Chapter 9: Serum Albumin and Serum Bicarbonate

Serum Albumin

Albumin measurement

In general serum albumin is measured by one of two methods, both of which utilise a colour change induced by a dye binding to albumin.

Bromocresol Green (BCG) is the most commonly used method but this has been criticised for the fact the BCG binds to a range of proteins other than albumin such that at low albumin concentrations there may be a significant overestimation of the albumin concentration

Bromocresol Purple (BCP) is slightly more expensive than BCG and is available on fewer clinical laboratory analysers. The advantage of BCP is that it predominantly binds to albumin and thus gives a more accurate measure of albumin concentrations especially below 30g/L

Immunoassay. The reference procedure for serum albumin measurement is to use a specific antibody along with either immunonephelometric or immunoturbidimetric detection.

Most of the above statements with regards the relative performance of BCG and BCP hold in true even in uremic serum where uremic toxins (unknown) bind to albumin and alter the ability of other substances to bind such as drugs and dyes such as BCP and BCG. This has recently been confirmed in two studies one published in NDT (Carfray A, Patel K. Whitaker P, Garrick P, Griffiths GJ, Warwick GL. Albumin as an outcome measure in haemodialysis patients: the effects of variation in assay method. Nephrol Dialysis Transplant 2000, 15, 1819-1822.) and one by the Laboratory supporting Unit "W " which has recently changed from BCG to BCP. This laboratory was concerned to investigate the difference in results found in their renal patients but not apparent in other patient populations which formed the majority of their clinical workload.

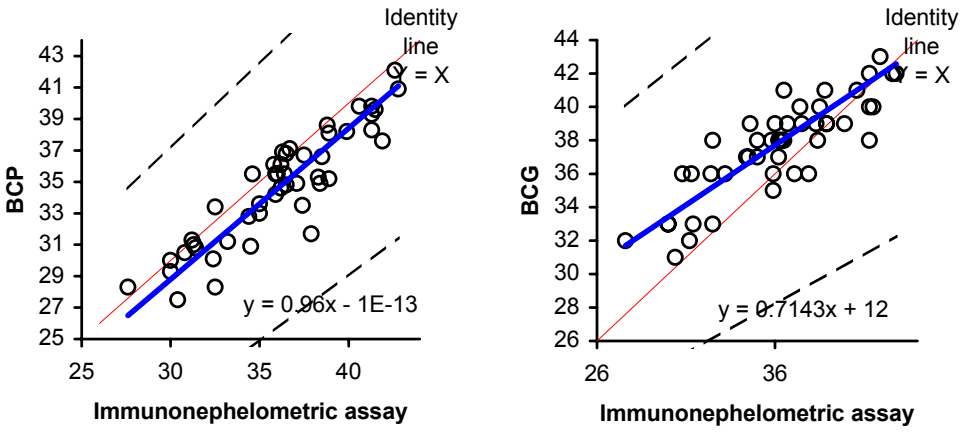

Figure 9.1 Comparison of methods of measuring albumin

BCP and BCG assays are compared with an albumin immunoassay in sera taken from patients on haemodialysis. Results are scattered around the line of identity indicating no significant

difference for BCP but deviate significantly for BCG. This data would suggest that BCP should be preferred to BCG methods for the monitoring of renal patients.

The remaining issue for albumin from previous Registry reports was the variation in reference ranges reported by laboratories and the different sources that had been used to obtain them. In principal and supported by most manufacturers and published sources there should be no large difference in the reference ranges that would be appropriate for use with BCG and BCP methodologies.

Indeed Unit W's laboratory provided information that

- BCG assay reference range (locally determined) was 35-53 g/L.
- BCP assay reference range (Manufacturers) was 34 – 48 g/L
- Immuno-turbidimetric assay reference range (Manufacturers) was 34-47 g/L

Whilst slight differences can be expected (± 1g/L) there seems no particular reason why two laboratories (one BCG and the other BCP using) should have reference ranges down to 30 g/L. It could be suggested that in order to assess compliance with a standard a fixed reference range of 35-50 should be applied to all units as has been tried here.

Unit	Method	Reference Range (g/L)
A	BCG	36-47
B	BCG	35-50
C	BCG	34-50
D	BCG	35-48
E	BCG	35-50
F	BCP	35-50
G	BCG	35-55
H	BCP	30-52
I	BCG	35-50
J	BCG	36-52
K	BCG	35-47
L	BCG	35-50
M	BCG	35-55
N	BCG	35-50
O	BCG	30-48
P	BCG	35-50
Q	BCG	35-50
R	BCP	34-48
T	BCG	36-50
U	BCG	35-50
V	BCG	37-49
W	BCP	35-53
X	BCP	36-50

Conversion g/dl = g/L x 0.1

Table 9.1 Methods and ranges of albumin measurement

To study the influence of albumin assay methodology on the distribution of results for centres a different symbol has been used to highlight those supported by laboratories using BCP methodology (●)

The Renal Association Standard for albumin is that ***all patients should be within the local normal range***

