Haemodialysis adequacy: looking for the holy grail

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Abstract

Goal: To review haemodialysis adequacy assessment.

Objectives:

• To define haemodialysis adequacy.
• To critique current measures of haemodialysis adequacy.
• To identify major clinical issues related to haemodialysis adequacy assessment in haemodialysis.

Background

Dialysis began in the 1940s and developed to a stage where the main aims were to control fluid overload and electrolyte balance. There have been enormous developments in dialysis-associated medical technology since then. People with end-stage chronic kidney disease (ESCKD) are surviving much longer than before as a result of these newer developments. Management strategies for those with ESCKD are to keep the patients healthy and functional. This has led to the need to evaluate dialysis adequacy, that is, how much dialysis is enough to keep those with ESCKD healthy, and to contain the costs of ESCKD to global health care systems.

What is dialysis adequacy? The traditional view

ESCKD leads to the accumulation of certain solutes which result in a “deterioration of multiple biochemical, biologic and physiologic functions … being the uremic syndrome” (Vanholder, De Smet & Lesaffer, 2002, p. 3). Haemodialysis (HD) is aimed at restoring the body's fluid and electrolyte status as near to normal as possible. Unfortunately there is no perfect method to evaluate the efficiency of a dialysis treatment at present. Dialysis adequacy refers to what 'dose' of HD is required to keep the patient healthy and functional. “Measuring the clearance of solutes that accumulate in patients with uraemia has become the mainstay for determining the dose of dialysis and determining its adequacy as delivered” (Himmelfarb & Ikizler, 2010, pp. 1833–34).

An adequate dialysis equates to a Kt/V of anywhere between 0.8 and 1.8. The Tassin unit in France, which is reported to have the best survival figures in the world, found a Kt/V of 1.6–1.9 led to better survival rates (Kemp, 2001; Vanholder et al., 2002). It is generally accepted that a minimum Kt/V of 1.2 for HD thrice-weekly is acceptable; however, to aim for a Kt/V of 1.4 is recommended (this is supported by the DOQI, CARI and European Best Practice guidelines).

How do we measure dialysis adequacy?

Any marker which is chosen to assess the adequacy of dialysis “should be easy and cheap to measure, its blood concentrations should correlate with symptoms, it should be retained in parallel with other significant toxins, and the extent of its removal with dialysis should correlate with improvements in the patient's morbidity and mortality” (Kemp et al., 2001, p. 20), and urea meets most of these criteria. The most common dialysis adequacy assessments in general are the Kt/V and the urea reduction ratio (URR).

Kt/V was developed from a specific group of patients, “a group of renal failure patients with few comorbidities, submitted to short frequent dialysis with small pore bio incompatible membranes very likely using dialysate of lower quality than that used today” (Vanholder et al., 2002, p. 5).

The formula for Kt/V involves the dialyser clearance of urea (K), the dialysis session time (t) and the volume of water in the body (V), and was developed and published by Gotch and...
Sargent (1985). The development of this formula was from analysis of the data obtained from the National Cooperative Dialysis Study (NCDS). For example, if a patient is dialysed for 350 minutes, and the urea clearance is 300 ml/minute and the patient weighs 70 kilograms, (if water is 60% of the body then this would account for 42 litres volume).

\[
Kt = 300 \text{ ml/min x 240 minutes} = 72 \text{ litres}
\]

\[
V = 70 \text{ kg x 0.6} = 42 \text{ litres}
\]

Then the \(\frac{Kt}{V}\) = 72/42 = 1.7

As \(V\) is a fixed value the manipulation of \(K\) and/or \(t\) will improve the \(\frac{Kt}{V}\) – or dialysis adequacy.

It should be remembered that this formula was developed in relation to thrice-weekly dialysis. It is recommended that \(\frac{Kt}{V}\) targets be reviewed for other dialysis schedules; for other than thrice-weekly sessions the KDOQI recommends a minimum of 2.0 be the aim of \(\frac{Kt}{V}\) (Daugirdas et al., 2012).

