International variation in classification of dialysis withdrawal: a systematic review

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ABSTRACT

Background and objectives. In patients with end-stage renal disease (ESRD), the rate of deaths preceded by dialysis withdrawal is high. However, rates vary across studies and national renal registries. This study aimed to (i) determine how dialysis withdrawal mortality is defined in the literature and (ii) whether mortality rates preceded by dialysis withdrawal change over time.

Methods. MEDLINE (1946 to March 2012) and EMBASE (1980 to March 2012) databases were searched. We included epidemiological studies that reported data permitting calculation of crude (unadjusted) mortality rates preceded by dialysis withdrawal. Definitions of dialysis withdrawal were also extracted. Crude mortality rates and 95% confidence intervals were calculated using OpenEpi software. Non-English language studies were excluded.

Results. Twenty-three eligible studies were identified; these included 14 527 885 dialysis patients at risk from six countries. Crude mortality rates preceded by dialysis withdrawal ranged from 3 to 50.2 per 1000 person-years. Seven different definitions of dialysis withdrawal were identified, with no assessment of validity. Crude mortality rates preceded by withdrawal have increased over time across the study period 1966 (3 per 1000 person-years) to 2010 (48.6 per 1000 person-years), although these rates are difficult to interpret because of differences in classification. In the USA crude mortality rates preceded by dialysis withdrawal are higher in the older population and have increased over time in the age group 65+ years. In this age group, the crude mortality rate preceded by dialysis withdrawal was 89.4 per 1000 person-years (2008–10) compared with 26.1 per 1000 person-years in the age group 50–64 years (2008–10).

Conclusion. Mortality rates preceded by dialysis withdrawal have increased over time should be interpreted with caution because of
INTRODUCTION

A 1949 editorial in the British Medical Journal stated that the artificial kidney brought ‘difficulties to the doctor and real hazards to the patient’ [1]. Despite technical advances in dialysis for patients with chronic kidney disease, dialysis remains associated with high mortality, increased symptom burden and substantial quality of life impairment [2–5]. Dialysis is no longer viewed as restorative in many groups of patients, with professionals appreciating that there are limits on the ability of chronic dialysis to maintain quality of life. In patients with significant co-morbidities, it is common for dialysis to be withdrawn prior to death [6–8].

Despite the literature spanning >40 years and advances in renal palliative care, dialysis withdrawal remains a conundrum for patients, families and professionals. The epidemiology of dialysis withdrawal today is strikingly different from that of the past. In the early days of dialysis, only relatively young patients without co-morbidities were offered dialysis. Withdrawal was unusual and often associated with loss of vascular access, rarely with patient emotional fatigue with the demands of treatment. Dialysis withdrawal is now associated with a heterogeneous group of diseases with varying symptom burden and illness trajectories. Most dialysis withdrawal occurs in the context of debilitating pre-existing co-morbidities in an elderly frail population. Often the patient is actively dying with ‘failure to thrive’, or an acute, catastrophic event. This heterogeneity results in difficulties defining, classifying and tabulating dialysis withdrawal deaths. To some clinicians, the cause of death may be the disease under treatment (ESRD) or a complication withdrawal deaths. To some clinicians, the cause of death may be the disease under treatment (ESRD) or a complication of the disease; to others, the cause of death is the terminal disease (other co-morbidity) or the mode of dying [9]. The lack of a unified classification of dialysis withdrawal has implications for studying and improving care at the end of life following dialysis withdrawal [10].

Comparisons of dialysis withdrawal patterns across countries and units are difficult. In 2007, there were 207 (14%) treatment withdrawals reported as a cause of death to the UK national Renal Registry [11]. In the USA from 2006 to 2008, the crude (unadjusted) mortality rate preceded by withdrawal was 48.4 per 1000 person-years [12]. Indeed, the first and only UK study to analyse dialysis withdrawal practice reported that 17% of all deaths were preceded by dialysis withdrawal [13]. However, 15 years later the figures reported by renal units to the UK Renal Registry remain fundamentally the same (14% of all deaths), although this should be interpreted cautiously as there is significant variability between centres regarding completeness of cause of death data [14]. Taking into account the increasing prevalence of type 2 diabetes mellitus, the ageing population and changing dialysis withdrawal practice, a higher figure might be expected. This is already happening in the USA, where mortality rates preceded by dialysis withdrawal continue to rise [12].

