Second Generation Logarithmic Estimates of Single-Pool Variable Volume Kt/V: An Analysis of Error

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ABSTRACT

The original formula proposed to estimate variable-volume single-pool (VVSP) Kt/V was Kt/V = -ln(R - 0.008 * f - t + UF/W), where in the Kt/V range of 0.7 to 1.3, f = 1.0 (· denotes multiplication). This formula tends to overestimate Kt/V as the Kt/V increases above 1.3. Because higher Kt/V values are now commonly delivered, the validity of both the urea generation term (0.008 · t) and correction for UF/W were explored by solving VVSP equations for simulated hemodialysis situations, with Kt/V ranging from 0.6 to 2.6. The analysis led to the development of a second-generation formula, namely: Kt/V = -ln(R - 0.008 · t) + (4-3.5 · R) · UF/W. The first and second generation formulas were then used to estimate the modeled VVSP Kt/V in 500 modeling sessions in which the Kt/V ranged widely from 0.7 to 2.1. An analysis of error showed that this second-generation formula eliminated the overestimation of Kt/V in the high ranges found with the first-generation formula. Also, total error (absolute value percent error + 2 SD) was reduced with the second-generation formula. These results led to the proposal of a new formula that can be used for a very wide range of delivered Kt/V.

Key Words: Urea, kinetic modeling, hemodialysis

The classical (variable-volume, single-pool [VV SP]) method of urea kinetic modeling as proposed by Sargent and Gotch (1) is based on three measurements of plasma urea nitrogen (UN) levels and on estimates or measurements of dialyzer and residual renal urea clearances. From the predialysis and postdialysis plasma UN values, a mean plasma UN value during the dialysis session can be estimated. This is multiplied by the estimated or measured dialyzer urea clearance to arrive at the amount of urea removed during the treatment. Once the amount of urea removed is known, the urea distribution volume (V) can be estimated from the predialysis and postdialysis plasma UN values. The next step is to estimate the urea generation rate (g). Once the urea distribution volume (V) has been determined, the urea generation rate (g) can be calculated from the increase in the plasma UN value over the interdialytic interval plus the amount of urea excreted in the urine. Because urea generation during the dialysis session will have an effect (albeit a minor one) on the computation of V, simple algebra cannot be used to solve for V and g. These are derived by the iterative solution of two equations (1,2) that take into account the decrease in urea distribution volume that occurs during dialysis because of ultrafiltration and the subsequent increase in V during the interdialytic period.

There are a number of problems with the classic VVSP model, including difficulties in estimating dialyzer urea clearance accurately (3), the need to consider the arteriovenous urea gradient that develops during dialysis (4), and the effect of postdialysis rebound in the plasma urea concentration as the result of intracellular/extracellular urea gradients and/or differences in urea removal from the regional blood circulations (5). A discussion of these is beyond the scope of this report. Problems with the VVSP urea kinetic model have led to new approaches to urea kinetics on the basis of dialysate urea sampling (6,7) and/or to multipool blood-side modeling (2).

One valuable construct of the urea kinetic model is the term Kt/V, which is the fractional clearance of urea (8). If K is the urea clearance and t is time, the term Kt will be a volume. The ratio of Kt to V will represent that part of the urea distribution volume that has been totally cleared of urea. In the U.S. National Cooperative Dialysis Study, a Kt/V of less than 0.8 was associated with a poor outcome (8). Publication of that study greatly increased the interest in urea kinetic modeling and in monitoring Kt/V.

Because of the complexity of urea kinetic modeling, a number of shortcut methods of estimating Kt/V have been proposed (9–12). According to the urea kinetic modeling equations, Kt/V is determined principally by the natural logarithm (ln) of the ratio of the postdialysis to the predialysis plasma UN concen-
trations R. Thus, Kt/V = -ln(R). Because of urea generation during dialysis and because of urea removal in the course of ultrafiltration (which contributes to the urea clearance K, but does not affect R), Kt/V computed as -ln(R) will overestimate the Kt/V derived from three-point VVSP by an average of about 18% (10,13). To correct for this, we proposed deriving a value called R'. R' was what the value of R would have been if there had been no urea generation during the dialysis session and if the amount of urea removed by ultrafiltration was instead removed by diffusion dialysis with a fixed, postdialysis volume V. R', then, was always less than the measured value of R, expressed as follows:

