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The medical risks of severe anorexia nervosa during initial re-feeding and medical stabilisation

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SUMMARY

Background & aims: Objective evidence about the risks associated with anorexia nervosa and how to manage them, is limited. The aim of this study is to describe the medical risk profile, management and outcomes of a cohort of patients with severe anorexia nervosa (sAN) during medical stabilisation treatment.

Methods: Retrospective analysis of case records gathered medical risk data for a 90 day high risk period, on 65 patients with sAN admitted to two specialist services. Prospectively established definitions of medical risk variables and significant complications were applied to the data to describe the risk profiles and outcomes.

Results: Amongst this population with an average initial BMI of 12.8 kg/m^2, 74% developed no significant medical complications. Oral re-feeding over 60 days achieved an increase in mean BMI to 14.4 kg/m^2 and mean weight gain of 4 kg. No patients developed severe hypophosphatemia (<0.45 mmol/L) or any other indicators of a re-feeding syndrome. All the medical complications that arose were temporary.

Conclusions: Initial re-feeding and medical stabilisation of patients with severe AN can be managed safely in specialist inpatient and community settings with slow re-feeding. Although the prevalence of complications was shown to be low, slight worsening of medical risk markers and increased incidence of complications did occur during initial re-feeding. The limited comparable published data appears to support slower rates of re-feeding, showing fewer abnormal results and complications. There is however a need for a definitive prospective multi-centre observational cohort study to investigate risks factors, and the effects of treatment on medical outcomes, in a large sample with varied rates of re-feeding.

1. Introduction

There is good practice guidance about the management of medical risks associated with anorexia nervosa [1–6], yet objective evidence supporting such guidance is limited. There is even less objective evidence to guide clinicians on when a patient with anorexia nervosa (AN) requires inpatient admission for medical stabilisation. Mean BMI provides an approximate indication of medical risk. Studies published in the last 5 years describing mean BMI for patient cohorts on admission to specialist inpatient services, range from 11.3 [7] to 16.2 [8]. It is clear from this simple marker and descriptions and commentaries in other articles, that there is marked variation in the management of medical risk for people with severe anorexia nervosa (sAN) [9–18]. This is in large part because there is a lack of adequate research to guide evidence-based practice.

There are known medical risks in sAN. Rigorous recent meta-analyses have estimated Standardised Mortality Ratio's (SMRs) of 5.2 [19] and 5.9 [20] respectively. Published mortality rates for populations of patients with severe Anorexia Nervosa, over varied timescales, describe mortality rates ranging from 4% [21] to greater than 10% [22,23]. Rosling and colleagues [22] describe a SMR of 10 in their 14 year follow up study of patients treated in an ED inpatient unit, rising to an SMR of over 30 for those with lowest recorded BMI's of less than 11.5.

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Re-feeding syndrome is a risk but it is unclear how common it is and how to mitigate against it, with many varying views. Rates of re-feeding used in treatment vary substantially, with higher rates in North America and Australia, but lower rates in Europe [13,24–27]. There are many other potential causes of death or serious medical sequelae in sufferers of sAN, including cardiac, gastro-intestinal, hepatic, renal, and pancreatic complications. Although there are some important studies of medical outcomes in patients with sAN [7,9,11,13,18,24,28], the sample sizes are not large enough to reliably establish the frequency of serious adverse medical outcomes, as these are relatively uncommon. Furthermore, the data gathered on risk factors and medical complications varies between studies making comparisons difficult.

Inpatient treatment services for patients with sAN vary hugely, from specialist physician led units [13] to specialist psychiatrist led units [8], to non-specialist psychiatric or medical units. There are a small number of community services providing treatment for patients with sAN [21,29,30]. For cost-effective yet safe treatment services to be developed for people suffering sAN, we require a greater understanding of the frequency and nature of the medical risks arising in both community and inpatient settings.

The primary aim of this study is to describe the medical risk profile, the medical and dietetic management and the medical outcomes of a cohort of patients with severe anorexia nervosa (sAN), treated in two services. The secondary aim is to establish and test a methodology for defining and collecting reliable data on a set of risk profile variables and serious medical complications that could be used in a future prospective multi-centre study.

2. Method

2.1. Study setting

The *Naomi Unit* at The Retreat Hospital (York, England), is an inpatient multi-disciplinary eating disorders service treating people with anorexia nervosa. The unit uses a recovery focused pathways model, aiming for medical stabilisation and skills acquisition followed by transfer of skills to the home environment. The mean length of treatment in the service is slightly over 6 months. The *Anorexia Nervosa Intensive Treatment Team (ANITT)* at the Royal Edinburgh Hospital (Edinburgh, Scotland) is a community multi-disciplinary service exclusively treating people with anorexia nervosa who have reached a starvation state. The service uses a psychotherapy-based model based on the concept of core needs [21]. Length of treatment ranges from 2 years to continuous (for patients remaining at persistent high risk).

