Meta-Analysis: Peritoneal Membrane Transport, Mortality, and Technique Failure in Peritoneal Dialysis

K. Scott Brimble,*† Michelle Walker,* Peter J. Margetts,*† Kiran K. Kundhal,‡ and Christian G. Rabbat*†

*Department of Medicine, McMaster University, and †Division of Nephrology, St. Josephs Healthcare, Hamilton, Ontario, and ‡Department of Nephrology, University of Toronto, Toronto, Ontario, Canada

Peritoneal membrane solute transport in peritoneal dialysis (PD) patients is assessed by the peritoneal equilibration test, which measures the ratio of creatinine in the dialysate to plasma after a standardized 4-h dwell (D/Pc). Patients then are classified as high, high-average, low-average, or low transporters on the basis of this result. A meta-analysis of observational studies was carried out to characterize the relationship between D/Pc and mortality and technique failure in patients who are on PD. Citations were identified in Medline by using a combination of Medical Subject Heading search terms and key words related to PD, peritoneal membrane permeability/transport, and mortality and technique failure. The table of contents of relevant journals and bibliographies of relevant citations were reviewed in duplicate. Twenty studies that met study criteria were identified. Nineteen studies were pooled to generate a summary mortality relative risk of 1.15 for every 0.1 increase in the D/Pc (95% confidence interval 1.07 to 1.23; \( P < 0.001 \)). This result equated to an increased mortality risk of 21.9, 45.7, and 77.3% in low-average, high-average, and high transporters, respectively, as compared with patients with low transport status. Meta-regression analysis showed that the proportion of patients who were on continuous cycler PD within a study was inversely proportional to the mortality risk (\( P = 0.05 \)). The pooled summary relative risk for death-censored technique failure was 1.18 (95% confidence interval 0.96 to 1.46; \( P = 0.12 \)) for every 0.1 increase in the D/Pc. This meta-analysis demonstrates that a higher peritoneal membrane solute transport rate is associated with a higher mortality risk and a trend to higher technique failure.


Patients with ESRD, including those who are on peritoneal dialysis (PD), are at a much higher risk for premature death than the general population. Well-accepted risk factors for early mortality that have been identified in the PD population include age, diabetes, preexisting cardiovascular disease, and malnutrition/hypoalbuminemia (1–6).

The peritoneal equilibration test (PET) characterizes the peritoneal membrane transport properties by determining the ratio of the creatinine concentration in the dialysate to that in the plasma after a standardized 4-h dwell (D/Pc) and has been shown to vary considerably among individuals (7). Patients with a greater rate of membrane solute transport (i.e., higher D/Pc) will tend to have enhanced clearance of small solutes, including urea and creatinine, during shorter dwells. However, these patients will have greater peritoneal losses of protein, will be more prone to fluid retention as a result of rapid reabsorption of glucose from the dialysate and subsequent ultrafiltration dysfunction, and will have greater systemic exposure to glucose. These differences may have competing effects on both patient and technique survival such that from a biologic basis, it is unclear what, if any, the effect of peritoneal membrane solute transport rate on these outcomes will be. We therefore performed a meta-analysis to characterize the relationship between peritoneal membrane solute transport rate, as measured by the PET, and mortality and technique failure in patients who are on PD.

Materials and Methods

We systematically reviewed studies that evaluated the impact of peritoneal membrane transport properties, as measured by the PET, on mortality and/or technique failure in patients who were on PD.

Study Selection

We searched the Medline database from 1987 (the date when the PET test was first described [7]) to January 2006 by using a combination of Medical Subject Heading terms and text words related to PD, peritoneal membrane transport properties, and mortality and technique failure. The full search string is available in the Appendix. All English abstracts were reviewed in duplicate, and any potentially relevant articles were retrieved for more detailed analysis. Articles with English abstracts but non-English text were translated to determine their eligibility for inclusion. We also manually reviewed references of relevant reviews and the table of contents of relevant nephrology journals, including published abstracts from associated scientific meetings.

Our prespecified criteria for study inclusion were as follows: (1) Subjects were on PD, and (2) the impact of the PET test on the outcomes of interest (mortality and/or technique failure) was evaluated. Studies were excluded when they (1) had no original data, (2) involved fewer than five patients, or (3) did not report a measure of peritoneal mem-
brane solute transport in their risk analysis. When more than one published study on the same or overlapping cohort of subjects was identified, the most complete data were extracted from the contributing studies.

