Influence of Erythrocyte Transfusion on the Risk of Acute Kidney Injury after Cardiac Surgery Differs in Anemic and Nonanemic Patients

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ABSTRACT

Background: Acute kidney injury (AKI) after cardiac surgery is a major health issue. Two important risk factors for AKI are preoperative anemia and perioperative erythrocyte transfusion, and elucidating their relationship may help in devising preventive strategies.

Methods: In this cohort study of 12,388 adults who underwent cardiac surgery with cardiopulmonary bypass and received three units or less of erythrocytes on the day of surgery, the authors used propensity score methods and conditional logistic regression to explore the relationship between preoperative anemia (hemoglobin less than 12.5 g/dL), erythrocyte transfusion on the day of surgery, and AKI (more than 50% decrease in estimated glomerular filtration rate from preoperative to postoperative day 3–4).

Results: AKI occurred in 4.1% of anemic patients (n = 94/2,287) and 1.6% of nonanemic patients (n = 162 of 10,101) ($P < 0.0001$). In the 2,113 propensity-score matched pairs, anemic patients had higher AKI rates than nonanemic patients (3.8% *vs.* 2.0%; $P = 0.0007$). AKI rates increased in direct proportion to the amount of erythrocytes transfused, and this increase was more pronounced in anemic patients: in anemic patients, the rate increased from 1.8% among those not transfused to 6.6% among those transfused three units (chi-square test for trend $P < 0.0001$), whereas in nonanemic patients, it increased from 1.7% among those not transfused to 3.2% among those transfused three units (chi-square test for trend $P = 0.1$).

Conclusions: Anemic patients presenting for cardiac surgery are more susceptible to transfusion-related AKI than nonanemic patients. Interventions that reduce perioperative transfusions may protect anemic patients against AKI.

What We Already Know about This Topic

- Acute kidney injury is a common and important complication of cardiac surgery, but few therapeutic approaches exist to address this problem

What This Article Tells Us That Is New

- The risk of acute kidney injury was substantially increased by blood transfusion in patients undergoing cardiac surgery, and this risk was increased to a greater extent in patients with preoperative anemia

ACUTE kidney injury (AKI) is a common and prognostically important complication of cardiac surgery. It occurs, to various degrees of severity, in approximately one-third of cases that require the use of cardiopulmonary bypass (CPB)[1] and is associated with markedly worse short- and long-term outcomes.[2–6] To mitigate the burden of this complication, numerous therapies have been tested but none have proved efficacious.[1] Lacking efficacious therapies, risk

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factor modification may be one reasonable means for reducing the burden of AKI after cardiac surgery.

Two potentially modifiable risk factors are preoperative anemia and perioperative erythrocyte transfusion.[6–11] These variables, however, are closely interrelated, and the influence of this relationship on postoperative AKI is not clear. Elucidating this relationship may help in devising preventive strategies. To that end, we conducted this cohort study in patients who had undergone cardiac surgery to determine whether the influence of erythrocyte transfusion on AKI differs in anemic and nonanemic patients.

Materials and Methods

Patient Sample

After ethics board approval from the University Health Network (Toronto, Ontario, Canada), which waived the requirement for informed consent, data from consecutive patients age 18 yr or older who underwent cardiac surgery with CPB from January 2000 to May 2008 at Toronto General Hospital were included in this single-center cohort study. To reduce the confounding effect of excessive blood loss, patients who received more than three units of erythrocytes on the day of surgery or had a hemoglobin concentration of more than 16 g/dL (upper limit of normal) were excluded from the study. Other exclusion criteria were: preoperative erythrocyte transfusions, dialysis, severe anemia (hemoglobin less than 9 g/dL), intraaortic balloon pump support, and active endocarditis; emergent surgery; deep hypothermic circulatory arrest; death within 3 days of surgery (to allow for assessment of AKI in all patients); or missing relevant hemoglobin and creatinine measures. For patients who had multiple operations requiring CPB during the study period, only the data from their first admission were included in the analysis.