This formula has continued to be developed, for example, the European Best Guidelines recommend the use of an equilibrated \(\frac{Kt}{V}\) formula (this is a double pool formula which includes some aspect of urea rebound):

\[
eKt/V = spKt/v - (0.6 x spKt/V/T) + 0.03 \text{ (for an arteriovenous access)); where } e = \text{ equilibrated and } sp = \text{ single pool.}
\]

(<http://ndt.oxfordjournals.org/content/17/suppl_7/17. abstract>, viewed 08/02/2013)

Online \(\frac{Kt}{V}\) measurement, or online clearance monitoring (OCM), is now possible in newer HD machines available in Australia today, and allows for a consistent measure of adequacy (Vanholder et al., 2002). The automatic technological developments which have made this possible vary depending on the make of the HD machine. OCM uses ionic dialysance to measure \(\frac{Kt}{V}\). Ionic dialysance is a measure of the conductivity of the dialysate waste via a conductivity probe and compares this to the conductivity of the fresh inflow of dialysate during the HD session. (Conductivity is generally the measure of the ability of a material to conduct electricity. In this case the electrical conductivity is measured by \(Na^+\) ions which are positive, electrically charged particles.) This ionic dialysate involves the measurement of the difference in Sodium (\(Na^+\)) between the electrically charged particles.) This ionic dialysate involves the measurement of the difference in Sodium (\(Na^+\)) between the fresh inflow of dialysate and the dialysate waste. \(Na^+\) has “similar transfer characteristics to urea” (Manzoni et al., 1996, p. 28).

“Effective ionic dialysance has been assumed to be equivalent to effective urea clearance because of the similar molecular weight and osmotic distribution volumes of sodium chloride and urea” (Lameire et al., 2009, p. S31). Generally the dialysance is measured at 30-minute intervals and allows for an estimation of \(Kt/V_{\text{fr}}\) and each measurement takes approximately 2–4 minutes. This is an important point in that the ionic dialysance is not measured continuously.

**Urea Reduction Ratio (URR)**

The urea reduction ratio (URR) measures how much the urea level decreases during a dialysis session; however, this is a crude measurement. The formula for the URR is very simple:

\[
URR = \frac{U_{\text{predialysis}} - U_{\text{post dialysis}}}{U_{\text{predialysis}}} \times 100
\]

The aim is for a URR ratio of 65% for an adequate dialysis. However, the URR may vary at each HD session, which equates to approximately a \(Kt/V\) of 1.2.

The URR may underestimate the adequacy of HD because the formulae does not account for urea removal during ultrafiltration in HD (Kerr et al., 2005, p. S63). Therefore the more fluid is removed the lower the URR. Further, the URR is a crude measure of adequacy.

**Key messages**

- \(Kt/V\) should be at least 1.2 (but target in general for 1.4).
- URR should be >65%.
- \(Kt/V\) or the URR can be improved by increasing the clearance of urea (increased BFR &/or dialysate flow rate &/or dialysis session time).

**Current dialysis adequacy controversies**

There is much discussion in recent literature as to what constitutes the best method/s to assess dialysis adequacy. Generally \(Kt/V\) and the URR are used to assess adequacy as they are relatively simple to use. The major publication from the NCDS focused on the analysis of urea clearance, and it has become one of nephrology’s classic papers. The follow-on publication by Gotch and Sargent introduced the measurement of \(Kt/V\) (Gotch & Sargent, 1985).

Recent research is challenging \(Kt/V\)’s relevance in HD today (Henderson, 2004; Mehta, 2010; Miller, 2010; Meyer, 2011; Daugirdas, 2012) “Our knowledge of which uremic toxins confer injury and of how they can be optimally removed during dialysis therapy remains incomplete” (Himmelfarb & Ikizler, 2010, p. 1843). There are many factors which influence urea retention and removal and therefore the accuracy of \(Kt/V\) (Vanholder et al., 2002; Henderson, 2004). \(Kt/V\) may be irrelevant today because of the technological developments which have impacted on dialysis time, dialysate membranes and patient characteristics since the original formula development (Vanholder et al., 2002).

**Kt/V as a marker of dialysis adequacy**

\(Kt/V\) is based on urea kinetic modelling and “assumes that urea is generated at a constant rate by protein metabolism and is removed at a constant rate by residual renal function” (Mehta & Fenves, 2010, p. 1). The original mathematical modelling for \(Kt/V\) was based upon general dialysis practices which included short, intermittent HD, with small pore bio-incompatible membranes and poorer quality dialysate than is available in...
current practice. Moreover, the Kt/V formulae was developed using a single pool of urea formulae, and urea is contained in multiple ‘pools’ within the body. If the Kt/V formula is compared to that of the estimated glomerular filtration rate (eGFR) both “provide the conveniences of eliminating the need to adjust the dose according to body size but both are also confounded by variations in body composition” (Depner, 2008, p. 406). That is, the percentage of body fat and body muscle will affect the accurate assessment of adequacy (Depner, 2008; Chertow et al., 1999; Lowrie et al., 1999). Calculation of eGFR adjusts for gender and ethnic origin ‘but no such adjustment is currently part of the dialysis dose expression’ (Depner, 2008, p. 406). Further more recent research is suggesting that body surface area should be included in any mathematical modelling for adequacy. The use of body surface area (BSA) (Himmelfarb & Ikizler, 2010) led to conclusions from Daugirdas et al. (2008) that in actual fact small people and women need an increased dose of dialysis to have better outcomes and to this time these have not been factored into the Kt/V formulae which is in general use. Even Ward et al. (2011) suggests that men need a Kt/V of 1.25 compared to women who need 1.65. The mortality of those with ESCKD is reported as being associated with time and dose of dialysis as well as gender and racial groups (Miller et al., 2010; Himmelfarb & Ikizler, 2010).