**Data Abstraction**

Two investigators independently reviewed each article that met the selection criteria and abstracted the data of interest; discrepancies were resolved by consensus. Data that were abstracted, when available, were sample size, mean age, percentage of male participants, percentage of subjects who had diabetes, study location, PD method (continuous ambulatory peritoneal dialysis (CAPD), continuous cycler peritoneal dialysis [CCPD], or either), method of measuring PET, population type (incident versus prevalent), mean D/Pc with SD, study design (prospective versus retrospective), duration of follow-up, outcome(s), main results, statistical methods, and variables that were included in the adjusted model. Attempts to contact authors were made when further information was required to extract a risk estimate for the outcome of interest.

For each study that met inclusion and exclusion criteria, we abstracted the adjusted risk estimates (relative risk [RR] or hazard ratio [HR]) for the associations between subject mortality or technique failure and the 4-h D/Pc. SE and/or confidence intervals (CI) for the estimates were either abstracted or derived using data that were reported in the study.

**Statistical Analyses**

We conducted separate meta-analyses of the studies for the three outcomes: Patient mortality, technique failure and the combination of mortality and technique failure. Data were abstracted directly from studies that analyzed PET results in their model using the continuous variable, D/Pc (8–14); authors from two additional studies provided these data upon request (5,11). A number of studies (5,15–23) categorized subjects according to their D/Pc, as described previously (7). In this classification, subjects are defined as high (H) transporters when their 4-h D/Pc was more than 1 SD above the median value, high-average (HA) when between the median and 1 SD above, low-average (LA) when between the median and 1 SD below, and low (L) when below 1 SD (in the original publication, mean and SD D/Pc were 0.65 and 0.15, respectively). In studies (16–18,22) that compared H/HA with L/LA transporters, a normal distribution for D/Pc was assumed and the 4-h D/Pc, mean and/or confidence intervals (CI) for the estimates were either abstracted or derived using data that were reported in the study.

Sensitivity analysis was performed to assess the influence of individual studies on the pooled estimate by excluding one study at a time as described previously (34). When the point estimate of the revised pooled estimate was outside the 95% CI of the original estimate, the study in question was deemed to have excess influence. We assessed for potential publication bias using the Begg and Egger tests and funnel plots as described previously (35–37). Meta-regression analysis was performed to determine the effect of the following prespecified variables on heterogeneity in the individual study results: PD method (proportion of subjects on CCPD); PET method; population type (incident or prevalent); study design (prospective versus retrospective); statistical model (univariate versus multivariate); and inclusion of age, diabetes, or albumin in the multivariate model. P ≤ 0.05 was considered significant. All statistical analyses were conducted using Stata software, version 9.1 (Stata Corp., College Station, TX).

**Results**

**Search Results**

Our search identified 957 published articles, 160 of which were retrieved for detailed evaluation on the basis of the published abstract. Figure 1 outlines the reasons for study exclusion; the absence of PET data were the most common reason (81 studies). Two studies that were analyses of the Stoke PD cohort (8,38) were identified; the study with the longest follow-up was included in the analysis (8). Two studies (11,39) evaluated the impact of different variables and described an overlapping cohort of patients from a single center; the most complete of the two studies was included (11). Three studies were analyses of an accumulating cohort of subjects (40–42); in two studies, incomplete information was provided to calculate a risk estimate (41,42), whereas the third study provided sufficient information to determine a risk estimate for technique failure only (40). We were unable to retrieve further information from the authors. One study (13) carried out separate analyses on subjects from Sweden and Korea; the latter group seemed to rep...
Thus, it cannot be combined quantitatively with those that use the PET. Twenty studies that met inclusion and exclusion criteria were identified and used in the pooled analyses; these studies and their characteristics are described in Table 1. The majority of studies evaluated CAPD patients; two studies included only CCPD patients (23,33). Sample size varied from 41 to 3702 subjects, with average follow-up between 14 and 87 mo. Nine studies were identified as clearly prospective in design (5,8,10,12,15–17,20,11). All but one study (40) included the outcome of subject mortality; seven studies evaluated the impact of peritoneal membrane transport on technique failure (5,8,11,14,16,23,40).