Study Setting

A full range of adult cardiac surgery procedures was performed at Toronto General Hospital during the study period, which is a quaternary-care teaching hospital within the University Health Network and is affiliated with the University of Toronto (Toronto, Ontario, Canada). Clinical care during the study period was guided by standardized protocols that have been previously described.[12,13] Blood product transfusions were guided by standard clinical practice guidelines.[14] Specifically, erythrocyte transfusions were guided by patients' hemoglobin concentration in conjunction with their medical status. The recommended hemoglobin threshold for transfusion was 7.0 g/dL during CPB and 8.0 g/dL after CPB. All transfused erythrocytes were leukoreduced by the Canadian Blood Services (Toronto, Ontario, Canada).

Management of CPB included intravenous heparin administration to achieve an activated clotting time greater than 480 s, systemic temperature drift to 32–34°C, α-stat pH management, targeted mean perfusion pressure between 50–70 mmHg, and pump flow rates of 2.0–2.5 l/min/m^2. Myocardial protection was achieved with intermittent antegrade and, occasionally, retrograde blood cardioplegia. During CPB, shed pericardial blood was salvaged into the cardiotomy suction reservoir and reinfused *via* the CPB circuit for as long as patients were anticoagulated. Antifibrinolytic drugs aprotinin (Trasylol®, Bayer AG, Toronto, Ontario, Canada) or tranexamic acid (Cyclokapron®, Pharmacia & UpJohn Inc, Mississauga, Ontario, Canada) were used routinely.[13]

Data Collection

All perioperative data were prospectively collected in institutional databases, as has been previously detailed.[15,16] Full-time research personnel, who were blinded to the details of this study, adjudicated all outcomes from patients' records. Quality assurance checks of the databases have consistently revealed a missing data rate of less than 2% and an error rate of less than 2%. Patients with missing values for variables used in the multivariable analyses were excluded (less than 1% of cases).

Definition of AKI

AKI was defined as a more than 50% reduction in estimated glomerular filtration rate from preoperative to postoperative day 3 or 4. The Cockcroft-Gault equation was used to calculate estimated glomerular filtration rate.[17] Creatinine values before and after surgery (daily for 5 days) were routinely measured in all patients. Postoperative creatinine values before day 3 were not used in determining AKI because that much time is required to achieve postcardiac surgery steady-state equilibrium,[18] and values after day 4 were not used because they may reflect postoperative rather than intraoperative insults. The 50% threshold corresponds to the injury category of the consensus-based RIFLE (Risk, Injury, Failure, Loss, and End stage kidney disease) classification criteria for AKI,[19] which has been shown to be prognostically important.[6]

Definition of Anemia

Anemia was defined as a preoperative hemoglobin concentration of less than 12.5 g/dL, which is the average threshold of the World Health Organization's sex-based definition of 12.0 g/dL in women and 13.0 g/dL in men.††

Principal Exposure

The principal exposure was number of units of erythrocytes transfused (zero, one, two, or three units) on the day of surgery.

Covariates

Measured perioperative variables that may be associated with erythrocyte transfusion, blood loss, or adverse events were examined. These included patient characteristics (weight, age, sex) and baseline status (major comorbidities including renal dysfunction, anemia, and coagulopathy), surgery-related variables (year of surgery, surgeon, procedure, urgency, CPB duration, nadir hemoglobin concen-

†† World Health Organization. Iron deficiency anaemia: Assessment, prevention, and control. 2001. Available at: http://whqlibdoc.who.int/hq/2001/WHO_NHD_01.3.pdf. Accessed May 25, 2011.

tration during CPB, need for inotropic or mechanical support to separate from CPB), and post-CPB variables on the day of surgery (lowest hemoglobin concentration, lowest platelet count, highest international normalized ratio of prothrombin time, platelet and plasma transfusions, and surgical reexploration).

Statistical Analyses

Categoric variables were summarized as frequencies and percentages and continuous variables as means and SDs. To determine whether the influence of erythrocyte transfusion on AKI differs in anemic and nonanemic patients, propensity score methods[20,21] were used to match anemic patients to nonanemic patients with approximately similar risk profiles first, and then the effect of erythrocyte transfusion on the rate of AKI in the matched group was measured.