The rate of any solute removal depends on size, weight, charge, volume of distribution and protein binding (Mehta & Fenves, 2010, p. 1). The Kt/V uses only urea to assess adequacy. However, there are many other solutes which may be important in the uraemic syndrome such as those categorised as “middle molecules”. Multiple compounds are involved in the ‘uraemic toxins’ therefore how can a single compound (urea) really indicate adequate dialysis (Vanholder, et al., 2002). Uraemic solutes’ behaviour during dialysis sessions is different depending on their size. Solutes can be divided into three categories: those that are smaller (<300 Da), such as urea (60 Da); those described as “middle molecules” (300–1200 Da) such as β₂-microglobulin; and those that are small molecules but are largely protein-bound (Vanholder et al., 2002; Meijers, 2008). “The unified atomic mass unit or Dalton is the standard unit that is used for indicating mass on an atomic or molecular scale” (http://en.wikipedia.org/wiki/Atomic_mass_unit). Protein-bound uraemic solutes are more difficult to remove during HD but by increasing the mass transfer rate and the dialysate flow rate these substances do have a better clearance; however, what is unknown currently is if the better removal of these substances would lead to better outcomes for those with ESCKD (Luo, 2009). These protein bound substances have been found to be better removed by HDF than conventional HD — it is thought that albumin bound solutes play an important role in uraemia (Meijers, 2008).

The size of the molecules being removed during dialysis impacts on the time taken for movement across the dialysis membrane. That is the larger the molecule the more time taken to pass through the membrane depending on size. Therefore, ‘in the context of this complex retention and removal pattern, it is remarkable that the nephrology community has largely remained focused on Kt/V as a single index of adequacy...’ (Vanholder et al., 2002). A study undertaken by Eloot et al. (2012) investigated whether Kt/V was representative of a wide array of uraemic toxins. Their conclusions were that the uraemic toxin concentration was more related to the intake of dietary protein and residual renal function than adequacy as assessed by Kt/V (Eloot et al., 2012, p. ii198).

Online clearance monitoring (OCM)

Because of changes in a patient’s status during the HD session the accuracy of the Kt/V by OCM may not be accurate. Factors which may affect this accuracy include episodes of hypotension, decreasing the blood flow rate, or the infusion of colloid or crystalloid solutions between the OCM measurement times (Tam, 2004, p. 58). The advantage of using OCM is that there is no need for blood to be collected, readings are available at regular intervals and is available immediately (Tam, 2004).

Although it would appear that OCM Kt/V is a very positive addition to the care provided to HD patients, again there are some issues to be considered. “In vitro, the amount of urea movement across the dialyser membrane is equal to the amount of sodium movement. In vivo, the correlation between urea movement and sodium movement is good, but they are never identical and there are always discrepancies” (Tam, 2004 p. 58). (In vitro refers to results from experiments which occur outside the human — for example in a test tube and in vivo refers to experimentation or medical test which is done on a human.)

A small study undertaken by Al Saran et al. (2009, p. 30) reported that the Kt/V obtained using the OCM capability indicated ‘a lower intermittent HD adequacy than those calculated from urea measurements’; however, further rigorous research is required to support or refute this finding. Ongoing research is required into the accuracy of OCM in relation to adequacy needs and patient clinical outcomes. OCM continues to evolve but does provide a relatively accurate estimation of Kt/V compared to the manual method (Carl & Feldman, 2008).

DOPPS found that many patients’ dialysis regimes met the recommended Kt/V targets; however, the incidence of poor blood pressure control, poor nutritional status, cardiovascular issues and bone disorders remained problematic and have a major impact on mortality (Port et al., 2006). Therefore as well as considering the effect middle molecules may have to play in the uraemic spectrum, other clinical issues may need to be factored into any measurement of dialysis adequacy.

Key messages

Urea has not been shown to be associated with the severity of uraemic symptoms, “Urea generation and removal are not representative of the entire spectrum of uraemic toxicity” (Vanholder et al., 2002, p. 6).