Both services are multi-disciplinary yet have psychological formulation and therapy central to their treatment approach. The *ANITT* service offers treatment 5 days a week in the patient's home environment or an outpatient clinic, with maximum direct staff contact of approx. 3 h per day and a minimum of approximately 2–3 h per week. The *Naomi Unit* patients are cared for in a ward environment with seven days a week staff availability. Daily direct staff contact ranges from 3.5 to 5 h per day.

The *ANITT* service aims to initiate re-feeding at around 20 kcal/kg/day and to increase by 200–300 kcal every 3–4 days, although rates of re-feeding are individually tailored. Patients in the community may not comply fully with the prescribed rate, so actual consumption may be lower. All patients are prescribed a multivitamin and thiamine, but again do not always comply. If dietetic assessment reveals a deficit in phosphate intake and the patient is judged unable to increase phosphate rich foods such as dairy products to correct this, or serum phosphate levels are low, an oral phosphate supplement is prescribed. Oral nutritional supplements are used infrequently. Naso-gastric feeding is never used. Twice weekly medical monitoring consists of vital signs, and blood screens (including electrolyte and phosphate levels) as the standard initial regime. Medical monitoring is carried out by the specialist nurse or the consultant psychiatrist. This is supported by active specialist dietetic management and the monitoring of symptomatic presentation by all members of the multi-disciplinary team at appointments.

The *Naomi Unit* initiates re-feeding around a rate of 30 kcal/kg/day with individual assessment determining the starting rate and a standardised eating plan prescribed. The rate is increased to the next stage of the standardised eating plan at day 4, unless there is a strong clinical reason not to. All patients are prescribed a multivitamin, thiamine and vitamin B and tend to comply. The standardised eating plans are rich in phosphate so oral phosphate supplements are only prescribed if indicated by serum levels. Oral nutritional supplements are not used unless there is a medical reason, such as malabsorption, necessitating this. Naso-gastric feeding is not used on the *Naomi Unit*. Patients are symptomatically monitored in the inpatient setting, with input from the consultant psychiatrist, specialist dietitian and the team of two specialist nurses per shift. Vital signs are monitored 4 hourly initially with blood screens, including phosphate and electrolyte levels daily. The frequency of monitoring reduces as risks reduce.

2.2. Study design

All patients admitted to either service over a five year period from July 2008–July 2013, with a diagnosis of anorexia nervosa and a BMI of $\leq$13, or BMI $\leq$15 and weight loss of $\geq$1 kg in the preceding month, were included in the study sample. This defines a population with sAN.

Using existing literature and in consultation with a consultant physician, definitions of thirty-eight risk profile variables (RPV's: see Appendix A) and twenty-one significant medical complications (SMC's: see Appendix B), were established. The RPV's cover a broad range of clinical examination and investigations such as BMI, heart rate, serum potassium levels, serum phosphate levels; and dietary and behavioural factors such as kilocalorie intake, purging behaviour, and alcohol use. The group of SMC's were chosen to reflect a broad range of possible adverse outcomes, including severe biochemical or haematological disturbance which would inevitably be associated with significant symptoms and risks, e.g. hyponatraemia <120 mmol/L.

Data collection involved review of case-notes and electronic investigation results systems. Demographic, risk profile, treatment and outcome data on the sample was gathered. Estimates of daily kilocalorie (kcal) intake, lowest daily kcal intake and phosphate intake were carried out by specialist dietitians. For community-based patients the estimate relied on patient report and dietetic assessment, with some inevitable reduction in confidence of accuracy. We defined a 90 day high risk window, with three time periods for data collection: the 30 days including and preceding the day of entry to the service, during which the patient was deteriorating; day 1–30 of treatment with initial re-feeding and stabilisation; and days 31–60 of treatment with further re-feeding and stabilisation. All data used in this study was collected as part of routine clinical care and collated retrospectively.

Univariate statistics were used to describe the sample, risk profiles, treatment interventions and outcomes. For categorical variables, data are expressed as frequencies and percentages. For continuous variables, data are expressed as means with standard deviations (SDs) for normal distributions and as medians and interquartile range (IQR) for non-normal distributions. Changes in risk profile variables between the time periods were explored using paired sample t-tests for normal distributions, Wilcoxon signed

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rank test for non-normal distributions and McNemar's test for categorical variables. We explored the relationships between risk factor variables and significant medical complications using multiple logistic regression analysis.