Haemodialysis

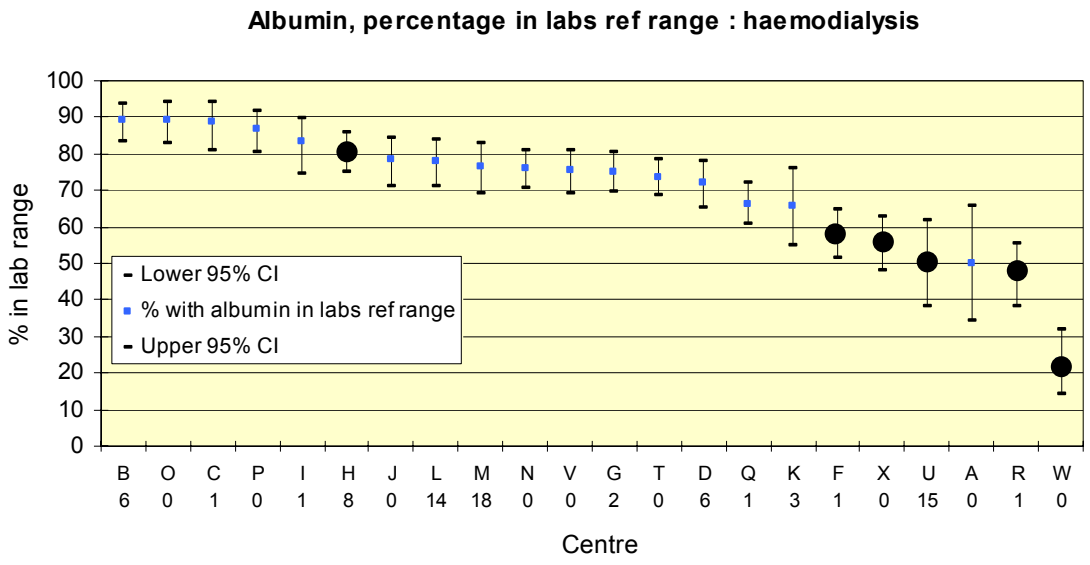

Figure 9.2 Percentage albumin in laboratory reference range on haemodialysis

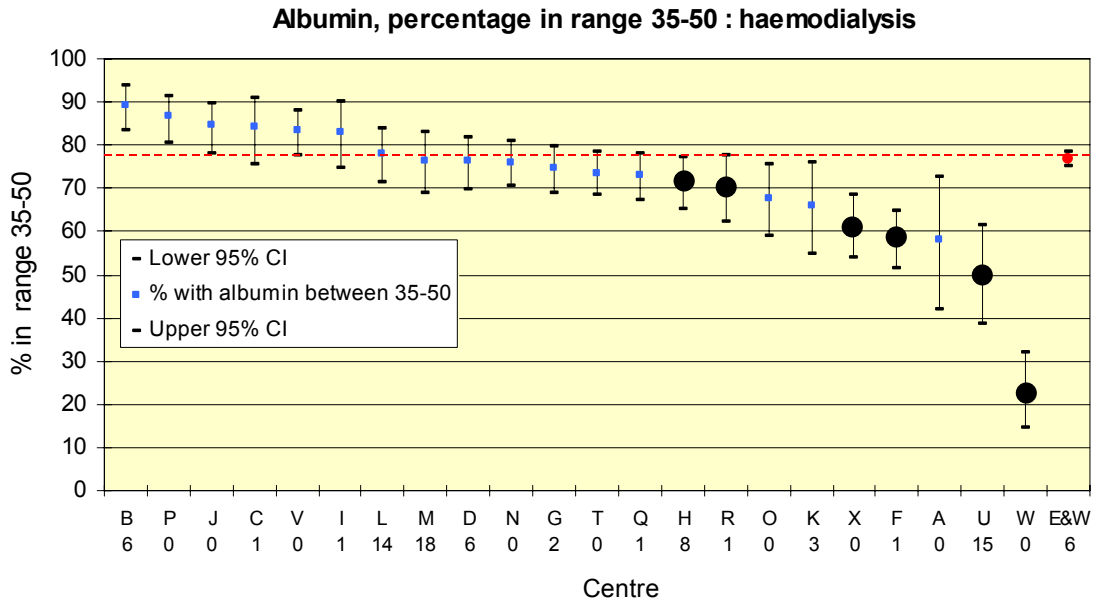

Figure 9.3 Percentage albumin in range 35-50 g/L on haemodialysis

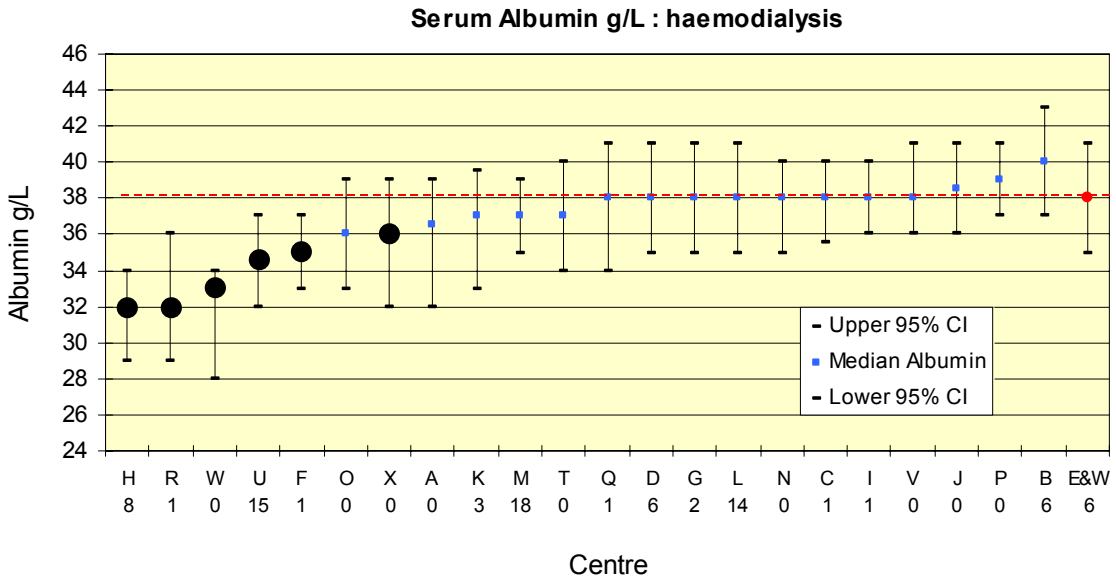

Figure 9.4 Serum albumin on haemodialysis

There was variation in median serum albumin both within the BCP group (32-36 mmol/L) and within BCG group (36-40 mmol/L). For patients on HD and laboratories using the BCP methodology, the percentage of patients with albumin greater than or equal to the labs lower reference range limit differed significantly between centres (X^2 = 305.9, d.f. = 20, p<0.001). This analysis was not performed for the 6 centres using BCP.