Recognition of the palliative care needs of the dialysis population has resulted in the development of services and improved care [15]. Historically, the quality of dying following dialysis withdrawal has been reported to be a good, quick death, one with few symptoms and little suffering [16]. Nevertheless, many patients with ESRD experience variability in symptoms and survival following dialysis withdrawal [17]. In the past, studies have reported dialysis withdrawal as a leading ‘cause’ of death [6, 7, 18, 19], suggesting these patients are dying from uraemia per se. In the majority of patients whose death is preceded by dialysis withdrawal, a non-renal cause is responsible for the decision to withdraw from dialysis. In order to anticipate symptoms and survival following dialysis withdrawal, we must first ask the question ‘what is my patient dying from?’

Against this background, the purpose of the present review is to define and determine dialysis withdrawal mortality rates in patients with ESRD managed on dialysis. Specifically, the questions were (i) how dialysis withdrawal is defined and (ii) whether mortality rates preceded by dialysis withdrawal change over time. This review represents a step towards understanding the modern dialysis withdrawal phenomena.

MATERIALS AND METHODS

Search strategy

The review was undertaken following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We searched MEDLINE (1946 to March 2012) and EMBASE (1980 to March 2012) using MeSH headings and keywords. The MEDLINE search strategy is shown in Supplementary data, Appendix Fig. A1). For all included studies, cited reference searching was also undertaken using the electronic database Scopus. We also searched reference lists of narrative reviews and recent conference abstract reference lists from the British Renal Society, the Renal Association and the American Society of Nephrology.

Study selection. Studies were eligible for inclusion if they studied mortality and causes of death in patients with ESRD on dialysis. Studies were included if they contained data that permitted calculation of crude mortality rates preceded by dialysis withdrawal and 95% confidence intervals. Non-English language studies were excluded.

Data extraction. Data were extracted on to a standard form. With headings of general information (author, year of publication, study period and site), eligibility criteria, study design, sample population, total number in the dialysis cohort (population at risk), total number of deaths, number of deaths preceded by dialysis withdrawal and deaths on dialysis not preceded by dialysis withdrawal, data source, definition and classification of dialysis withdrawal, analysis and results.
Quality assessment and grading evidence. The methodological quality of all eligible studies was assessed to investigate validity (scored and classified as being low-, medium- or high-risk) with the following attributes (i) description of dialysis withdrawal definition (ii) the completeness and adequacy of data source and (iii) adjustment of mortality rates against a standard or reference population.

Outcome measures. The primary outcomes were crude mortality rates preceded by dialysis withdrawal. Secondary outcomes were (i) all-cause mortality rates (all deaths including deaths preceded by dialysis withdrawal) and (ii) mortality rates, death not preceded by dialysis withdrawal. We also reviewed the dialysis withdrawal definitions used by each study.

Statistical analyses. We have calculated crude (unadjusted) mortality rates and 95% confidence intervals. Crude mortality rates preceded by dialysis withdrawal were calculated where possible in studies that included information on all deaths, population at risk and the time interval in order to calculate population time. For comparison, mortality rates for all deaths on dialysis were calculated. The model to undertake these calculations assumed the underlying mortality rates are roughly proportional to one another over time. Mortality rates and 95% confidence intervals were calculated using OpenEpi software.