3. Results

3.1. Demographics

Sixty-five patients fulfilled our entry criteria, defining a sAN population in starvation, with one male patient. The *Naomi Unit* contributed 48 patients, the majority of the sample, with an *ANITT* sub-sample of 17 patients. Patients had a median age of 24 years (IQR 12). Restrictive AN accounted for 72.3% and 27.7% had binge–purge subtype. At entry to the service the patients had a median BMI of 12.8 (IQR 1.9).

3.2. Dietetic and medical management

Medical and dietetic treatment interventions are described in Table 1. Details of re-feeding are described in the re-feeding related outcomes paragraph below.

3.3. Risk profile at intake and during treatment

At entry to the treatment service, our sample had a median BMI of 12.8 (IQR1.9), with a rate of weight loss of 0.7 kg/week (IQR 0.68) and a median calorie intake of 633 kcal/day. Few of the average RPV's were outside the normal range for the 30 days prior to entering the service (Table 2), but these included: lowest recorded heart rate; lowest random glucose; lowest white cell count; and lowest neutrophil count. Only 3 patients had low serum phosphate recordings. However only 46 of our 65 patients (70%) had a serum phosphate level checked during the 30 days preceding admission.

Change in the risk profile variables did occur during initial treatment (Table 2). During the initial 30 days, the median lowest heart rate showed a drop from 56 to 49 bpm ($p < 0.001$) and median lowest systolic BP dropped from 92 to 80 mmHg ($p < 0.001$). The median lowest random glucose dropped from 3.6 mmol/L to 3.3 mmol/L ($p < 0.02$). The median lowest creatinine dropped to outside the normal range from 61 to 49 μmol/L ($p < 0.001$). Lowest WCC and Neutrophil count remained below the normal range but did not change significantly. Other tests such as highest ALT, highest GGT, lowest Phosphate and lowest Magnesium, showed statistically significant change, but within normal ranges.

Table 1
Medical and dietetic treatment interventions prescribed.

	30 days before entry to service (N = 65)[a]	Days 1–30 of treatment (N = 65)[a]	Days 31–60 of treatment (N = 60)[a]
Multivitamins	18 (27.7%)	59 (90.8%)	54 (90%)
Thiamine	15 (23.1%)	49 (75.4%)	11 (18.3%)
Phosphate supplement	2 (3.1%)	6 (9.2%)	1 (1.7%)
Meal support	2 (3.1%)	49 (75.4%)	49 (81.7%)
Nutritional supplements	9 (13.8%)	7 (10.8%)	5 (8.3%)
Nasogastric feeding	0	0	0
Psychotropic medication	38 (58.5%)	47 (72.3%)	44 (73.3%)
Antidepressant	31 (47.7%)	40 (61.5%)	38 (63.3%)
Antipsychotic	4 (6.2%)	4 (6.2%)	5 (8.3%)
Sedative/sleeping	10 (15.4%)	20 (30.8%)	15 (25%)
Mood stabiliser	2 (3.1%)	2 (3.1%)	1 (1.7%)
Use of the mental health act	4 (6.2%)	3 (4.6%)	2 (3.3.%)

[a] Data expressed in frequencies and percentages of the population in the sample.

The average RPV values returned to or remained in the normal range, or showed improvement, during days 31–60 of re-feeding and stabilisation treatment compared with days 1–30 (Table 3).

3.4. Significant medical complications

In the 30 days prior to entry to the services, 9 patients (13.8%) experienced one or more SMC. During days 1–30 of medical stabilisation and re-feeding, 13 patients (20%) had one or more SMC. During days 31–60 of treatment, only 5 patients (7.7%) experienced a SMC. Overall, 17 patients (26%) developed one or more SMC's during 60 days of treatment.

Significant hepatic dysfunction (defined as any LFT elevated greater than 3 times above the normal range), was the most common SMC and occurred in 11 patients. Severe hypoglycaemia, defined as <2.2 mmol/L arose in 2 patients. One patient developed severe hypokalemia, defined as <2.5 mmol/L. Acute renal failure developed in two patients during initial treatment, but for both patients this resolved within the first month of re-feeding. Two patients suffered loss of consciousness. One suffered a grand mal seizure in the context of a pre-existing diagnosis of epilepsy. The other was of unknown cause, but was brief with no recurrence. One patient developed pneumonia which was successfully treated with antibiotics and physiotherapy. Although the frequency and nature

Table 2
Change in risk profile variables during initial 30 days of treatment.

