should be guaranteed by manufacturers. Many parts of the CDDS are not approved as medial devices, and, as they are manufactured by different companies, the company actually responsible is difficult to determine. Particularly, the manufacturing standard of the ETRF, which is important for water quality control, is determined as an industrial standard, but there is no standard for its management, and its application life, for example, is unknown. It must be determined according to the degree of purity upstream and treatment mode. This is particularly important in online HDF. As mentioned earlier, there is no equipment exclusively for online HDF in Japan at present, so the CDDS must be managed based on the responsibility of each facility, but if equipment exclusively for online HDF is approved in the future, as is the case in Europe, it will be initially limited to equipment for personal use. To retrospectively approve the present situation, in which online HDF can be provided to many patients under the CDDS, a validation system for the entire CDDS must be formulated by manufacturers. Articles concerning the CDDS could be incorporated into the draft ISO standard through a proposal by Japanese participants, but if articles concerning the central online HDF system can also be included in the standard in the future, it will be established as an industrial standard, and will facilitate validation.

The most notable clinical effect of dialysis fluid purification is improvement in anemia. Sitter et al. [8] reported significant decreases in interleukin-6 and C-reactive protein levels and an associated improvement in the response to recombinant human erythropoietin after replacement of the standard dialysis fluid (bacterial count:

85 CFU/ml) with ultrapure dialysis fluid (bacterial count <0.1 CFU/ml). Such a phenomenon has been reported by many facilities and is presently considered to be the clearest benefit of dialysis fluid purification. Retention of the residual kidney function [9, 10], prevention of dialysis amyloidosis [7], and a decrease in advanced glycation end-products [11] have also been reported. However, effects on atherosclerosis or the survival rate have not been reported because of the necessity of a long-term follow-up and the presence of many confounding factors. Also, most of the studies to date have been small-scale observational studies, and the evidence level of their results has been low. Large-scale comparative studies are necessary in the future.

According to the JSDT statistical survey [17], the 1-year mortality rate was significantly higher at facilities with an endotoxin concentration of ≥0.100 EU/ml. This significant difference, though it was obtained by a short-term survey, is expected to exert an even greater effect on the long-term survival rate. Further reports on the results of the JSDT statistical survey are awaited.

The survival period of dialysis patients has long been considered to be about half of that of healthy individuals, and it is not being improved even today after the development of dialysis therapy. The most important cause of this low survival rate is known to be irregular and intermittent treatment [18]. The only measure to overcome this problem is considered to be frequent and long-term dialysis [19–21], but the use of dialysis fluid of insufficient purity would increase the frequency of exposure to contaminants compared to that by routine dialysis. Purification is essential for state-of-the-art dialysis therapy. It is necessary for conditions regarding dialysis therapy in Japan to be further improved, with the hope that the dialysis fluid purification standard will improve the prognosis for dialysis patients.

## Conclusion

JSDT has published a new quality standard of dialysis water and dialysis fluids for hemodialysis and related therapies. This standard is similar to the criteria of the ISO, which is currently under review for revision. This standard is aimed to be applied to CDDS, which is widely used in Japan. Since high-performance dialyzers are frequently used for most patients in Japan, the standard recommends the use of ultrapure dialysis fluid for all dialysis modalities at all dialysis facilities. This standard also requires the use of online-prepared substitution fluid with validation by the dialysis equipment safety management committee at each facility. This standard would help protect hemodialysis patients from adverse effects arising from microbial contaminants and can contribute immensely to long-term positive patient outcomes.

## Disclosure Statement

None of the authors declared conflicting interests.

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