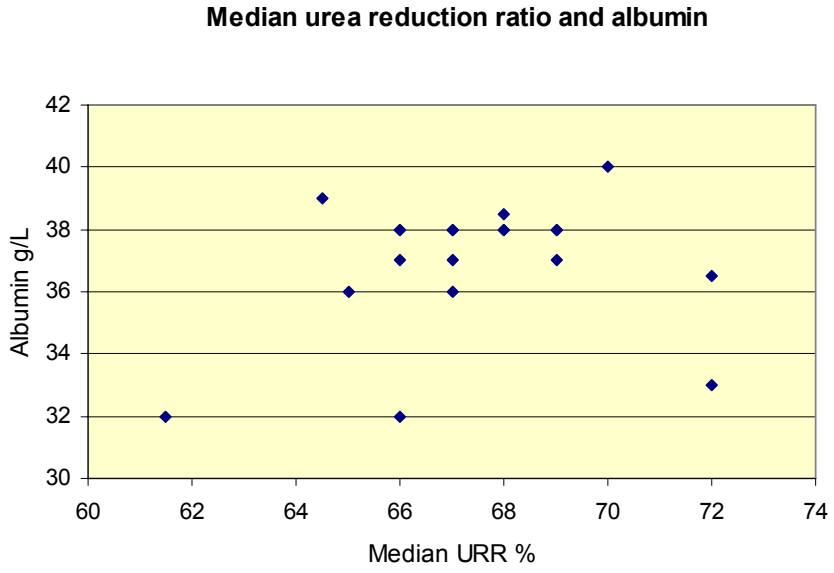

Figure 9.5 Median urea reduction ratio and albumin

Although figure 9.5 includes centres using BCP, even after excluding these centres, there was no relationship between the median urea reduction ratio achieved by each centre and the median serum albumin.

Peritoneal dialysis

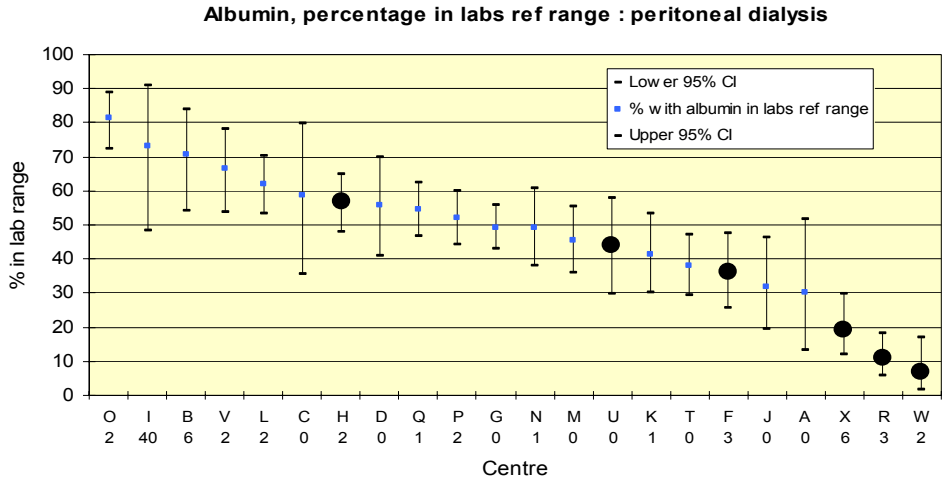

Figure 9.6 Percentage albumin in laboratory reference range on peritoneal dialysis

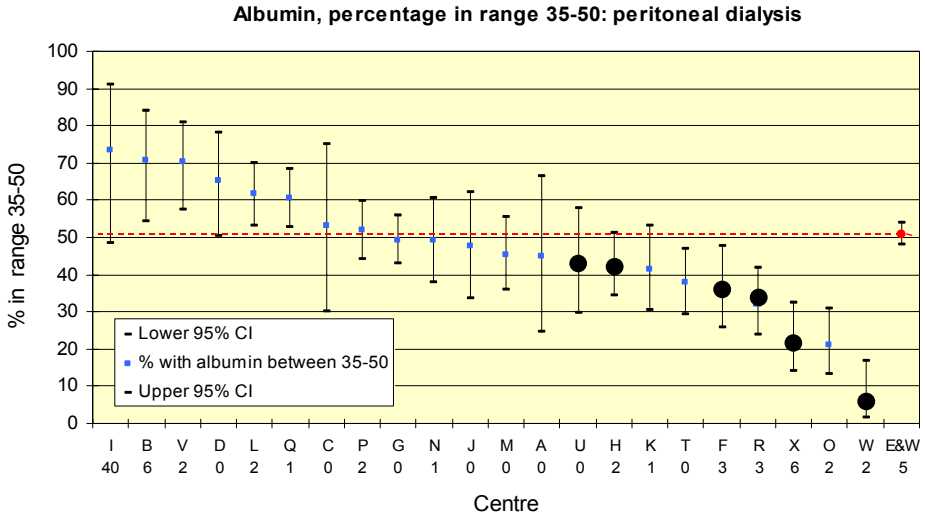

Figure 9.7 Percentage albumin in range 35-50 g/L on peritoneal dialysis

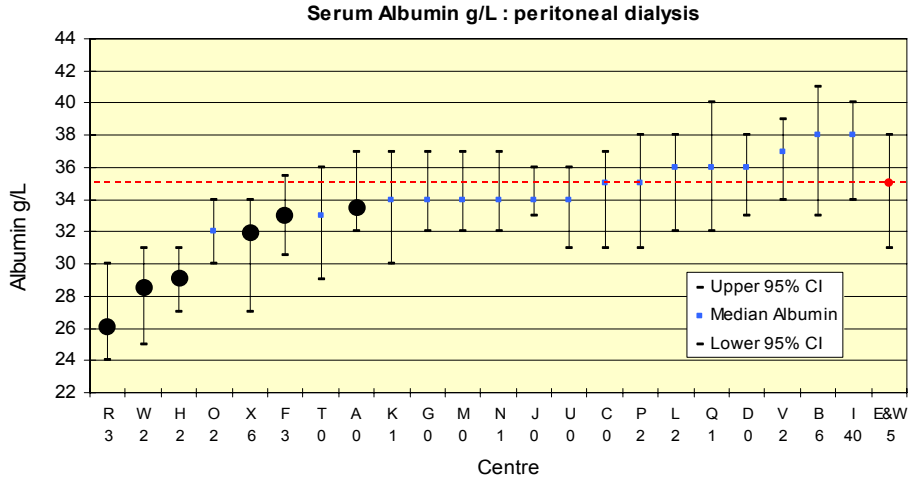

Figure 9.8 Serum albumin on peritoneal dialysis

For patients on PD and laboratories using the BCG method, the percentage of patients with albumin greater than or equal to the labs lower reference range limit differed significantly between centres ($X^2 = 200.4$, d.f. = 21, $p<0.001$)

Discussion

The BCP using Centres are clearly grouped towards one side of the figures. The relative positions can be modulated by applying different reference ranges (particularly centres H and O) but it is clear that not all the variation in albumin concentration is due to methodological factors as the median serum albumin varied from 28-34 mmol/L in the BCP group.