To identify the matches, the propensity score for anemia was first derived using a multivariable logistic regression model that included all measured preoperative covariates that could be related to anemia, as well as important two-way interaction terms (criteria for inclusion $P < 0.05$). The covariates included patient demographics (sex, age, weight, height), preoperative medical status (creatinine concentration, platelet count, functional status, hypertension, diabetes, hyperlipidemia, smoking status, peripheral vascular disease, cerebrovascular disease, congestive heart failure, atrial fibrillation, myocardial infarction, unstable angina, coronary angiogram within 2 days of surgery, ventricular function), and surgical variables (previous sternotomies, type of surgery, year of surgery, and surgeon). Each anemic patient was then matched to a nonanemic patient with similar propensity scores, using a $5 \rightarrow 1$ computerized greedy-matching technique.‡‡ Covariate balance in the matched group was assessed by the standardized mean difference, which is the absolute difference of the group means as a percentage of their pooled SD.[20] If the model failed to achieve balance for any covariate (standardized mean difference 10% or greater), subsequent models included the cross-products of that covariate with other clinically related variables. This process was repeated until the matched groups were balanced on all important covariates.[22]

Once balanced matches were identified, conditional logistic regression was used to compare the rate of AKI between anemic and nonanemic patients.[20] The effect of erythrocyte transfusions on the rate of AKI in anemic and nonanemic patients in the matched group was then assessed by comparing the rates of AKI with increasing number of erythrocyte transfusions using the Mantel-Haenszel chi-square test for trend.

To determine whether the results of the matched analysis were unduly influenced by potential perioperative confounders that could not be included in the propensity score derivation model for preoperative anemia, multivariable (conditional) logistic regression was performed on the matched groups to calculate the "expected" AKI rates after controlling for these confounders. The model included the following variables: anemia; number of erythrocyte transfusions; two-way interaction of anemia and number of erythrocyte transfusions; cardiopulmonary bypass duration; need for inotropic or mechanical support to separate from cardiopulmonary bypass; lowest hemoglobin, lowest platelet count, and highest prothrombin time on day of surgery; surgical reexploration; plasma transfusion on the day of surgery; and platelet transfusion on the day of surgery. The model was then used to calculate the risk-adjusted probability of AKI for each individual patient in the matched group. The averages (and 95% CI) of the probabilities, representing the "expected" rates of AKI, were then calculated and plotted for anemic and nonanemic matched patients according to the number of erythrocyte transfusions.[23]

Statistical analyses were performed using SAS® version 9.1.3 (SAS Institute, Inc., Cary, NC). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

During the study period, 18,433 patients underwent cardiac surgery with CPB, of whom 12,388 were included in the analysis (appendix). Characteristics of anemic and nonanemic patients in the entire sample and in the matched sample are shown in table 1. As can be seen, there were many prognostic differences between anemic and nonanemic patients in the entire sample. Specifically, anemic patients were generally sicker than nonanemic patients: they were older, underwent more nonelective surgeries, and had more comorbid conditions such as kidney dysfunction, diabetes, and vascular disease. As expected, anemic patients had lower hemoglobin concentrations and received more erythrocyte transfusions than nonanemic patients. Plasma and platelet transfusion rates, on the other hand, were similar between the two groups.

The matched group included 2,113 pairs of anemic and nonanemic patients. As is illustrated by the standardized mean differences, the groups were well balanced for prognostically important covariates but retained their differences in hemoglobin concentration and erythrocyte transfusion. The groups were also well balanced for some (the need for inotropic support to separate from CPB, surgical reexploration, and nonerythrocyte transfusions) but not all (lowest hemoglobin concentration, lowest platelet count, and highest prothrombin time) potentially confounding variables that could not be included in the propensity score modeling for preoperative anemia because they occurred either during or after surgery.

‡‡ Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. In: Proceedings of the Twenty-sixth Annual SAS Users Group International Conference, Cary, North Carolina, 2004. Available at: http://www2.sas.com/proceedings/sugi26/p214-26.pdf. Accessed May 25, 2011.