RESULTS

Study flow and characteristics

The review process is summarized in Fig. 1. From an initial number of 96 electronic citations (hand searching and citation tracking using the electronic database Scopus added a further 21 papers), 23 studies were included in the review. Of these, most data were collected during the late 1980s and 1990s (earliest publication included was 1986) in white populations from North America and Europe. Eight of the 23 studies were retrospective observational cohort studies; 2 were prospective cohort studies and 13 were United States Renal Data System (USRDS) annual reports. The proposed mortality rates could be calculated from all included studies (Table 1). Studies covered

FIGURE 1: Results of the database, citation tracking and hand searches showing the number of references found, those excluded and the final number of papers included in this review.
Table 1. Crude (unadjusted) mortality rates in included studies, with 95% confidence intervals where applicable

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<th>Cohort years</th>
<th>Author and country</th>
<th>Date published</th>
<th>Person-years</th>
<th>Death n</th>
<th>Pop at risk</th>
<th>DW deaths, n</th>
<th>Deaths on dialysis, n</th>
<th>MR/all cause</th>
<th>DW/all cause</th>
<th>DNW</th>
<th>DW/uremia</th>
<th>DW defined</th>
<th>Data source</th>
<th>Study design</th>
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<td>1996</td>
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<td>589</td>
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<td>501</td>
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<td>1996</td>
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### Table 1. Continued

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<th>DW deaths, n</th>
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<th>DW/all cause</th>
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<td>2012</td>
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</tbody>
</table>

Shading denotes estimated figures based on the mortality rates supplied by the USRDS. The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.

UK, United Kingdom; US, United States; CA, Canada; FI, Finland; CH, Switzerland; FR, France.

(i) All-cause dialysis deaths = total number of deaths from any cause.
(ii) DW deaths = total number of deaths preceded by dialysis withdrawal—all causes of death.
(iii) Deaths on dialysis = total number of deaths not preceded by dialysis withdrawal.
(iv) All-cause/MR = mortality rate per 1000 person-years—cause of death.
(v) DW/all cause = mortality rate per 1000 person-years preceded by dialysis withdrawal—cause of death.
(vi) DNW = mortality rate per 1000 person-years not preceded by dialysis withdrawal.
(vii) DW/uraemia = mortality rates per 1000 person-years preceded by dialysis withdrawal—cause of death, dialysis withdrawal/uraemia.
(vi) Ret-CS, retrospective cohort study.
(x) P-CS, prospective cohort study.

### United States Renal Data System

The USRDS annual data reports included [12, 13, 18, 19, 20–22]. Two studies excluded patients if the length of time from stopping dialysis until death was less than the usual inter-dialysis interval (<3 days) [18, 19]. One study defined dialysis withdrawal as ‘death with manifestations of uremia because of withdrawal from dialysis’ [7]. Others included all patients where a decision was made to discontinue dialysis irrespective of cause of death [11]. The review of the literature shows that the validity of the various definitions of dialysis withdrawal has not been investigated.
(all cause/MR) have decreased over time in the US dialysis population (Fig. 3a).

(2) Death preceded by dialysis withdrawal—all cause (DW/all cause, i.e. DW/uraemia + DW/other cause): mortality rates preceded by dialysis withdrawal all cause, all ages (DW/uraemia + DW/other cause) have remained relatively unchanged (Fig. 3a) from 1995 to 2010. Mortality rates preceded by dialysis withdrawal (DW/all cause) are higher in the older dialysis population and have increased in this age group over time (Fig. 3b). Over the age of 65 years the mortality rate preceded by dialysis withdrawal (DW/all cause) was 89.4 per 1000 person-years (2008–10) compared with 26.1 per 1000 person-years in the age group 50–64 years (2008–10).

(3) Death preceded by dialysis withdrawal—cause of death uraemia (DW/uraemia): mortality rates preceded by dialysis withdrawal where the cause of death is DW/uraemia have increased over time from 1.5 per 1000 person-years (2002–04) to 20.6 per 1000 person-years (2008–12), accounting for 0.7 and 10.6% of all dialysis deaths, respectively (Fig. 4).

(4) Death preceded by dialysis withdrawal—other causes of death (DW/other cause, i.e. malignant disease, MI etc.): mortality rates preceded by dialysis withdrawal where the cause of death is not attributed to uraemia (DW/other cause) have declined over time from 21.2 per 1000 person-years (2002–04) to 14.4 per 1000 person-years (2008–10), accounting for 21.2 and 14.4% of all dialysis deaths, respectively (Fig. 4).