\[ R' = R - 0.008 \times t - f \times UF/W \]

where: R is the post/pre plasma UN ratio, t is the dialysis session length (in hours), f is the "fudge factor," UF is the ultrafiltrate volume (in liters), W is the postdialysis weight (in kilograms), and \( \cdot \) denotes multiplication. The term 0.008 \times t represented the ΔR value during the dialysis session as the result of urea generation, and the term f \times UF/W represented the ΔR as the result of the additional urea removed due to volume contraction. Using this information, we derived a highly precise formula for Kt/V that corresponded very well with the Kt/V value computed from three-point VVSP modeling (10,11):

\[ Kt/V = -\ln(R') = -\ln(R - 0.008 \times t - f \times UF/W) \]  

(Equation 1)

It was recognized that the correction factor f for UF/W varied as a function of Kt/V. It was proposed that f be set to 1.0 in the usual clinical Kt/V range of 0.7 to 1.3, to 1.25 when Kt/V was less than 0.7, and to 0.75 when Kt/V was more than 1.3 (10). However, Kt/V is not known beforehand, which limits the usefulness of this approach. Also, high values of Kt/V are now commonly delivered. For this reason, a more generalized formula is needed. The purpose of this article was to derive and test such a formula.

**METHODS**

**Simulated Dialysis Situations**

By the use of a spreadsheet, approximately 200 simulated dialysis situations were created. A three-times-a-week dialysis schedule was assumed, and residual renal urea clearance was set to zero. Dialyzer clearance (K) was kept constant at 200 mL/min. Patient weight was set at 50, 70, or 90 kg. The urea distribution volume (V) was assumed to be 55% of the postdialysis weight. For each "patient," the dialysis session length (t) was varied to arrive at Kt/V values of 0.6 through 2.6, in 0.2-U increments. The predialysis plasma UN level (CO) was either fixed or based on the expected steady-state predialysis value based on the normalized protein catabolic rate (nPCR) and Kt/V. Computation of the steady-state CO was done by the use of a two-point single-pool urea kinetic model (14). In the analyses, g was computed from the nPCR (2), based on nPCR values of 0.8, 1.0, or 1.2 g/kg per day. The ultrafiltrate volume during dialysis was set to zero (negligibly low) or to 1, 2, 3, or 4 L. Thus, these simulations included most clinical situations encountered when a three-times-a-week treatment schedule is delivered.

**Effect of Urea Generation (g) on the Post/Pre-Ratio (R)**

Equations derived from "classic" three-point, urea kinetic modeling (2) were used to derive, in each simulated patient, a value for the postdialysis plasma UN concentration (Ct):

\[ Ct = CO(Vt/VO) \times ((K-U)/U) + \]

\[ (g/K-U) \times (1 - (Vt/VO)) \times ((K-U)/U) \]

Where Ct is the postdialysis plasma UN level (in milligrams per milliliter), CO is the initial plasma UN level (in milligrams per milliliter), Vt is the postdialysis urea distribution volume (in milliliters), VO is the predialysis urea distribution volume (in milliliters), K is the dialyzer clearance (in milliliters per minute), U is the ultrafiltration rate (in milliliters per minute), g is the urea generation rate (in milligrams per minute), and \( \times \) represents multiplication. Ct was computed both when g = 0 and when g corresponded to nPCR values of 0.8, 1.0, and 1.2 g/kg per day. U, the ultrafiltration rate in milliliters per minute, was varied to corresponding UF values of 1, 2, 3, 4, and 5 L removed per session.

To derive the effect of g on ΔR, ΔR was computed by use of the following equation:

\[ \Delta R = (Ct_{g=0} - Ct_{g=0})/CO \]

The manner in which ΔR varied as a function of dialysis session length (t), CO, and nPCR was then explored by graphing and regression analysis.