Mortality Outcome
In most studies that used survival analysis, mortality was censored for transfer to hemodialysis (HD), transplantation, or loss to follow-up. Only four studies clearly indicated that deaths that occurred after transfer to HD were counted events (5,8,10,16). Heterogeneity testing permitted pooling of the studies to generate a summary risk estimate (Q statistic = 16.95, P = 0.53). Figure 2 presents the individual results and pooled estimate of the impact of a 0.1-unit increase in D/P\text{c} on mortality. The overall pooled RR is 1.15 (95% CI 1.07 to 1.23; P < 0.001); analysis of only studies that clearly were prospective in design generated a similar estimate (RR 1.18; 95% CI 1.07 to 1.30; P = 0.001). Translating these results to the more familiar transport status terms, the mortality risk was 21.9, 45.7, and 77.3% higher in LA, HA, and H transporters, respectively, as compared with patients with L transport status (Figure 3). Although formally excluded from this analysis, inclusion of the ADEMEX study (22), which used the distinct 24-h DATT as a measure of peritoneal solute transport rate, did not change the conclusions of the study (RR 1.11; 95% CI 1.04 to 1.19; P = 0.003).

Table 1. Studies that evaluated impact of peritoneal membrane transport on patient outcomes

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Patient Type (n)</th>
<th>PET Method</th>
<th>Follow-Up (average, mo)</th>
<th>Mean Age (yr)</th>
<th>Men (%)</th>
<th>Diabetes (%)</th>
<th>Country</th>
<th>Prospective Study</th>
<th>Incident Patients</th>
<th>Patient Survivala</th>
<th>Technique Survivalb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaz-Buxo, 1999 (9)</td>
<td>Both (198)</td>
<td>Standard</td>
<td>17.1</td>
<td>54.8</td>
<td>50.1</td>
<td>38.4</td>
<td>United States</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Brown, 2006 (33)</td>
<td>CCPD</td>
<td>—</td>
<td>—</td>
<td>54</td>
<td>57.6</td>
<td>15.0</td>
<td>Europe</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Hung, 1999 (23)</td>
<td>CCPD (50)</td>
<td>Standard</td>
<td>25.2</td>
<td>44.6</td>
<td>40</td>
<td>20.0</td>
<td>Taiwan</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Ates, 2001 (15)</td>
<td>Both (125)</td>
<td>Standard</td>
<td>30.6</td>
<td>46.3</td>
<td>61.6</td>
<td>10.4</td>
<td>Turkey</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rocca, 1993 (27)</td>
<td>CAPD (45)</td>
<td>Standard</td>
<td>47.6</td>
<td>54</td>
<td>48.9</td>
<td>77.8</td>
<td>United States</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Wang, 1998 (20)</td>
<td>CAPD (46)</td>
<td>Modified</td>
<td>—</td>
<td>57.4</td>
<td>52.2</td>
<td>19.6</td>
<td>Sweden</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Passadakis, 2000 (19)</td>
<td>CAPD (44)</td>
<td>Standard</td>
<td>47.9</td>
<td>65.5</td>
<td>—</td>
<td>25</td>
<td>Greece</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Agarwall, 2002 (17)</td>
<td>CAPD (41)</td>
<td>Standard</td>
<td>17.1</td>
<td>54</td>
<td>80.5</td>
<td>61</td>
<td>India</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Chung, 2000 (12)</td>
<td>CAPD (213)</td>
<td>Modified</td>
<td>—</td>
<td>49.5</td>
<td>56.3</td>
<td>40.4</td>
<td>Korea</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Illiescu, 2002 (10)</td>
<td>Both (54)</td>
<td>Standard</td>
<td>14.8</td>
<td>58.1</td>
<td>44.4</td>
<td>51.9</td>
<td>Canada</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Bhaskaran, 2000 (18)</td>
<td>Both (122)</td>
<td>Standard</td>
<td>19.5</td>
<td>55.5</td>
<td>51.6</td>
<td>41.8</td>
<td>Canada</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<td>Szeto, 2001 (16)</td>
<td>CAPD (235)</td>
<td>Standard</td>
<td>20.4</td>
<td>51</td>
<td>50.2</td>
<td>18.3</td>
<td>China</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>Davies, 1998 (8)</td>
<td>CAPD (303)</td>
<td>Standard</td>
<td>—</td>
<td>58.8</td>
<td>—</td>
<td>14.8</td>
<td>United Kingdom</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Park, 2001 (21)</td>
<td>CAPD (212)</td>
<td>Standard</td>
<td>—</td>
<td>48.6</td>
<td>54.2</td>
<td>38.4</td>
<td>Korea</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Aslam, 2002 (11)</td>
<td>Both (208)</td>
<td>Standard</td>
<td>14.4</td>
<td>56.1</td>
<td>60</td>
<td>40</td>
<td>United States</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cuesta-Manzano, 2000 (52)</td>
<td>CAPD (162)</td>
<td>Standard</td>
<td>87.4</td>
<td>54.8</td>
<td>43.7</td>
<td>38.9</td>
<td>Mexico</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Churchill, 1998 (5)</td>
<td>CAPD (606)</td>
<td>Standard</td>
<td>14.9</td>
<td>54.8</td>
<td>60</td>
<td>30.6</td>
<td>United States/Canada</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chung, 2005 (13)</td>
<td>Both (106)</td>
<td>Standard</td>
<td>20.4</td>
<td>55.6</td>
<td>58.0</td>
<td>37.0</td>
<td>Sweden</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Rumpf, 2005 (14)</td>
<td>Both (3702)</td>
<td>Standard</td>
<td>—</td>
<td>59.4</td>
<td>54.0</td>
<td>38.0</td>
<td>Australia/New Zealand</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Wu, 1996 (40)</td>
<td>CAPD (171)</td>
<td>Standard</td>
<td>—</td>
<td>501</td>
<td>45.6</td>
<td>33.8</td>
<td>Taiwan</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycler peritoneal dialysis; PET, peritoneal equilibration test.