**DISCUSSION**

We do not understand fully how and when our patients die. It is evident from our review that dialysis withdrawal definitions vary markedly, and this raises important questions about the comparability of mortality rates and associated factors. Even comparing similar definitions, we found no agreement in the mortality rates preceded by dialysis withdrawal. We were able to make recommendations related to coding and classification of deaths preceded by dialysis withdrawal due to ‘renal related/uraemia’ or other causes of death (Box 1). It is possible to compare mortality rates over time if standard coding and classification of deaths preceded by dialysis withdrawal are used. These need clarification in order to understand better the phenomena of dialysis withdrawal.

Due to the lack of definition (or guidance) on cause of death (dialysis withdrawal/uraemia), the practice of reporting mortality data across countries is notably different. The UK Renal Registry reported that in 2009 ‘treatment withdrawal’ accounted for 14% of all deaths [14], in comparison, the data
from this review show dialysis withdrawal (DW/all cause) in the USA to account for 24.8% of all dialysis deaths (2008–10) [35]. The UK Renal Registry has a data return on causes of death as <50% [12]. Whereas, in the USA, ascertainment of mortality in renal patients is virtually 100% complete [35].

The crude (unadjusted) mortality rates preceded by dialysis withdrawal ranged widely from 3 to 50.2 per 1000 person-years across all included studies and this may relate to differences in definitions as well as practice, but also in population differences. Overall, the mortality rates preceded by dialysis withdrawal reported by the USRDS (DW/all cause) have remained unchanged between 2005 and 2010 (Fig. 3a). In the age group over 65 years, rates have steadily increased (Fig. 3b).

In 2004–06, the mortality rate by cause of death ‘dialysis withdrawal/uraemia’ was 12.8 per 1000 person-years, rising to 20.6 per 1000 person-years in 2008–10, which accounted for 25.6 and 42.4% of those who withdrew, respectively. Conversely, mortality rates preceded by dialysis withdrawal where the cause of death is not attributed to uraemia (DW/other cause) have declined over time from 21.2 per 1000 person-years (2002) to 14.4 per 1000 person-years (2008–10) (Fig. 4). This is surprising given that the age and co-morbidity in the advanced renal failure population continues to increase. We might expect a lower number of patients with the cause of death attributed to ‘withdrawal from dialysis/uraemia’. There are no specific instructions provided as to how and when to use these fields, leaving the possibility for substantial variability in the interpretation of these important ‘end of life’ concepts and variability in coding of dialysis withdrawal deaths [10].

The crude mortality rates presented in this review are based on dichotomization of dialysis withdrawal, meaning that we did not fully take into account the heterogeneous nature of dialysis withdrawal definitions. Dialysis withdrawal mortality statistics necessarily depend upon the classification and coding of cause of death. It is likely that the manifestations (co-factors, symptom burden and time from last dialysis before death) of dialysis withdrawal will differ according to the specific cause of death. Time in days from the last dialysis treatment until death has been shown to be longer in patients who experience a uraemic death than in patients who stopped dialysis therapy but in whom cause of death was not coded as uraemia (12.5 vs. 5 days respectively, P = 0.01) [36]. Understanding the cause of death alongside the decision to withdraw will inform prognosis and preempt symptom burden at the end of life.

A limitation of our study is the comparison of crude (unadjusted) mortality rates which can be misleading. The age structure of the dialysis population can affect the number of deaths and thereby the crude mortality rate. In order to avoid these errors in interpretation, mortality rates must be adjusted to a common population with a known age structure. An international study has shown that adjusted (for other patient factors such as age and diabetes) mortality rates preceded by dialysis withdrawal were substantially lower than unadjusted rates mortality rates [37]. This reflects that dialysis withdrawal often coexists with other factors that are associated with adverse outcomes. However, calculating the crude mortality rates allows a degree of comparison.

