Guideline for the supplementation of Folic Acid in
Intermittent Haemodialysis & Peritoneal Dialysis

Beaumont Hospital
Department of Nephrology, Dialysis and Transplantation

DRAFT

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Document Number: 20 b	Reason for Change Update of 2009 Guideline
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SECTION 1

INTRODUCTION-

Rationale: The purpose of this guideline is to assist the multidisciplinary team in the appropriate supplementation of folic acid to patients receiving intermittent haemodialysis or peritoneal dialysis.

Scope: This guideline applies to all staff working within the renal department in Beaumont Hospital.

Principles: The Department of Nephrology, Dialysis and Transplantation has a responsibility to ensure Hospital Guidelines are developed where required/appropriate and implemented effectively. It is intended as a guide towards best practice for all members of the multidisciplinary team involved in the care of the renal patient on intermittent hemodialysis or peritoneal dialysis.

SECTION 2

PURPOSE / OBJECTIVES

The objectives of this guideline are to:

- Prevent sub-clinical and frank deficiency.
- Avoid over-supplementation.
- Use therapeutic amounts to prevent additional pathology.

Reference Range (Beaumont Hospital Laboratory Reference Range)

Target	> 3.0 ng/ml
Borderline Deficiency	2.3 – 3.0 ng/ml

SECTION 3

PROCEDURE

Folic acid is one of the B vitamins. Adequate folate intake is necessary for the formation of tetraydrofolate (THF). A lack of THF means the one-carbon transfer reactions required for the DNA synthesis are limited.

Minor Deficiency symptoms	Major Deficiency symptoms
Tiredness, Weakness, Irritability, Insomnia, Forgetfulness	Anaemia, Muscular cramps, Confusion

The nutritional intake of the renal replacement therapy patient can be suboptimal due to:

The therapeutic dietary restrictions, cooking procedures.

The disease state and co-morbidities, e.g. uraemia causes decreased absorption and/or activity of vitamins.

Drug nutrient interaction.

Fluid removal during dialysis.

Laboratory and epidemiological data have suggested that Folic Acid supplementation has a role in both cancer prevention, by having an antineoplastic effect, and cardio-protection by reducing homocysteine levels. However, more recent randomized controlled trials have shown that folic acid supplementation does not reduce colorectal adenoma risk and in fact may increase the risk of advanced lesions and adenoma multiplicity, Fife et al, 2009, Cole et al, 2007, Kim YI, 2007.

In relation to cardio protection, the evidence is weak with a recent randomized trial showing folic acid supplementation did not reduce a combined end point of total cardiovascular events despite significantly lowering homocysteine levels, Albert *et al*, 2008.

Based on the lack of compelling supportive evidence and on the potential tumour promoting effect it is felt it is prudent to avoid excessive supplementation and only provide the recommended dose to help prevent deficiency.

Current Daily Folate Recommendations:

NKF (2002)	Renal Dietetic Practice Group of the ADA (2004)	INDI, RIG (2006)
1 mg	1mg	1mg

FSAI (2006) recommended upper limit for the general population: 1 mg

Responsibilities of the multidisciplinary team

The medical team must:

- On commencing dialysis prescribe 5mg Folic Acid once weekly (Sunday - non-dialysis day).
- If the serum level drops below the reference range of 2.3ng/ml, despite administration of 5mg weekly, increase dosage to 5mg once daily x 3/12 or until level rises to >3.0 ng/ml.

The nursing staff must:

- Monitor serum Folate levels on a quarterly basis to allow for dose adjustment

The dietitian must:

- Routinely monitor serum Folate levels to allow for dose adjustment.

SECTION 4

DEVELOPMENT AND CONSULTATION PROCESS – Consisting of:

An outline of who has been involved in developing the PPPG (use template below)

CONSULTANT SUMMARY	
Date PPPG issued for consultation	15/11/11
Number of versions produced for consultation	1
Committees/meetings where PPPG was formally discussed	Dates:15/11/11

Where Received	**Summary of Feedback**	**Actions/Response**

SECTION 5

REFERENCES

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APPENDIX 1.