- Kt/V may be influenced by gender and body mass.
- Kt/V minimum targets may need to change if the dialysis schedule is other than thrice-weekly.
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**Strategies to improve dialysis adequacy and to define the ‘dose’ of dialysis**

*Increase the dialysis treatment time and dose*

The time for each dialysis session has been found to be associated with comorbidities and mortality reported from ESCKD; for example, a patient can lose up to 8% of their dialysis if they were to finish their dialysis 20 minutes early at each of their thrice-weekly sessions (Ellis, 2012). This behaviour would impact on the accuracy and interpretation of any adequacy assessment. The DOPPS reported that longer and slower ultrafiltration rates were associated with better outcomes for the patients (Saran et al., 2006).

There are many times where there appears to be a discrepancy between the prescribed dose of HD and the actual dose of HD delivered. Some of these include, “Failure of staff to ensure the pre-determined treatment time is given (usually in the face of variable patient resistance) is a common failing. However, other factors such as suboptimal needle placement, hemodynamic instability and progressive access malfunction all militate against this optimal delivery” (Al Saran et al., 2009).

The use of high-flux membranes, higher BFR, higher dialysate fluid flow rate, higher UFR, and HDF will increase clearances of some molecules. Some are more effective at small molecule clearance (high BFR, DFR, UFR and use of high flux membranes) and others at middle molecule clearance (HDF, high flux membranes). However, research does not support the use of these to demonstrate clear improved clinical outcomes for patients at this time.

Research continues into dialysis adequacy and controversies still abound. The DOPPS study and the ANZData have shown that longer treatment times do have a positive effect on dialysis adequacy (Locatelli & Canaud, 2012) because of a reduced ultrafiltration rate, decreased risk of hypotension, better fluid volume control and larger dialysis dose. However, increased treatment time and/or frequency are problematic because of the current capacity of HD units. The development of high flux dialysers and online haemodiafiltration with their reported better middle molecule clearance may lead to improved control of the metabolic alterations which are associated with ESCKD (Locatelli & Canaud, 2012).

*Maintaining residual renal function*

Residual renal function (RRF) is vital to improving mortality, QOL and severity of inflammation in HD (Shafi et al., 2010).

“In a single centre US study of 114 prevalent HD patients, the presence of any urine output (>100 ml/day) was associated with a 65% lower risk of death during the subsequent 2-year period” (Shafi et al., 2010, p. 354). The assessment of urine output could be as simple as asking patients if they are producing 1 cup of urine per day (Shafi et al., 2010). All efforts should be made to maintain RRF (Perl & Bargman, 2009; Shafi et al., 2010). HD impacts on RRF by depleting the blood volume, and hypertensive episodes during the dialysis sessions. To preserve RRF in those with ESCKD it is wise to consider the impact of the dialysis modality, decrease the risk of volume depletion, the blocking of the renin-angiotensin-aldosterone system, avoiding nephrotoxic injury, and the control of blood pressure.

**Clinical issues for dialysis adequacy assessment**

Factors which affect the dialysis adequacy assessment include:

- dialysate surface area
- length of treatment
- blood flow rate
- dialysate flow rate
- type of vascular access
- re-circulation
- nutritional status
- correct blood sampling procedures
- reduced treatment time and missed treatments
- cardiopulmonary recirculation
- cooperation from patients
- residual renal function

These factors will affect the accuracy of any dialysis adequacy no matter if collecting blood for the measurement of Kt/V or automatic measurement via the OCM. In the manual method the correct sampling procedure (particularly the timing of the post-dialysis sample) is vital for adequacy assessment accuracy. Therefore the care of those with ESCKD on HD should take note of the above factors. That is how the dialysis dose prescribed relates to the dialysis dose actually delivered. It is the actual dialysis dose delivered which will affect the Kt/V measurement the most.

Can nephrology nurses provide better care to their patients by “decreasing their emphasis on Kt/V [and] not be seduced by mathematics or technology and become ‘technically enframed’” (Bennett & Neill, 2008, p. 35) as patients’ quality of life whilst on HD is not wholly reliant upon the technology. Further, patients should be encouraged to consider longer and more frequent dialysis to improve their life. However, this may involve adopting a home dialysis program because of the lack of capacity of renal units in Australia to support longer and more frequent dialysis for all patients. A home dialysis program may not be possible for some patients due to factors outside dialysis.