**Effect of UF/W**

In these simulations, g was set to zero. The effect of UF/W was explored in the context of two estimation equations:

\[ Kt/V = -\ln (R - f_1 \times UF/W) \]  

(Equation 2)

\[ Kt/V = -\ln (R) + f_2 \times UF/W \]  

(Equation 3)

In the first approach, (Equation 2), a corrected value for R is computed, namely, (R-f1*UF/W). This term represents the value of R that would have been achieved if the same amount of Kt/V had been deliv-
ered without volume contraction. In the second approach (Equation 3), the volume contraction component of Kt/V is estimated separately, as f2 * UF/W, and this term is added to the Kt/V obtained from diffusion dialysis, -ln(R). The effect of Kt/V and R on f1 and f2 was explored by graphing, and regression lines were computed for f1 and f2 versus R.

**In Vivo Validation**

The simulation analysis (see Results) suggested that a new formula would be even more precise and would have less systematic error:

\[ \text{Kt/V} = -\ln(\text{R} - 0.008 \cdot t) + (4.35 \cdot \text{R}) \cdot \text{UF/W} \]  

(Equation 4)

This equation was used to estimate Kt/V in a large population (N = 500) of three-times-a-week dialysis sessions in 374 patients, in which the Kt/V ranged widely from 0.7 to 2.1. For purposes of analysis, 160 sessions in which the Kt/V was above 1.4 were analyzed separately, because this is the range in which Equation 1, -ln (R - 0.008 * t - f * UF/W), was expected to have problems. To avoid a step function in the values for f, Equation 1 was evaluated twice, once with f = 1.0 and once with f = 0.75 for the entire Kt/V range. The Kt/V as determined by VVSP three-point modeling (2) was compared with the Kt/V value estimated from variations of Equations 1 and 4. The modeled Kt/V values were divided into subgroups 0.1 Kt/V unit wide; for each subgroup, the mean ± SD percent error of the estimate, as well as the absolute value of the mean percent error, was computed. The total error was calculated as |percent error| + 2 SD. This method of comparison has been shown to be more valid than regression analysis (15,16). Statistical comparison among the different formulas was by regression analysis and by paired t testing.

In the "low Kt/V" group of 340 modeling sessions, the mean Kt/V was 1.03 ± 0.19 (SD). The mean dialyzer blood water urea clearance was 196 ± 34 mL/min. The mean patient weight was 69 ± 11 kg, and the mean ratio of V/W was 0.56 ± 0.08. In the "high Kt/V group" of 160 modeling sessions, the mean Kt/V was 1.61. The mean dialyzer blood water urea clearance was 235 ± 23, the mean patient weight was 61 ± 9.65 kg, and the mean ratio of V/W was 0.54 ± 0.09.

**RESULTS**

**Simulation Studies: Effect of Dialysis Session Length (t) on R**

The effect of urea generation on R will be determined primarily by the length of the dialysis session (t). As t increases, the total amount of urea generated will be increased, and the effect on Ct and R will be more pronounced. For example, if a Kt/V of 1.0 is delivered in 6 h, Ct and therefore R will be higher than if a Kt/V of 1.0 is delivered in 2 h. Although time is the main factor, the effect of t on R also depends on whether g is high or low. In Figure 1, the effect of g, expressed as nPCR, is shown. When nPCR is high, there will be more urea generated per unit time, and Ct, as well as R, will be higher than expected. On the other hand, when g is low, the effect of g on R will be less, and the regression curve of ΔR versus time will have a lower profile.

In Figure 1, the value for C0 was kept constant at 75 mg/dL. In Figure 2, we explore the effect of C0 on the relationship between dialysis session length (t) and ΔR. High values of C0 will dampen the effect of t on R. This can be understood intuitively: assume that g is such that, in the absence of dialysis, the amount of urea produced would raise the plasma urea level by 4 mg/dL over 4 h. This amount of urea generation will have much less effect on Ct/C0 when C0 is 200 mg/dL than when C0 is 20 mg/dL. In the simulations used to derive Figure 2, C0 was varied whereas g was held constant, corresponding to an nPCR of 1.0 g/kg per day.

