October 23, 1992

TO: Hemodialysis personnel
SUBJECT: New studies on dialyzer germicides

I am writing to inform you about the initial results of two new studies that report an association between mortality rates among dialysis patients and the type of germicide used on their dialyzers between treatments. I also want to let you know about the plans of the U.S. Department of Health and Human Services to assess the clinical significance of the findings, and provide you with interim guidance until the issue is resolved.

The studies

The studies report a statistical association between patients whose dialyzers are reprocessed with certain germicides for reuse and an increased mortality rate. Since the increased mortality was associated only with certain germicides, neither study indicates that reusing dialyzers, per se, necessarily carries more risk than using them only once.

One of the studies was conducted by The Urban Institute of Washington, D.C., a non-profit research foundation, with support from the Health Care Financing Administration. The study involved roughly 34,000 patients treated in 859 free-standing dialysis centers using conventional (or "low flux") dialysis during the period 1989-90.

This study reports that patients treated with dialyzers that have been reprocessed with either Renalin or glutaraldehyde experience a higher mortality, on average, than patients who are dialyzed in non-reuse facilities. The increase in mortality was observed for both manual and automatic reprocessing with these two germicides. No increase in mortality was observed for facilities that use formaldehyde in reprocessing dialyzers.

The other study, conducted by the National Institute of Diabetes and Digestive and Kidney Diseases, a part of the National Institutes of Health, directly compared patients treated with new dialyzers each time against those whose dialyzers were reused. This "case-mix" study examined ESRD cases from 1986 and 1987 and followed patients through 1989. It matched approximately 3100 reuse and non-reuse patients from 290 dialysis units and arrayed them by a number of medical and demographic characteristics.

In this study, the only statistically significant increase in mortality rate was reported among those whose reused dialyzers were manually reprocessed using Renalin. Patients whose dialyzers were reprocessed automatically using either Renalin or glutaraldehyde showed no statistically significant increase in mortality. (There were too few patients in the glutaraldehyde-manual group to assess mortality risk.) Like The Urban Institute study, the NIH study showed that patents treated with dialyzers reprocessed using formaldehyde experienced no statistically significant increase in mortality.

HHS Actions In Response to the Study Findings

These studies raise questions about Renalin and glutaraldehyde and their use. However, the studies report only a statistical association between Renalin and glutaraldehyde and increased mortality. The data do not explain the cause of the increased mortality. For example, the source of the difference could be problems intrinsic to these germicides. Or it could relate to the reprocessing techniques used. Or the patients who showed increased mortality might have been at greater risk for other reasons - - for example, their delivered dialysis, on average, could have been less adequate, or they could have been more ill to begin with. At present, the data do not permit assessment of such variables.

Although the studies have not been completed, HHS has set in motion plans to ensure that the overall quality of dialysis care is maintained.

For example, FDA has asked the manufacturer of Renalin to contact dialysis facilities, notifying them of the study results and providing technical assistance in proper use of this product. The manufacturer will provide facilities with additional instructions for both manual and automatic reprocessing procedures, including a comprehensive protocol.

FDA is also evaluating the labeling and instructions for glutaraldehyde labeled for use with dialysis to see whether they are adequate; if not, the agency will propose similar action with this manufacturer. FDA will also test these germicides to assess their effectiveness. And, since FDA is aware that many dialyzers labeled for single-use only are re-used, the agency will require the manufacturers of dialyzers that can be re-used to include instructions for reprocessing.

At the same time, both the Urban Institute, with the support of the Health Care Financing Administration, and the National Institutes of Health, will expand and refine their studies to clarify the significance of the early results.

Interim guidance

Until we know more about the relationship between the two types of germicides in question and the reported increases in mortality rate, dialysis facilities that reprocess their dialyzers should review their reprocessing procedures to assure that they are following the recommendations of the germicide manufacturer. Since both studies reported an increased mortality rate for patients whose dialyzers were manually reprocessed using Renalin, facilities that use this procedure should be particularly careful to confirm to the manufacturer's current instructions, as well as to any revisions reflected in the comprehensive protocol, which will be issued by the company within 30 days.

I have enclosed a letter to dialysis patients that summarizes this issue. The ESRD Networks will be receiving a supply of the patient letter which they will provide to you for distribution to your patients. Note that we are also making copies of the patient letter available to several professional and patient organizations for distribution. The ESRD Networks will also be communicating with patients through the units and are available to help address patient inquiries.

Again, we are not certain about the clinical relevance of these two studies. Their significance should become more clear as they are refined and expanded; we will continue to keep you informed as progress is made in this area. In the meantime, the actions outlined above, which we are taking in conjunction with the manufacturers of the germicides in question, will help assure that they are used optimally.

Sincerely yours,

James S. Benson
Director
Center for Devices and
Radiological Health

October 23, 1992

LETTER TO DIALYSIS PATIENTS:

New Studies on Dialyzer Germicides

You may have heard or read about two recent studies which compared dialyzers that were re-used with those that were used only once. It is important for you to know that neither study found that re-using dialyzers was less safe than using them once. The studies do, however, raise some questions about certain germicides used to reprocess dialyzers for re-use. Because the studies are not complete, the Food and Drug Administration and other Agencies in the Department of Health and Human Services will continue to monitor the situation to assure the safety of all dialysis patients. We have sent detailed information about the new studies to all U.S. dialysis facilities, so your doctor will be ready to discuss this with you, if you wish.

What do the studies show?

The studies show an association between certain germicides and slightly higher mortality rates but are not conclusive, and they do not explain the cause.

- In one study, patients whose dialyzers were reprocessed with either Renalin or glutaraldehyde, two of the commonly used germicidal solutions, had a slightly higher mortality rate than patients whose dialyzers were not re-used.

- In the other study, the only increased mortality was seen among patients whose dialyzers were reprocessed manually using Renalin; no increase in mortality was observed for Renalin when used in automatic reprocessing machines, or for glutaraldehyde.

- Neither study showed increased mortality for patients whose dialyzers were reprocessed using formaldehyde as the germicide.

What do the studies mean?

Again, the studies do not find that re-using dialyzers was less safe than using them once. The studies lack specificity to help us determine if the problem is the germicide themselves, or the way they are used. It might also be that patients who showed increased mortality may have been at greater risk for other reasons, such as non-compliance to diet, insufficient dialysis time, or their other medical problems.

What's ahead?

Through additional research and analysis, FDA and other government agencies are working to resolve the unanswered questions about these studies. Because of the concerns for dialysis patients, the Department of Health and Human Services has set in motion plans to insure that the overall quality of dialysis care is maintained.

FDA is taking action to assure that dialysis facilities receive the latest information from the manufacturers about the correct way to use the two germicides most effectively. For example, we have directed the manufacturer of Renalin to contact dialysis facilities to provide information about proper use this product. We are evaluating whether to take similar steps with the manufacturer of glutaraldehyde. FDA is planning its own tests of all commercially available germicides used in dialyzer reprocessing. We will also require dialyzer manufacturers to provide specific instructions for reprocessing.

Again, please bear in mind that these studies have not yet been completed, and that it is unclear at this point what caused the higher mortality rates. We will continue to investigate this matter in order to help assure the safety of dialysis patients. You can also contact your local ESRD Network directly if you have questions or concerns.

Sincerely yours,

James S. Benson
Director
Center for Devices and
Radiological Health