Changes in albumin 1998-1999

Haemodialysis

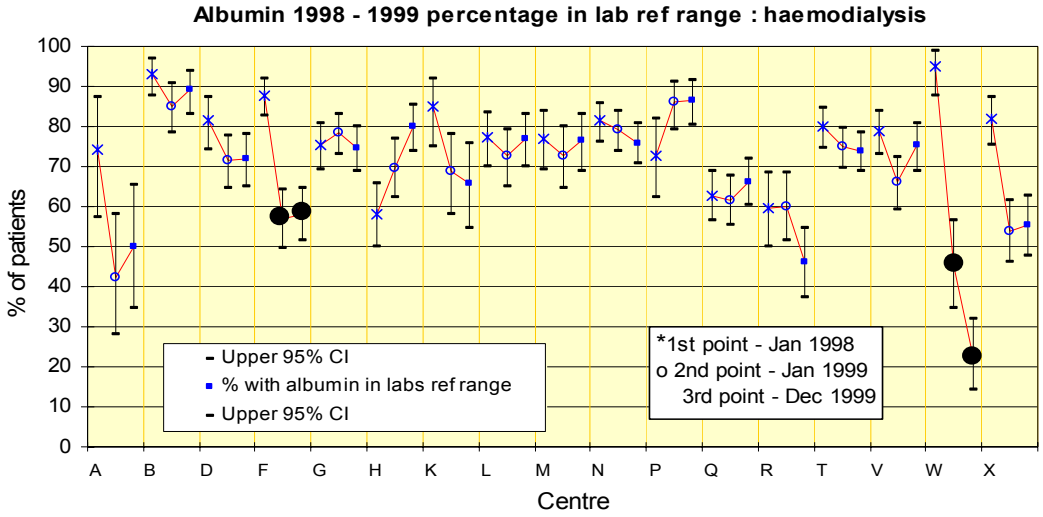

Figure 9.9 Percentage albumin in lab reference range on haemodialysis, 1998-1999

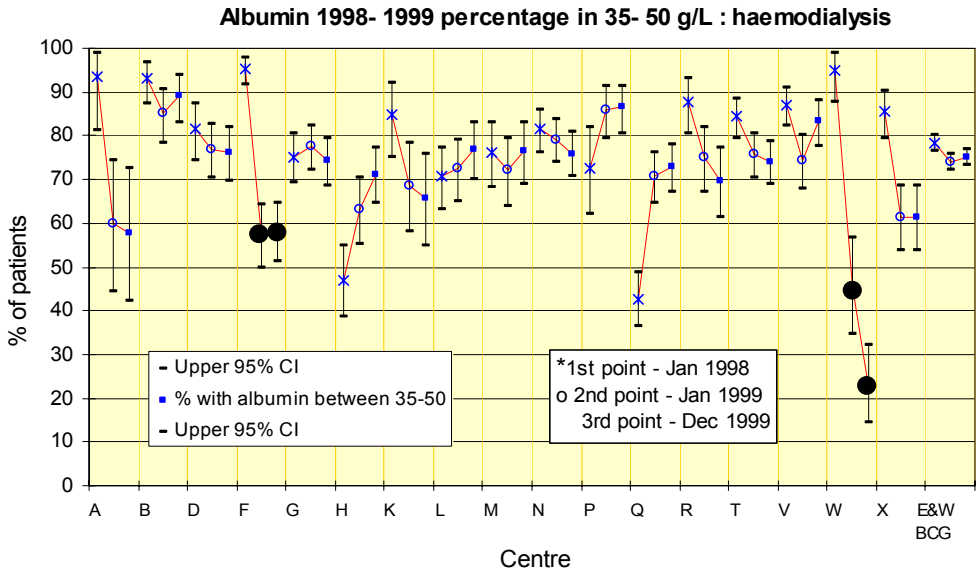

Figure 9.10 Percentage albumin in range 35-50 g/L on haemodialysis, 1998-1999

Two laboratories have changed from BCG in 1998 to BCP in 1999 and this is reflected in the large shifts in albumin concentration shown above and in the following diagrams. Only these two changes are identified (●).

Peritoneal dialysis

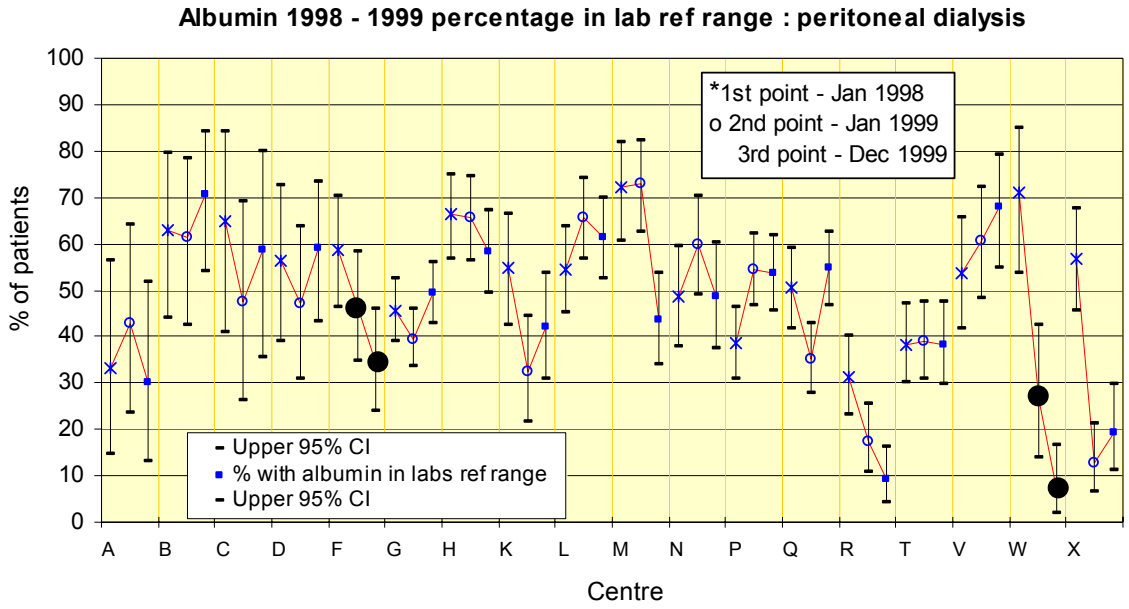

Figure 9.11 Percentage albumin in laboratory reference range on peritoneal dialysis, 1998-1999