From Figures 1 and 2 together, an interesting insight is obtained: high values of g magnify the effect of dialysis session length on ΔR, whereas high values of C0 dampen the effect. Because g and C0 are usually correlated, their effects tend to cancel. This is shown by the graph in Figure 3. In this figure, the same simulation points as those in Figures 1 and 2 were used, except that the value for C0 used de-
nPCR = 1.0 g/kg/day

\[ Y = 0.008 \times t \]

Figure 2. The effect of dialysis session length (t) on \( \Delta R \). This time, g was fixed and C0 was varied. It can be seen that \( \Delta R \) is dampened at high values for C0 and exaggerated at low values of C0.

nPCR = 0.8 g/kg/day

Figure 3. Effect of dialysis session length (t) on \( \Delta R \) when C0 and g are linked. C0 was set at the steady-state value expected for each datum point based on Kt/V and nPCR, using a two-point VVSP urea kinetic model. Because g and C0 have opposite effects on \( \Delta R \), when C0 and g tend to rise and fall in tandem, their combined effect \( \Delta R \) is reduced and the principal variance of \( \Delta R \) is now the dialysis session length (t). The modeling line of 0.008 \times t selected was slightly lower than the ideal regression line in order to minimize overestimation of Kt/V.

\[ Y = 0.008 \times t \]

Figure 3. Effect of dialysis session length (t) on \( \Delta R \) when C0 and g are linked. C0 was set at the steady-state value expected for each datum point based on Kt/V and nPCR, using a two-point VVSP urea kinetic model. Because g and C0 have opposite effects on \( \Delta R \), when C0 and g tend to rise and fall in tandem, their combined effect \( \Delta R \) is reduced and the principal variance of \( \Delta R \) is now the dialysis session length (t). The modeling line of 0.008 \times t selected was slightly lower than the ideal regression line in order to minimize overestimation of Kt/V.

\[ Y = 0.008 \times t \]

Figure 4. Effect of Kt/V on \( f1 \) by the use of Equation 2 (see text). It can be seen that the value of \( f1 \) is close to 1 when 0.7 < Kt/V < 1.3.

\[ Kt/V = -\ln(R - 0.008 \times t - (1.9 \times R + 0.2) \times UF/W) \] (Eq. 1a)

The Effect of UF/W on R and Kt/V: Comparing Equation 2 With Equation 3 and Deriving Robust Values for \( f1 \) and \( f2 \)

Figure 4 presents the values of \( f1 \) (Equation 2) necessary to arrive at a correct Kt/V value for each simulation point. In these simulations, g was set equal to zero. It is evident that \( f1 = 1 \) when Kt/V is close to 1.0. The optimal value for \( f1 \) is 0.75 when Kt/V is close to 1.5. This is the basis of our previously advocated Equation 1 (10). Because the modeled Kt/V is not known, the \( f1 \) values from Figure 4 were replotted against the predicted R (Figure 5). The data suggest that \( f1 \) could be approximated beforehand as 1.9 \times R + 0.2 and that a more general form of Equation 1 would be:

\[ Kt/V = -\ln(R - f1 \times UF/W) \]
\[ Kt/V = -\ln (R - f1 \times UF/W) \]

For \( f1 \):

\[ f1 = 1.9 \times R + 0.2 \]

Figure 5. Effect of \( R \) on \( f1 \). The data fit a linear regression line of \( f1 = 1.9 \times R + 0.2 \).

\[ Kt/V = -\ln (R) + f2 \times UF/W \]

For \( f2 \):

\[ f2 \text{ should be about 2.6 to 3.2 in the } Kt/V \text{ range of 1.0 to 1.5.} \]

Figure 6. Effect of \( f2 \) on \( Kt/V \) by the use of Equation 3 (see text). It is evident that the \( f2 \) should be about 2.6 to 3.2 in the \( Kt/V \) range of 1.0 to 1.5.

\[ Kt/V = -\ln (R - 0.008 \times t - 3.5 \times R) \times UF/W \quad \text{Equation 4} \]

We then had two potentially useful equations: 1a and 4, above. Equation 4 was chosen, because the slope of \( f2 \) versus \( R \) is much less than the slope of \( f1 \) versus \( R \). Also, at high \( Kt/V \) values, very small errors in \( R \) will result in large errors in \( Kt/V \); attempting to modify \( R \) in the high \( Kt/V \) range, if done incorrectly, can lead to relatively large errors.