The nephrology community needs to accurately classify, tabulate and return data to the national renal registries in order to help further epidemiological and clinical research. It is also important for clinical practice to understand the patterns and likely causes of death to improve the quality of care. Asking the question ‘what is my patient dying from?’ (regardless of dialysis) will help clinicians answer the important questions that patients frequently ask, How long do I have to live? What will happen at the end? We assume that to withdraw from dialysis and die in a place of your choice, in a dignified way, with good symptom control and an awareness of prognosis is the preference of our patients. However, there are a considerable proportion of patients who do not wish to participate in making the difficult decision to withdraw from dialysis. If death is imminent either from co-morbid disease or patients are deteriorating despite dialysis, then raising the issue of dialysis withdrawal and the consequent distress this may cause

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Table 3. USRDS ESRD death notification form—changes over time 1986 to date

<table>
<thead>
<tr>
<th>Year</th>
<th>Death notification form</th>
<th>USRDS ESRD death notification form—changes over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986–90</td>
<td>HCFA 2746</td>
<td>Dialysis withdrawal is a specific cause of death code (no guidance given as to what constitutes a dialysis withdrawal death). Patients who stopped treatment before death were recorded into the withdrawal from dialysis category, resulting in an apparent increase in the percentage of deaths due to withdrawal. It is likely this increase is due to the change in coding. Comparisons of cause of death before and after 1990 must be treated with caution (USRDS)</td>
</tr>
<tr>
<td>1990–04</td>
<td>CMS 2746</td>
<td>In March of 1990, a revised ESRD Death Notification Form came into use. The new Death Notification Form uses a revised set of categories for cause of death, and withdrawal from dialysis is no longer considered a cause of death. Instead, a separate question asks whether the renal replacement therapy was discontinued prior to death and reason for discontinuation</td>
</tr>
<tr>
<td>2004 to date</td>
<td>CMS 2746</td>
<td>Provides instructions for completing the ESRD death notification form. In 2004, a new Cause of Death item #104, ‘Withdrawal from dialysis/uraemia’ is added to Form 2746. There are separate questions that ask whether renal replacement therapy was discontinued prior to death, the reason for discontinuation and the date of last dialysis treatment</td>
</tr>
</tbody>
</table>

*HealthCare Financing Administration (HCFA), the federal agency that administers the Medicare program. Centers for Medicare and Medicaid Services (CMS, formerly HCFA).
**FIGURE 3:** (a) Crude mortality rates, all ages. USRDS data 1995–2010. (b) Crude mortality rates preceded by dialysis withdrawal (all causes of death), by age groups, USRDS 1995–2010.

\[ \text{All cause MR} = \text{Mortality rate - all causes of death} \]
\[ \text{DNW} = \text{Mortality rate - death not preceded by dialysis withdrawal} \]
\[ \text{DW} = \text{Mortality rate - death preceded by dialysis withdrawal, all causes of death} \]
\[ \text{MD} = \text{Missing data} \]
\[ \text{DW/Uraemia} = \text{Mortality rate - cause of death dialysis withdrawal/uraemia} \]
should be considered very carefully. We need to better understand which group is dying with a rapid trajectory regardless, and in which group withdrawal may change the speed or pattern of outcome. There is a need to better communicate information on dialysis withdrawal to patients and families. But first we need to know what symptoms and trajectory to

Box 1. Suggestions for coding causes of death and when to check the ‘withdrawal’ question, based on trajectories and causal criteria

(1) Death preceded by dialysis withdrawal—yes (cause of death, renal related/uraemia)
- Patient choice but not recommended by the treating medical team.
- Without significant medical problems other than renal failure.
- Active decision to withdraw from dialysis treatment.
- Co-morbidity—there may not be significant co-morbidity.
- Time from last dialysis until death may be greater than the average of 8 days depending on the residual renal function.

Primary cause of death renal related/uraemia checked and withdrawal checked.