Only includes studies that evaluated impact of peritoneal solute transport on the outcome of interest.
No study had a significant, influential effect on the overall mortality estimate in sensitivity analysis; exclusion of individual studies changed the summary RR to values that ranged from 1.13 (12) to 1.16 (10), well within the overall 95% CI values. The lowest and highest 95% CI values with any single study excluded were 1.04 for the lowest CI (12) and 1.26 for the highest CI (14), very similar to the overall 95% CI values described above. There was no evidence of publication bias (Begg’s test: adjusted Kendall’s score \( t = 1.11, P = 0.73 \); Egger’s test: slope = 0.16, \( P = 0.07 \); bias = 0.15, \( P = 0.76 \)). Meta-regression analysis demonstrated that only PD method had an impact on the findings (Figure 4); studies with greater proportions of CCPD patients demonstrated a less significant impact of D/Pc on mortality (\( P = 0.05 \)).

Technique Failure

There was between-study variability in the definition of technique failure. Many studies censored for death, an adverse competing event that may provide a misleading estimate of the event risk when using standard Kaplan-Meier methods (44). Therefore, analyses were carried out summarizing separately studies that provided information on death-censored technique failure (transfer to HD) (5,8,11,14,16,23) and those that analyzed transfer to HD or death as an outcome (5,16,40). One study did indicate that peritoneal transport status did not influence technique failure; however, no data were provided or could be obtained, and, therefore, the study was not included in this analysis (33). Figures 5 and 6 present the individual results and pooled estimate of the impact of a 0.1-unit increase in D/Pc on death-censored technique failure and death or transfer to hemodialysis, respectively. The overall pooled RR were very sim-
ilar (1.18 [95% CI 0.96 to 1.46; \( P = 0.12 \)] and 1.17 [95% CI 0.94 to 1.44; \( P = 0.16 \]), with no evidence of excessive heterogeneity in either analysis \( P = 0.1 \). Because of the small number of studies, sensitivity and regression analyses were not conducted.

**Discussion**

This analysis indicates that a higher rate of peritoneal membrane solute transport is associated with increased mortality in PD patients. This finding was present in studies from diverse geographic regions with a variety of comorbidities. Adjustment for other variables within individual studies, particularly age, diabetes, and albumin, did not influence the findings of this study. It is estimated that patients with H transport status have a 77% higher risk for mortality than those with L transport status. A trend to a similar relationship was seen between transport status and technique failure, although it did not reach statistical significance. Surprising, whether death was a censored event or an outcome in studies did not seem to have an impact on the effect of \( D/P_c \) on technique failure. These observations may be partially attributable to the small number of analyzable studies.

There is the potential for competing biologic effects of higher peritoneal membrane solute transport on patient outcomes. On the one hand, the greater membrane solute transport rate will enhance small solute clearance (although not necessarily during more prolonged dwells [45]); on the other hand, it may enhance protein losses, leading to malnutrition and diminished fluid removal. Recent randomized trials and observational studies now support the notion that peritoneal solute clearance does not significantly influence patient outcome within usual PD dosing regimens (22,46,47), whereas clinical volume status may (15,46,48,49). Our meta-analysis is consistent with these observations.