In Vivo validation: Correlation Coefficients

Correlation coefficients are listed in Table 1. They were computed separately for the lower and higher \( Kt/V \) data sets. It can be seen that all of the tested formulas had high (>0.96) correlation coefficients with the modeled \( Kt/V \) except in the very high range where the range of \( Kt/V \) values was small. The distribution of the number of cases in each 0.1 \( Kt/V \) interval is shown in Figure 8.

Systematic Error

Systematic error results are shown in Figure 9. As predicted by the simulations and as previously noted (10), the formula \(-\ln (R - 0.008 \times t - 3.5 \times R) \times UF/W\) using an \( f \) value of 1.0 for all \( Kt/V \) values (which should not be done clinically) results in marked overestimation of \( Kt/V \) in the high range. This can be corrected to some extent by using \( f = 0.75 \) for all \( Kt/V \).
Second-Generation Logarithmic Estimates

TABLE 1. Correlation coefficients with modeled Kt/V

<table>
<thead>
<tr>
<th></th>
<th>Lower Range</th>
<th>Higher Range</th>
<th>Very High Range</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0.7 &lt; Kt/V &lt; 1.4</td>
<td>1.4 &lt; Kt/V &lt; 2.1</td>
<td>Kt/V &gt; 1.7</td>
</tr>
<tr>
<td>−ln(R-0.008 * t-UF/W)</td>
<td>0.990</td>
<td>0.960</td>
<td>0.886</td>
</tr>
<tr>
<td>−ln(R-0.008 * t-0.75 * UF/W)</td>
<td>0.988</td>
<td>0.976</td>
<td>0.929</td>
</tr>
<tr>
<td>−ln(R-0.008 * t) + (4-3.5 * R) * UF/W</td>
<td>0.990</td>
<td>0.976</td>
<td>0.920</td>
</tr>
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Figure 8. Number of cases for each Kt/V interval. The total number of modeling sessions studied was 500.

values. However, the first-generation formula with f = 0.75 is not neutral in terms of systematic error; it slightly underestimates Kt/V when Kt/V < 1.3 and overestimates Kt/V when Kt/V > 1.8. Overestimation is marked when Kt/V > 2.0 (data not shown). On the other hand, the second-generation formula has very little systematic error over a broad Kt/V range (0.7 to 2.0); the mean percent error is <2% throughout the entire tested Kt/V range, and the error does not vary as a function of Kt/V.

Very similar results analyzing total error are shown in Figure 10. By the use of Equation 1 and an f1 of 1.0 for all Kt/V values, total error is within the acceptable 5% range until Kt/V increases beyond 1.4. Then, total error becomes unacceptable. The use of a multiplier of 0.75 corrects the situation partially, in that total error is within the 5% bounds when 1.4 < Kt/V < 1.9. However, there is loss of precision in the "low" Kt/V range (Kt/V < 1.4). With the new second-generation formula, total error remains 5% or less throughout the tested Kt/V range.

TABLE 2. Percent error and |Percent Error| of Kt/V estimates

<table>
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<tr>
<td>% Error</td>
<td></td>
<td></td>
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<tr>
<td>−ln(R-0.008 * t-UF/W)</td>
<td>−0.7 ± 2.5°</td>
<td>4.0 ± 3.4°</td>
<td>5.2 ± 4.1°</td>
</tr>
<tr>
<td>−ln(R-0.008 * t-0.75 * UF/W)</td>
<td>−3.1 ± 2.6°</td>
<td>0.60 ± 2.5°</td>
<td>1.4 ± 2.8°</td>
</tr>
<tr>
<td>−ln(R-0.008 * t) + (4-3.5 * R) * UF/W</td>
<td>−1.1 ± 2.4°</td>
<td>−0.71 ± 2.1</td>
<td>−1.1 ± 2.4</td>
</tr>
<tr>
<td>[% Error]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−ln(R-0.008 * t-UF/W)</td>
<td>2.0 ± 1.6°</td>
<td>4.2 ± 3.2°</td>
<td>5.5 ± 3.7°</td>
</tr>
<tr>
<td>−ln(R-0.008 * t-0.75 * UF/W)</td>
<td>3.3 ± 2.4°</td>
<td>1.9 ± 1.6</td>
<td>2.8 ± 2.0°</td>
</tr>
<tr>
<td>−ln(R-0.008 * t) + (4-3.5 * R) * UF/W</td>
<td>2.0 ± 1.6</td>
<td>1.6 ± 1.4°</td>
<td>1.9 ± 1.8°</td>
</tr>
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° P < 0.05.
DISCUSSION