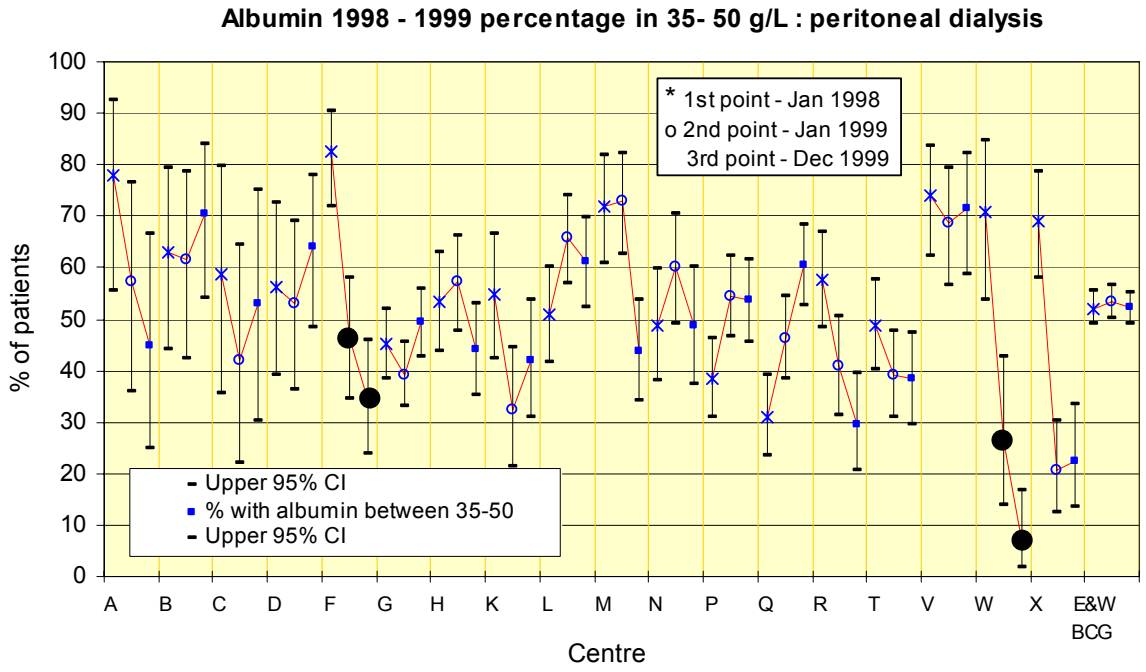

Figure 9.12 Percentage albumin in range 35-50 g/L on peritoneal dialysis, 1998-1999

Change in albumin for 1999

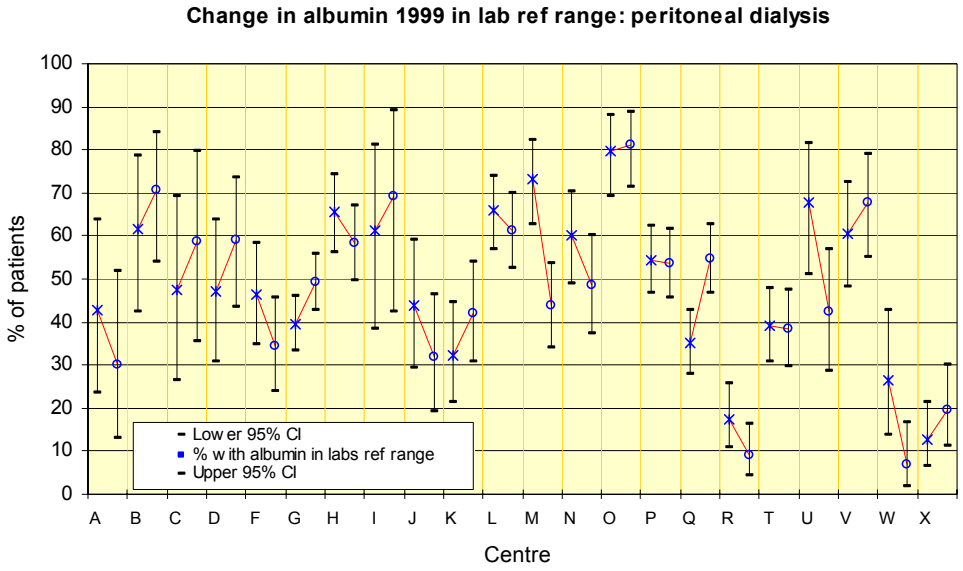

Figure 9.13 Change in albumin in laboratory reference range on peritoneal dialysis, 1999