Table 1. Characteristics of Anemic and Nonanemic Patients in the Entire Sample and in the Matched Sample

Variables	Entire Sample			Matched Sample		
	Anemic (n = 2,287)	Nonanemic (n = 10,101)	SMD	Anemic (n = 2,113)	Nonanemic (n = 2,113)	SMD
Variables included in the propensity score derivation model	—	—	—	—	—	—
Age (yr)	66 ± 12	62 ± 13	34%	65 ± 12	65 ± 11	0.9%
Female	48% (1,100)	20% (2,008)	67%	45% (947)	45% (945)	0.2%
Body surface area (m^2)	1.85 ± 0.22	1.94 ± 0.22	41%	1.86 ± 0.22	1.86 ± 0.22	0.1%
Hypertension	65% (1,477)	57% (5,767)	15%	64% (1,344)	64% (1,356)	1.2%
Diabetes mellitus (Type I or II)	39% (882)	25% (2,482)	32%	37% (779)	38% (793)	1.4%
Peripheral vascular disease (history of aortoiliac, femoropopliteal, or carotid artery disease)	21% (471)	14% (1,383)	19%	20% (422)	20% (412)	1.2%
Cerebrovascular disease (history of stroke or transient ischemic attacks)	12% (268)	7.6% (771)	15%	12% (246)	11% (238)	1.2%
Atrial fibrillation	8.5% (195)	6.8% (683)	6.9%	8.1% (172)	8.0% (169)	0.5%
Left ventricular ejection fraction <40%	19% (444)	16% (1,605)	9.5%	19% (399)	19% (405)	0.7%
Unstable angina (within 30 days of surgery)	49% (1,111)	33% (3,324)	33%	47% (991)	48% (1,022)	2.9%
Recent cardiac catheterization (within 2 days of surgery)	7.0% (159)	8.5% (861)	5.7%	7.0% (148)	7.0% (149)	0.2%
Preoperative eGFR (ml/min)	73 ± 32	87 ± 30	47%	74 ± 32	75 ± 29	2.7%
eGFR 90 ml/min or greater	24% (543)	41% (4,136)	—	25% (532)	25% (525)	—
eGFR 60–89 ml/min	37% (835)	41% (4,148)	—	38% (800)	39% (822)	—
eGFR 30–59 ml/min	37% (846)	17% (1,760)	—	35% (735)	34% (728)	—
eGFR 15–29 ml/min	2.6% (60)	0.5% (54)	—	2.0% (43)	1.7% (36)	—
eGFR <15 ml/min	0.1% (3)	0.03% (3)	—	0.1% (3)	0.1% (2)	—
Preoperative platelet count (10^9/L)	252 ± 83	230 ± 64	32%	249 ± 80	248 ± 75	0.6%
Preoperative hemoglobin (g/dL)*	11.6 ± 0.7	14.1 ± 0.9	288%	11.6 ± 0.7	13.8 ± 0.9	277%
Procedure	—	—	11%	—	—	0.5%
Isolated coronary artery bypass grafting	63% (1,444)	60% (6,105)	—	62% (1,318)	63% (1,325)	—
Any valve replacement or repair	25% (576)	22% (2,228)	—	25% (535)	25% (529)	—
Other procedures	12% (267)	18% (1,768)	—	12% (260)	12% (259)	—
Elective surgery	49% (1,118)	70% (7,079)	45%	51% (1,086)	50% (1,059)	2.6%
Redo sternotomy	6.9% (158)	6.8% (686)	0.5%	7.0% (148)	6.6% (140)	1.5%
Received aprotinin	3.8% (87)	3.5% (349)	1.9%	3.9% (83)	4.2% (89)	1.4%
Variables (intraoperative and postoperative) not included in the propensity score derivation model	—	—	—	—	—	—
CPB duration (min)	94 ± 30	96 ± 32	8.1%	94 ± 30	96 ± 31	6.5%
Inotropic or mechanical support to separate from CPB	12% (285)	8.7% (875)	13%	12% (248)	13% (275)	3.9%
Lowest hemoglobin on day of surgery (g/dL)	8.3 ± 1.1	9.1 ± 1.3	64%	8.2 ± 1.1	8.8 ± 1.2	47%
Lowest platelet count on day of surgery (10^9/L)	142 ± 55	129 ± 44	28%	142 ± 54	132 ± 50	16%
Highest international normalized ratio of prothrombin time on day of surgery	1.58 ± 0.27	1.59 ± 0.28	3.3%	1.58 ± 0.27	1.62 ± 0.3	14%
Surgical re-exploration	1.9% (44)	3.0% (303)	6.5%	2.0% (42)	2.7% (58)	5.0%