Studies that enrolled CCPD patients demonstrated a lower mortality risk for a given increase in peritoneal membrane solute transport rate compared with those that did not. This is consistent with the notion that CCPD may be more appropriate for patients with a higher membrane solute transport rate (50).
Shorter dialysis dwells as used in CCPD will allow effective clearance of small solutes while minimizing the negative impact of glucose reabsorption on ultrafiltration. A recent study that was included in our meta-analysis demonstrating that high transport status was a predictor of mortality in CAPD but not CCPD patients provides further support for this concept (14).

It has been hypothesized that informative censoring may occur in prevalent population studies; patients who did poorly would have been more likely to have been switched already to HD and not included in the study (14). However, incident subjects who do poorly may be transferred to HD during a study and therefore be censored from the analysis when mortality is considered as an outcome. Therefore, in both populations, this may lead to an underestimation of the impact of D/Pc on outcomes of interest. In this analysis, we did not observe a difference in the impact of the PET on mortality in incident and prevalent studies, although the possibility of a type II error cannot be excluded.

This study is not without limitations. By using D/Pc as the variable of interest, it was assumed that any relationship with patient outcome was linear. In the absence of patient-level data, it was not possible to explore this more fully. Many studies presented findings that were based on transport status, which required transformation to estimates of D/Pc on the basis of normal distribution assumptions. However, many studies, including a large recent one, indicate that this is not the case but rather is skewed to a greater proportion of patients having a higher D/Pc (51). This may systematically affect the within-study estimate of the impact of D/Pc on the outcome of interest. Therefore, there was no difference between the summary estimates from studies that used D/Pc as a continuous variable and those that did not (RR = 1.15 versus 1.12; P = 0.72).

The individual studies that were evaluated in this analysis vary in numerous ways, including study design, study population, and timing of the PET test. These differences may lead to heterogeneity in the results, although statistical evidence of this was not observed. Nevertheless, such statistical methods are known to be insensitive; therefore, additional efforts were made to address this potential concern, including the use of a random-effects model to account for potential heterogeneity and meta-regression analysis to assess the contribution of pre-specified variables on the findings of this analysis.

It also is conceivable that this analysis missed relevant published studies; nevertheless, the approach to data retrieval was comprehensive and redundant. There was no evidence of publication bias, although it is possible that unpublished, negative studies that were not included may exist. Finally, the impact of novel PD solutions, including icodextrin-based products, could not be evaluated in our analysis because most of these studies predate the introduction and general availability of such solutions.

Conclusion

This meta-analysis demonstrated that increasing peritoneal membrane solute transport rate was associated with an increasing risk for mortality with a trend to increased technique failure. Use of CCPD seemed to offset some of this negative effect on mortality. The introduction of novel PD solutions may influence the findings of this study and would be addressed best in the form of randomized, controlled trials.

Appendix

1. renal replacement therapy (MeSH)
2. kidney failure, chronic (MeSH)
3. ESRD (text)
4. end stage* (text)
5. end-stage*
6. 1 or 2 or 3 or 4 or 5
7. peritoneal dialysis (MeSH)
8. peritoneal dialysis* (text)
9. 7 or 8
10. prognosis (MeSH:NOEXP)
11. survival analysis (MeSH:NOEXP)
12. 10 or 11
13. 6 and 9 and 12
14. biologic transport, active (MeSH)
15. peritoneum/metabolism (MeSH)
16. peritoneum/physiopathology (MeSH)
17. transport* (text)
18. flux (text)
19. permeability (text)
20. 14 or 15 or 16 or 17 or 18 or 19
21. 9 and 12 and 20
22. 13 or 21
23. survival rate (MeSH)
24. survival analysis (MeSH)
25. treatment failure (MeSH)
26. treatment outcome (MeSH)
27. mortality (text)
28. failure (text)
29. survival (text)
30. 23 or 24 or 25 or 26 or 27 or 28 or 29
31. D/P* (text)
32. equilibration (text)
33. 14 or 15 or 16 or 17 or 18 or 19 or 31 or 32
34. 9 and 30 and 33
35. 34 or 22
36. restrict 35 to human and adults

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References