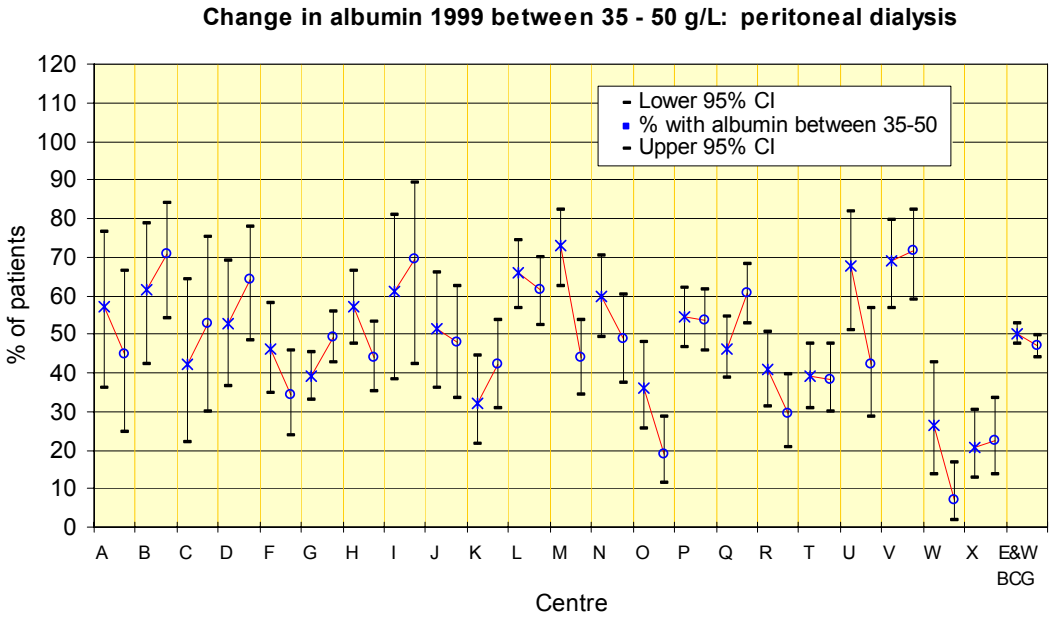

Figure 9.14 Change in albumin between 35-50 g/L on peritoneal dialysis, 1999

Discussion

Methodological change can clearly cause large shifts in the median albumin concentration for a unit. However not all centres had a methodological change and this data confirms that there are genuine differences in the albumin concentrations between centres and also changes over time. Shifts in median serum albumin over 2 years were more apparent for patients on peritoneal dialysis and explanations for these factors will be sought.

Conclusions

- Centres using BCP form a distinct grouping due to albumin assay methodology rather than clinical factors.
- BCP assay for serum albumin measurement should be recommended on uraemic sera.
- Reference ranges for BCG and BCP users should be identical
- Previously reported differences (Registry Report 1998) in interference in albumin methods in sera from haemodialysis vs peritoneal dialysis patients are probably due the different median albumin concentrations in these populations. At lower albumin concentrations (ie in PD patients) the BCG assay will show greater differences to the BCP assay due to interference from non-albumin proteins.
- Whilst compliance with RA standards is difficult to assess it is clear that clinical factors are responsible for a significant proportion of the changes in albumin concentration.

Serum Bicarbonate

Bicarbonate measurement

As can be seen from Table 9.2 there are two main methodologies in use for the measurement of bicarbonate. There is some variation in reference ranges but this is probably not the main factor that will determine the distribution of results between centres. Bicarbonate is a relatively unstable anion and concentration changes will result from delayed analysis as can happen with samples sent from General Practitioners, home haemodialysis and possibly satellite dialysis units. Home haemodialysis patients have been excluded from the haemodialysis analysis. Another factor that will alter bicarbonate distributions will be the proportion of patients receiving acetate dialysis solutions.

Centre	Methodology	Ref range mmol/L
A	PEPC	23-30
B	PEPC	22-29
C	PEPC	23-30
D	PEPC	22-30
E	PEPC	23-31
F	Electrode	20-30
G	PEPC	22-30
H	PEPC	19-28
I	PEPC	22-30
J	PEPC	23-29
K	PEPC	22-29
L	PEPC	22-30
M	Electrode	19-32
N	PEPC	20-29
O	Electrode	23-30
P	PEPC	24-30
Q	PEPC	24-30
R	PEPC	24-30
T	PEPC	22-31
U	Electrode	21-30
V	PEPC	20-28
W	Electrode	24-32
X	Electrode	22-31

Table 9.2 Bicarbonate methodology and reference ranges

Haemodialysis

The Renal Association Standard is that all patients ***should be within the local normal range***.

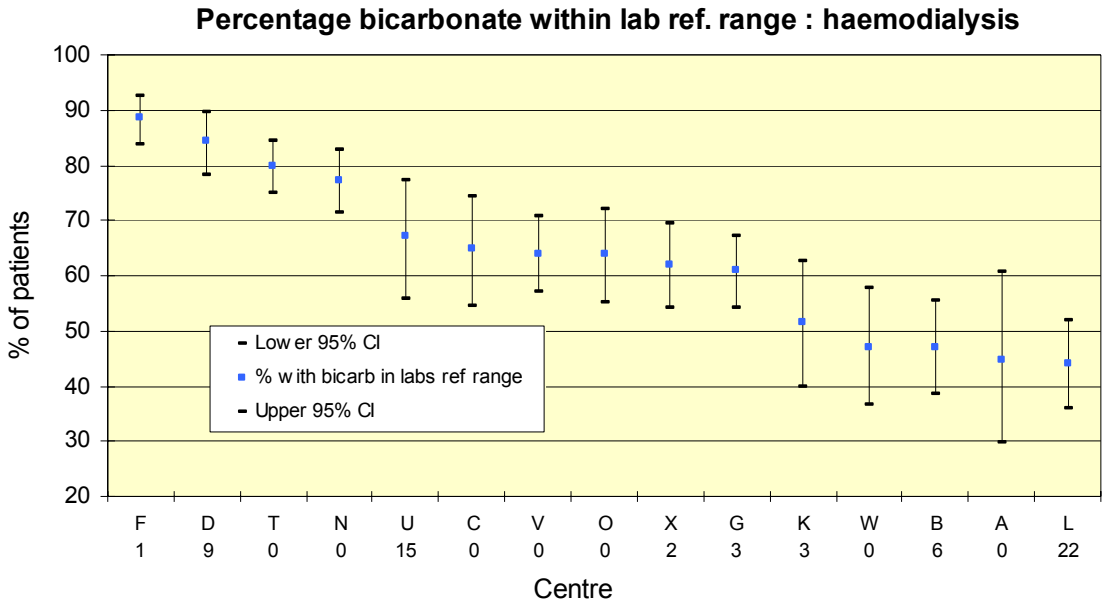

Figure 9.15 Percentage bicarbonate in laboratory reference range on haemodialysis

Bicarbonate was not available from centre E, and their was greater than 50% missing data from centres M and R