(*continued*)

Table 1. Continued

Variables	Entire Sample			Matched Sample		
	Anemic (n = 2,287)	Nonanemic (n = 10,101)	SMD	Anemic (n = 2,113)	Nonanemic (n = 2,113)	SMD
Erythrocyte transfusions on day of surgery	79% (1,810)	37% (3,707)	91%	78% (1,651)	53% (1,129)	54%
0 units	21% (477)	63% (6,394)	—	22% (462)	47% (984)	—
1 unit	21% (486)	17% (1,710)	—	22% (464)	22% (455)	—
2 units	33% (764)	14% (1,446)	—	33% (691)	22% (459)	—
3 units	24% (560)	5.4% (551)	—	23% (496)	10% (215)	—
Plasma transfusions on day of surgery	21% (480)	21% (2,167)	1.7%	23% (481)	24% (512)	3.5%
Platelet transfusions on day of surgery	11% (250)	12% (1,243)	3.5%	12% (245)	12% (252)	3.5%

All data are presented as mean ± SD or percentages (n).

* Dependent variable in the propensity score derivation model; all others in this section included as independent variables.

CPB = cardiopulmonary bypass; eGFR = estimated glomerular filtration rate; SMD = standardized mean difference.

In the entire group, 4.1% of anemic patients (n = 94 of 2,287) and 1.6% of nonanemic patients (n = 162 of 10,101) developed AKI ($P < 0.0001$). In the matched group, 3.8% (n = 81 of 2,113) of anemic patients developed AKI compared with 2.0% (n = 43 of 2,113) of nonanemic patients ($P = 0.0007$). Controlling for perioperative confounders by conditional logistic regression modeling did not have a material effect on these results: the expected AKI rate in anemic patients was 3.8% (95% CI 3.6–4.0%) and in nonanemic patients it was 2.1% (95% CI 1.9–2.2%).

The relationship between the number of erythrocyte transfusions and the risk of AKI among the matched anemic and nonanemic groups is shown in table 2. As can be seen, AKI rates increased in direct proportion to the number of units of erythrocytes transfused, with the increase being more pronounced in anemic patients. The expected AKI rates after controlling for perioperative confounders, which are plotted in figure 1, were not materially different.

Discussion

In this observational study, we explored the relationship among preoperative anemia, perioperative erythrocyte transfusion, and postoperative AKI in a cohort of patients who underwent cardiac surgery with CPB. To control for important confounders, we excluded patients who received more than three units of erythrocytes on the day of surgery, had active endocarditis, or underwent deep hypothermic circulatory arrest; used propensity score matching to compare anemic and nonanemic patients with similar baseline risk-profiles; and used conditional logistic regression to adjust for intraoperative and postoperative differences between the matched groups.

After controlling for important confounders, we found that the risk of AKI was nearly twofold higher in anemic than nonanemic patients. This finding is consistent with previous studies.[6–8,24] We also found that the risk of AKI increased in direct proportion to the number of erythrocyte transfusions, and that this increase was more pronounced in anemic patients. In anemic patients, the risk-adjusted rate of AKI increased from 1.8% in patients who received no transfusions to 6.6% in those who received three units (P value for trend less than 0.0001), whereas in nonanemic patients, the rate increased from 1.7% to 3.2% (P value for trend = 0.1). Whereas the association between erythrocyte transfusion and AKI in cardiac surgery is recognized,[6,10,25,26] the finding that the magnitude of this risk differs between anemic and nonanemic patients who receive low-volume erythrocyte transfusions, to our knowledge, has not been previously reported.

Table 2. Acute Kidney Injury Rates in the Matched Groups

Erythrocyte Transfusions	Acute Kidney Injury Rates	
	Anemic (n = 2,113)	Nonanemic (n = 2,113)
Zero units	1.9% (n = 9 of 462)	1.4% (n = 14 of 984)
One unit	2.2% (n = 10 of 464)	2.8% (n = 13 of 455)
Two units	4.6% (n = 32 of 691)	2.2% (n = 10 of 459)
Three units	6.0% (n = 30 of 496)	2.8% (n = 6 of 215)
Mantel-Haenszel chi-square P value	0.0001	0.1