**Key messages**

- Dialysis adequacy should be assessed every three months (CARI).
- Dialysis adequacy assessment should include good blood pressure and fluid volume management (Kerr et al., 2005).
- HD adequacy which maintains good health and function for the patient is the ‘holy grail’ for those who work in the nephrology sphere.
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- Dialysis adequacy needs to be assessed on an individual basis.
- Preserve residual renal function.

Conclusion
In spite of the many technological and pharmacological advances in the HD context these have not clearly demonstrated better clinical outcomes for those on dialysis for survival in the majority of cases will be determined by cardiovascular status at the commencement of dialysis (Lameire et al., 2009). The implementation of good clinical practice guidelines and extending dialysis time may have a better impact on clinical outcomes (Lameire et al., 2009). Evidence being reported in much recent research is suggesting that Kt/V is not the best method to evaluate the adequacy of dialysis (Lameire et al., 2009).

In conclusion there continues to be much debate re the best method to determine dialysis adequacy. However, Kt/V remains a method generally used at the present time. The main criticisms of Kt/V are related to the dialysis technology and methods available when the formula was developed and changes in these may impact on the accuracy of adequacy measurements. Further the fact that there is no correction factor for body size and gender may also have an effect on the accuracy of Kt/V. However, research continues into potential modifications of the Kt/V formulae and/or other potential substances which could be used to more accurately assess dialysis adequacy. The search continues to find the best marker for the assessment of dialysis adequacy. However, both hardware and computerised software are now available to monitor dialysis adequacy during HD sessions, and continuing developments of these may result in a more accurate, reliable and applicable measurement of dialysis adequacy.

Daugirdas et al. (2000) state that there are two major questions which remain indefinitely answered, these are whether more dialysis is needed and will the use of high-flux membranes demonstrate improved clinical outcomes. However, Kt/V and URR remain useful to use to avoid poor dialysis efficiency, until other uremic toxins are identified as useful to evaluate dialysis adequacy (Meyer et al., 2011).

Key messages
1. Factors which can affect the accuracy of the assessment of dialysis adequacy are the same in the manual or automated measurement of Kt/V.
2. The ‘magic formulae’ for the absolute accuracy of dialysis adequacy has yet to be determined and much controversy remains as to the appropriateness of the use of small molecule clearance to determine dialysis adequacy.

References
Review questions

1. The assessment of dialysis adequacy is important as poor adequacy is closely associated with which one (1) of the following?
   a. increased morbidity and mortality
   b. decreased morbidity and mortality
   c. increased erythropoiesis
   d. decreased erythropoiesis

2. The major aim of newer technological developments in dialysis is which one (1) of the following?
   a. to keep the patient healthy and functional
   b. to improve clinical outcomes
   c. to decrease the overall costs to the health sector
   d. all of the above

3. The calculation of Kt/V is done by the collection of a pre- and post-dialysis blood sample for the serum urea level these results are then mathematically calculated and a result is given. The biggest impact on the accuracy of this measurement is related to which one (1) of the following?
   a. the collection of the pre-dialysis blood sample
   b. the collection of the post-dialysis blood sample
   c. the actual mathematical equation used
   d. none of the above

4. An adequate haemodialysis is generally defined as a Kt/V of:
   a. less than 0.8
   b. equal to 10
   c. greater than 12
   d. there is no accepted level

5. There is much controversy at present in regard to the accuracy of Kt/V as a measure of dialysis adequacy. Technological developments have been posed as a possible cause for this. The technological developments which have affected the accuracy of Kt/V include which one (1) of the following?
   a. dialysis time
   b. dialyser membranes
   c. patient characteristics
   d. all of the above

6. Recent research is suggesting that which one (1) of the following be included in any mathematical equation for the assessment of dialysis adequacy?
   a. muscle mass and body fat distribution
   b. gender and body surface area
   c. years on dialysis
   d. estimated glomerular filtration rate (eGFR)

7. Online clearance monitoring (OCM) is based upon the measurement of which one (1) of the following?
   a. serum sodium level
   b. serum potassium level
   c. dialysate urea level
   d. dialysate sodium level

8. Generally the OCM reading occurs every:
   a. 10 minutes
   b. 15 minutes
   c. 20 minutes
   d. 30 minutes

9. The time taken to perform an OCM reading is:
   a. 1 minute
   b. 2–4 minutes
   c. 10–15 minutes
   d. more than 20 minutes

10. The OCM measurement of Kt/V is significantly affected by discrepancy between the prescribed dose of haemodialysis and the actual delivered dose of haemodialysis. Which one (1) of the following is not a factor in this discrepancy?
    a. blood flow rate
    b. access recirculation
    c. dialysate temperature
    d. length of haemodialysis treatment

Answers to review questions

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