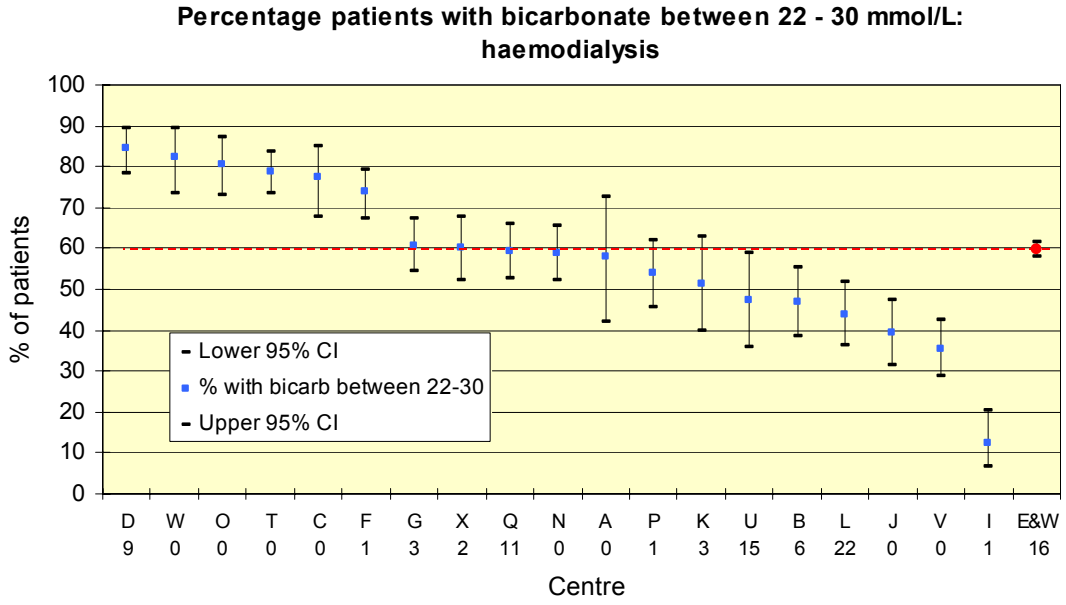

Figure 9.16 Percentage patients with bicarbonate in range 22-30 mmol/L on HD

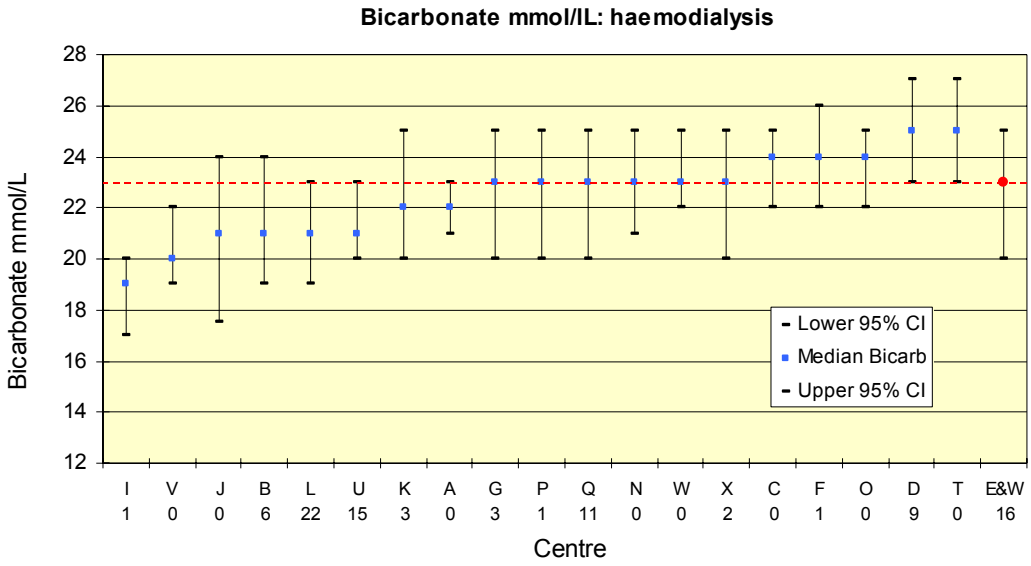

Figure 9.17 Median bicarbonate (mmol/L) on haemodialysis

Median serum bicarbonate varied from 18 –25 between centres. For patients on HD, the percentage of patients with bicarbonate within the Standard differed significantly between centres ($X^2 = 305.9$, d.f. = 21, $p<0.001$).

Discussion

There is a wide variation in median bicarbonate concentrations of 18-25 mmol/L, between centres. The relative distribution of centres is however not materially altered by applying a reference range factor whether local or Registry assigned (22-30 mmol/L).

Peritoneal dialysis

The Renal Association Standard is that patients should have a bicarbonate between ***the lower local normal to upper local normal +3mmol/L.***

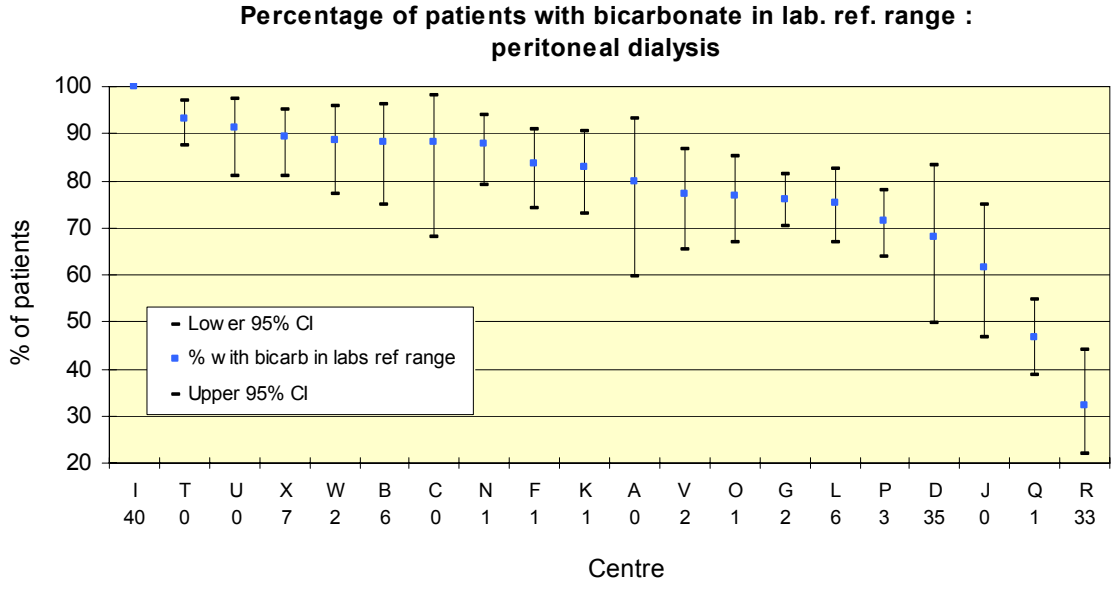

Figure 9.18 Percentage patients with bicarbonate in laboratory reference range on PD