(2) Death preceded by dialysis withdrawal—yes (other causes of death, i.e. malignant disease, MI etc.)
- Usually a shared decision of the medical team and patient/family with significant medical problems other than renal failure. Occasionally one party may make the decision unilaterally.
- Co-morbidity score—usually very high, or in a frail elderly patient.
- Time from last dialysis until death—on average 8 days, may be shorter if the patient is in the active dying process.

Primary cause of death is the disease that initiated the train of events leading directly to the death, secondary causes of death could include renal related/uraemia, and withdrawal checked.

Reasons for withdrawal:
(a) Following HD and/or PD access failure.
(b) Following chronic failure to thrive/frailty.
(c) Following acute medical complication (i.e. a new stroke, MI, ischaemic bowl, respiratory failure, septic shock etc.)
(d) Chronic debilitating problems (PVD, non-healing wounds, end-stage lung, liver, heart disease etc.)

(3) Death on dialysis—No dialysis withdrawal
- No decision to withdraw from dialysis.
- Time from last dialysis until death usually <3 days.

Primary cause of death—disease that initiated the train of events leading directly to death. Withdrawal not checked. Dialysis may have not been done as scheduled prior to death due to unstable condition.

**FIGURE 4:** Proportions of deaths preceded by dialysis withdrawal (uraemia and other causes of death) and deaths not preceded by dialysis withdrawal—USRDS 2002–10.
expect, which is clearly dependent on the disease they are dying from.

We suggest that the USRDS method of reporting all deaths (regardless of cause) preceded by dialysis withdrawal and more detailed data items such as the reason for withdrawal and the date of the last dialysis (prior to death) is the gold standard. In addition, recommendations to national renal registries are discussed under two categories: issues regarding withdrawal of dialysis as a cause of death and issues regarding withdrawal from dialysis. Finally, this more detailed cause of death and dialysis withdrawal data are recommended as being mandatory by all dialysis facilities nationally and internationally emphasizing the importance of reporting cause of death and facilitating future epidemiological studies.

**Recommendation for a modification in the death notification form**

Determining when to code the cause of death as dialysis withdrawal/uraemia is unclear. We propose that dialysis withdrawal should never be a cause of death, but a separate question asked, 'Renal replacement therapy withdrawn prior to death? Yes or No' added after the primary and secondary cause of death question. We recommend that 'renal related/uremia' is added to the list of causes of death. Proposed explanatory footnote to 'renal related/uremia' on the list of causes of death is: *Renal related/uremia means that a complication of ESRD was the cause of death. Such complications include, but are not limited to, uremic encephalopathy, uremic pericarditis, bleeding, acidosis, hyperkalemia and intravascular volume expansion.*

**Recommendations related to withdrawal from dialysis**

Our suggestion is to insert the following statement under the question 'Renal replacement therapy withdrawn prior to death? Yes or No': 'Withdrawn' means that the patient's regular course of renal replacement therapy was stopped with the expectation that it would not be resumed even in life-threatening complication, and means that the clinician made an explicit decision that renal replacement treatment should be stopped permanently. Do not answer this question 'Yes' if one or more treatments had been missed following acute medical complications, or because of non-compliance.

**CONCLUSION**

The study of the dialysis withdrawal epidemiology is restricted by the lack of consensus over the basic definition of the disease. There is considerable variation in reported rates across studies. Mortality rates over time are difficult to interpret because of differences in classification. In the absence of any consensus criteria, each nephrologist reporting to the renal registry will have his own internal set of rules and criteria for what did or did not constitute a dialysis withdrawal death. We recommend a classification that facilitates communication among clinicians and researchers about the basic epiphenomena of dialysis withdrawal. At the very least, establishing a core set of case definitions which incorporate the findings from this review will foster valid cross-study comparisons and permit valid epidemiological surveillance of dialysis withdrawal-related phenomena.

**SUPPLEMENTARY DATA**

Supplementary data are available online at http://ndt.oxfordjournals.org.

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**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**

1. The Artificial Kidney, BMJ 1949; 2: 1113


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