Serum Folate Levels of HD & PD patients in 2008 (Prior to Initial Guideline) & subsequent years.

APPENDIX 2.

Short summary of supporting evidence.

APPENDIX 1

Serum Folate Levels of HD & PD patients in 2008 (Prior to Initial Guideline) & subsequent years.

2008	<2.8ug/l	2.8-17ug/l	17-20ug/l	>20ug/l
HD, n=184	0%(0)	23% (42)	1% (2)	76% (139)
PD, n=25	0%(0)	68% (17)	8% (2)	24%(6)
2009				
HD, n=178	2%(3)	56% (99)	9% (17)	33% (58)
PD, n=28	3.5%(1)	43% (12)	7% (2)	46.5%(13)
2010				
HD, n=168	2%(3)	61% (103)	11% (19)	26% (43)
PD, n=40	0%(0)	70% (28)	5% (2)	25% (10)
2011				
HD, n=184	2%(3)	69% (128)	7% (13)	22% (40)
PD, n=38	3%(1)	61% (23)	8% (3)	29% (11)
Home HD, n=16	0%(0)	69% (11)	0% (0)	31% (5)

HD & PD

Year	< 2.8ug/l	2.8-17ug/l	17-20ug/l	>20ug/l
2008	0	59	4	145
n = 209	*0%*	*28%*	*2%*	*69.4%*
2009	4	111	19	71
n = 206	*2%*	*54%*	*9 %*	*35%*
2010	3	131	21	53
n = 208	*1.4%*	*63%*	*10%*	*25.5%*
2011	4	151	16	51
n = 222	*1.8%*	*68%*	*7%*	*23%*
Home HD	0	11	0	5
n = 16	0%	69%	0%	31%

APPENDIX 2

Cancer Prevention:

- Double blind, placebo controlled, two factor, randomized clinical trail. 1mg Folic Acid supplement, 1000 pts, f/u 10yrs

Results: 1) Did not reduce the risk of recurrence. 2) Suggestion of increased risk of advanced lesions and adenoma multiplicity. 3) Higher risk of non-colorectal cancers, specifically prostate cancer. **Cole *et al,* 2007**

- Critical review of epidemiologic, animal and intervention studies.

Results: Dual modulatory effects of folate on colorectal carcinogenesis depending on timing and dose of intervention.

1) In established colorectal neoplasms folate has an inhibitory effect and supplementation a promoting effect.
2) In normal colorectal mucosa folate deficiency appears to predispose it to neoplastic transformation and moderate supplementation suppress. While supraphysiologic supplemental doses enhance the development of cancer. ***Kim,* 2007**

- Meta – analysis of 3 studies. At three years colonoscopic follow up, folate supplementation had no effect on adenoma recurrence overall. However, beyond three years revealed an increased risk of colorectal adenoma (especially advanced adenoma). **Fife *et al,* 2009**

- WAFACS, 2.5mg Folic Acid, 5442 women, f/u 7.3 years

Results: No significant effect on overall risk of total invasive cancer or breast cancer. **Shumin *et al,* 2008**

Cardio-protective:

- WAFACS, 2.5mg Folic Acid, 5442 women, f/u 7.3 years

Results: Did not reduce a combined end point of cardiovascular morbidity or mortality among high risk women, despite significantly lowering homocysteine levels. **Albert, *et al.* 2008**

- Hope 2, 5522 subjects, f/u 5 years

Results: 1) Supplementation failed to significantly lower the risk of a combined outcome of cardiovascular death, MI and stroke. 2) Significant reduction in the secondary end point of stroke. **Lonn *et al,* 2006**

- VISP, 3680 subjects, f/u 2 years

Results: No benefit where stroke was taken to be the primary end point. **Toole *et al,* 2004**

- Norvit, 3749 subjects with recent MI, f/u 40 month

Result: Marginally significant increased risk of recurrent MI, stroke and sudden death. **Bonna *et al,* 2006**

- Meta-analysis of randomized controlled trials

Folic Acid has not been shown to reduce the rick of CVD or all cause mortality among participants with a prior history of vascular disease. **Lydia *et al,* 2006**