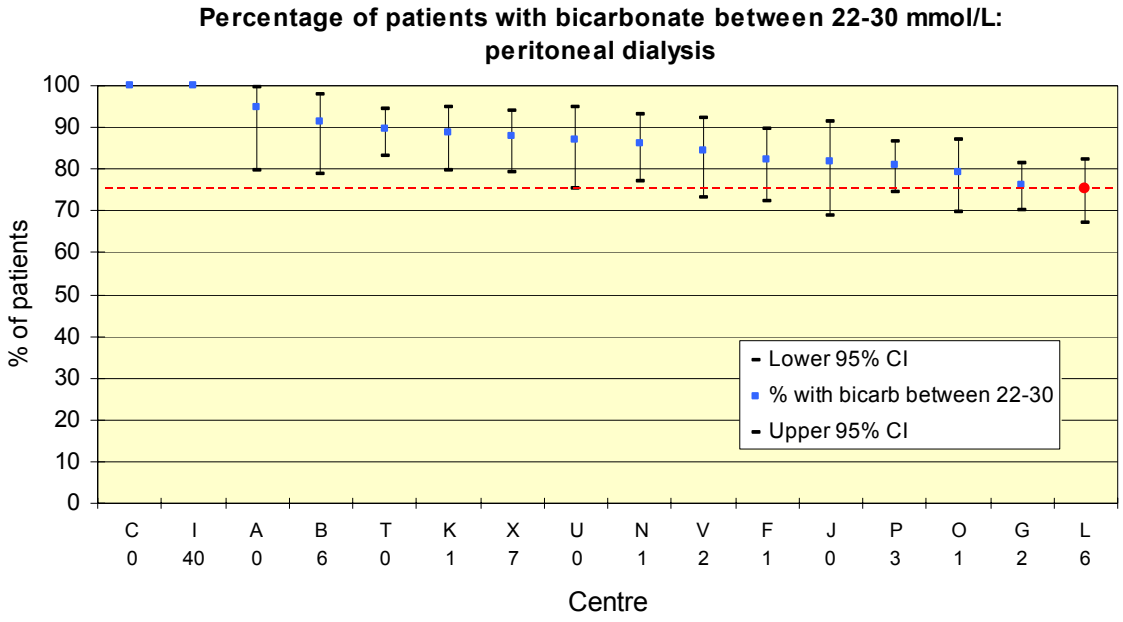

Figure 9.19 Percentage patients with bicarbonate in range 22-30 mmol/L on PD

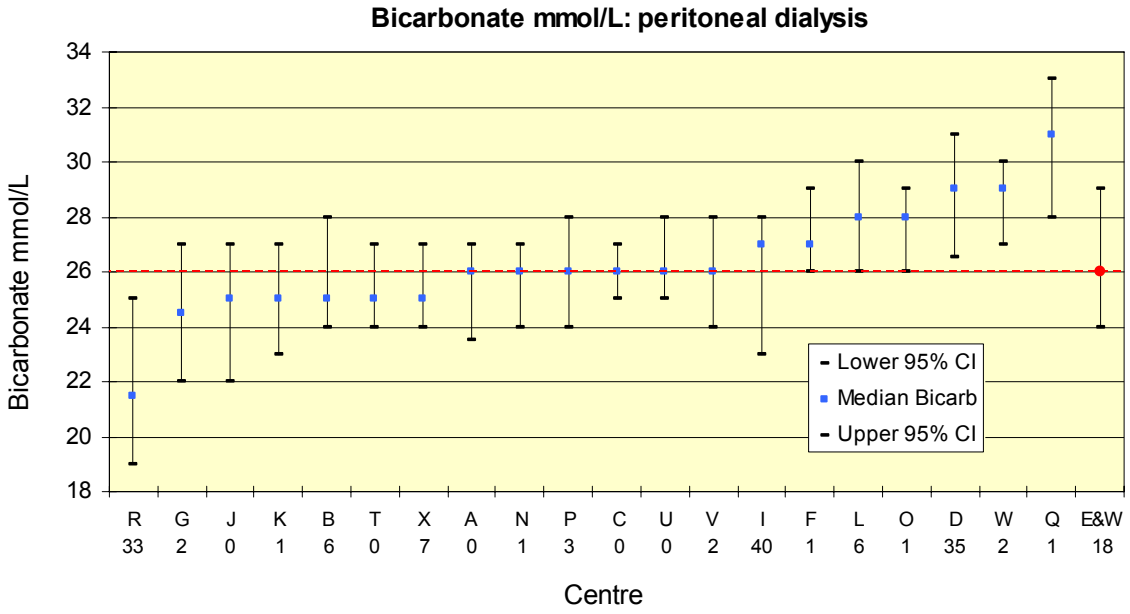

Figure 9.20 Bicarbonate (mmol/L) on peritoneal dialysis

For patients on PD, the percentage of patients with bicarbonate within the Standard differed significantly between centres ($X^2 = 195.8$, d.f. = 19, $p<0.001$)

Discussion

Bicarbonate concentrations appear even more variable in peritoneal dialysis patients, albeit the concentration range is different (21-31 mmol/L). Again use of reference ranges makes little different to the relative distribution of centres. A more in depth investigation of the usage of dialysate solutions and the delays in sample analysis is required to ascertain the significance of these difference to patient outcomes.