Our results lead to a new formula for estimating Kt/V, useful especially in units where high Kt/V amounts are routinely delivered. The formula is more complex than before, but it still can be calculated at the bedside and requires only a calculator capable of computing natural logarithms. The formula has been put into the form of a nomogram (Figure 11) for easy use. We emphasize our previous recommendation that the formula $-\ln(R - 0.008 \times t - UF/W)$ (assuming $f = 1.0$ and dropping the term) should not be used when delivered Kt/V values routinely exceed 1.3 to 1.4. A reasonable solution is to use the formula $-\ln(R - 0.008 \times t - 0.75 \times UF/W)$ as the standard, given the trend to deliver high Kt/V values. However, even less systematic error results when the new second-generation equation is used.

How do these formulas compare with others commonly advocated to estimate the Kt/V? For comparison purposes, Figures 12 and 13 analyze the error of two linear formulas, as advocated by Jindal et al. (9) and by Basile and colleagues (12). It is evident that these formulas are far less precise and, more importantly, that error is not constant but varies with the level of Kt/V.

"Bedside" estimations of Kt/V have been criticized from several points of view. Some say that Kt/V is a needless construct and that adequate morbidity/mortality information can be obtained by use of the Ct/C0 ratio (or the urea reduction ratio equal to 1-Ct/C0) (17). However, in patients with minimal residual renal function, knowledge of Kt/V allows the use of a nomogram to estimate the nPCR (2). Furthermore, much clinical information has been obtained in
Figure 13. Total error (95% confidence band) of two commonly used linear formulas. The y-axis scale is twofold higher than in Figure 10. Total error is never reduced to the desirable 5% range at any level of Kt/V, and total error is highly dependent on the level of Kt/V. PRU, percent reduction in urea.

terms of the VVSP-derived Kt/V, and thus, there is clinical value in knowing the Kt/V per se.

Another criticism is that by not modeling V, one loses the opportunity to identify problem dialysis sessions, in which the modeled V deviates markedly from the V derived by nomogram. For example, suppose that a given modeling session revealed a Kt/V of 1.5 and a modeled V of 20 L in an 80-kg patient. The fact that the modeled V is only 25% of the body weight does not make sense and immediately identifies the value for Kt/V as probable artifact. The results point to a laboratory error in measuring serum UN or to a mistake in the drawing of the blood (e.g., from the venous line). The use of an even a very precise bedside formula would generate a similar Kt/V value but would not flag it as a possible error. Similarly, if two similar dialysis treatments give widely different Kt/V values, an analysis of the modeled V can help determine which of the two values is more likely to be correct. For this reason, bedside techniques are best suited for the rapid estimation of Kt/V when a computerized analysis is not available or for monitoring dialysis delivery in units, programs, or nationwide by external auditing agencies. In defense of our bedside formula, however, it is not difficult to obtain a modeled V manually. Two further nomograms are required: one to estimate the dialyzer mass transfer urea coefficient from factory-supplied clearance data and another to estimate the in vivo dialyzer clearance K based on dialyzer urea mass transfer area coefficient (KoA) and the blood flow rate. Once K is known, the modeled V can be computed from the "bedside" Kt/V, the nomogram-derived K, and t (18).

A final critique has to do with precision versus accuracy. Although the formulas described may very precisely predict the value of Kt/V derived from VVSP modeling, the accuracy of single-pool modeling has been called into question, especially for modeling high-efficiency, short-session-length treatments. To compensate for this, two-pool blood-side modeling techniques and methods that depend on dialysate urea determination have been developed. In these situations, the bedside formulas described here can still be used, but the postdialysis urea sample should be drawn 30 min after dialysis (7,19).

In summary, a second-generation formula is proposed to estimate Kt/V by the VVSP approach. This new formula can be used across a wide range of Kt/V values.

REFERENCES