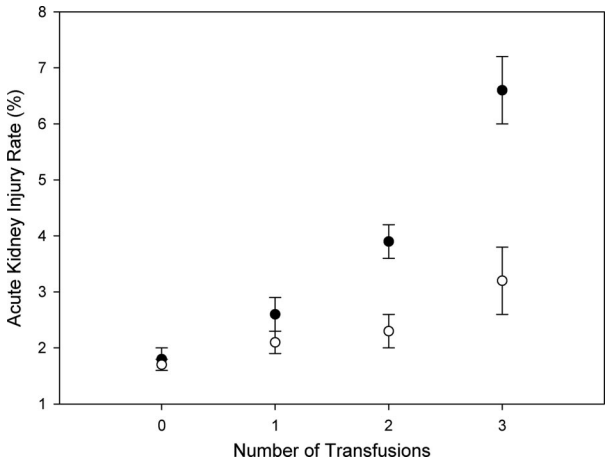

Fig. 1. Expected rates of acute kidney injury in matched anemic and nonanemic patients according to number of erythrocyte transfusions. Expected rates were calculated using a conditional logistic regression model that controlled for confounders that occurred on the day of surgery and hence could not be included in the propensity score derivation model for *preoperative* anemia (see text for list of variables). Presented are the point estimates and 95% confidence intervals of the expected rates. Black circles = anemic patients; white circles = nonanemic patients.

This finding, if proved valid in future studies, has important clinical implications because it suggests that patients who are most likely to require multiple erythrocyte transfusions during cardiac surgery – *i.e.*, anemic patients – are also most likely to be harmed by them. It would be reasonable to expect, therefore, that interventions that reduce perioperative transfusions in this susceptible group may offer protection against AKI. Interventions that may be applicable include early identification and correction of anemia before surgery, minimizing fluid administration during surgery, aggressive use of retrograde autologous priming of the CPB circuit, and tolerating moderate hemodilution during surgery.[27] Randomized clinical trials are required to determine whether such interventions reduce the risk of AKI in anemic patients.

Although our study was not equipped to delineate the pathogenesis of AKI, others have identified several mechanisms that may explain why anemic patients seem to be more susceptible to transfusion-related AKI than nonanemic patients. First, anemic patients routinely develop more severe anemia during cardiac surgery than nonanemic patients,[7] and the kidneys are known to be highly vulnerable to hypoxic injury in the setting of reduced oxygen delivery due to both chronic and acute anemia.[28,29] Second, despite having normal creatinine values, many anemic patients have subclinical kidney disease that is characterized by increased renal tubular oxygen consumption and oxidative stress,[30,31] predisposing them to acute-on-chronic kidney injury. Third, anemic patients have abnormal iron metabolism,[32] which may impair their ability to safely manage the excess iron load that can result from multiple erythrocyte transfusions (erythrocytes undergo progressive structural damage during storage, and as a result, up to 30% of them are quickly phagocytosed and their hemoglobin-iron is extracted by macrophages after transfusion),[33] predisposing them to iron-mediated oxidative kidney injury.[34–36]

This study has several important limitations that must be considered when interpreting its findings. Most importantly, because this is an observational study, causality of observed relationships cannot be assumed and the effects of unmeasured confounders on these relationships cannot be dismissed. Potentially important unmeasured confounders include duration of anemia, hemodynamics during CPB, and use of perioperative medications that may influence kidney function. Another is that anemic and nonanemic patients often undergo transfusion for different reasons. In anemic patients, the reason for transfusion is often excessive CPB-induced hemodilution, whereas in nonanemic patients it is blood loss. To control for this confounder, we excluded patients who received more than three units of erythrocytes during surgery, and adjusted for nadir hemoglobin concentration, coagulopathy, and nonerythrocyte transfusions. These steps, however, may not have fully controlled for this potentially important confounder. Finally, as this was a single-center study with few events in some of the transfusion categories, our findings need to be validated by larger, multicenter studies.

In summary, in this single-center retrospective cohort study of patients undergoing cardiac surgery with CPB, anemic patients were found to be more susceptible to transfusion-related AKI than nonanemic patients. Thus, clinical studies assessing the renal-protective effects of interventions that reduce perioperative transfusions in anemic patients are warranted.

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Appendix