Risk profile variable[a]	30 days before treatment (N = 65)[b]	Days 1–30 of treatment (N = 65)[b]	*p*-value[c]
Lowest heart rate (60–100 bpm)	**56 (18)**	**49 (13)**	<0.001
Lowest systolic BP (90–140 mmHg)	92 (19)	**80 (21)**	<0.001
Lowest sodium (135–145 mmol/L)	137 (8)	136 (5)	<0.34
Lowest potassium (3.6–5 mmol/L)	4 (.8)	3.8 (.6)	<0.09
Lowest bircarb (22–30 mmol/L)	28 (4)	28.5 (5)	<0.77
Highest bicarb (22–30 mmol/L)	29 (4)	29 (7)	<0.86
Lowest creatinine (60–120 μmol/L)	61 (18)	**49 (18)**	<0.001
Highest creatinine (60–120 μmol/L)	69 (28)	64 (16)	<0.02
Lowest urea (2.5–6.6 mmol/L)	3.4 (2.2)	3.5 (1.5)	<0.60
Highest urea (2.5–6.6 mmol/L)	4.6 (3.1)	5 (2.4)	=0.007
Lowest calcium (2.1–2.6 mmol/L)	2.41 (.24)	2.35 (.16)	<0.02
Lowest phosphate (0.8–1.4 mmol/L)	1.1 (.19)	1.04 (.3)	<0.001
Lowest magnesium (0.7–1.00 mmol/L)	0.88 ± 0.09	0.85 ± 0.08	=0.003
Highest ALT (10–50 U/L)	26.5 (30)	33.5 (54)	<0.001
Highest Alk Phos (40–125 U/L)	67 (34)	65 (27)	<0.87
Highest bilirubin (3–21 μmol/L)	10 (10)	10 (6)	<0.29
Highest GGT (0–51 U/L)	22 (17)	30 (18)	<0.02
Highest CK (30–135 U/L)	107 (130)	99 (118)	<0.43
Lowest albumin (30–45 g/L)	44 (7)	43 (7)	<0.11
Lowest glucose (4.4–6.1 mmol/L)	**3.6 (.93)**	**3.3 (1.47)**	<0.02
Lowest WCC (4–11 × 10^9/L)	**3.45 (2.4)**	**3.1 (1.75)**	<0.14
Highest WCC (4–11 × 10^9/L)	4.3 (2.95)	4.6 (2)	=0.001
Lowest neutrophil (2–7.5 × 10^9/L)	**1.88 (1.62)**	**1.81 (1.28)**	<0.51
Highest neutrophil (2–7.5 × 10^9/L)	2.2 (1.76)	2.9 (1.63)	<0.001
Lowest Hb (F 115–165 g/L)	129 (21)	117 (15)	<0.001
Lowest free T4 (9–21 mmol/L)	12 (3)	12 (5)	<0.02
Lowest daily intake (kcals/day)	**469 (565)**	**1039 (0)**	<0.001
Vegan	10 (15.4%)	7 (10.8%)	=0.25
Binge-purge behaviour	18 (27.7%)	9 (13.8%)	=0.004
Alcohol use	6 (9.2%)	0	<0.04
Illegal substances use	4 (6.2%)	0	=0.25
Diabetes	0	0	N/A
Sufficient dietary phosphate estimate	17 (26.2%)	51 (78.5%)	<0.001

Averages out of normal range highlighted in **bold**.

[a] Normal reference range shown in parentheses.

[b] Mean ± standard deviation for normally distributed variable. Median (interquartile range) for non-normally distributed variables. Frequency (percentage) for categorical variables.

[c] Paired samples t-test for normal distributions, Wilcoxon signed rank test for non-normal distributions. McNemar's test for categorical variables.

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of complications arising in individual patients is probably of greatest clinical relevance, Table 4 also describes the 30-day period prevalence's for each of the specific serious medical complications that arose.

3.5. Re-feeding related outcomes

The degree of starvation and the rate of initial re-feeding, are regarded as two potentially important variables in relation to the risk of developing re-feeding syndrome. The median BMI on entry to the study was 12.8. The estimated average rate of weight loss in the 30 days prior to entering treatment was 0.7 kg/week with an estimated calorie intake prior to re-feeding of 633 kcal/day. The daily kcal intake was started at a rate of 20–30 kcal/kg/day and increased by 30 days to an average of 1502 kcal/day, and by 60 days–2192 kcal/day. The BMI increased to a mean of 14.4, with average weight gain of 4.0 kg at 60 days. Whilst ten patients (6.5%) developed mild hypophosphatemia (<0.8 mmol/L) during the 60 day treatment period, no patients developed re-feeding syndrome.

3.6. Other outcomes

Four patients required detention under mental health legislation (see Table 1). We explored the relationship between risk variables or groups of risk variables and SMCs, using logistic regression analysis. The low prevalence of SMCs meant there was insufficient power to examine this. There were small differences in outcomes between the inpatient and community sub-samples, but there was insufficient power to examine these.

Nine patients from the community service (ANITT sub-sample) were admitted to inpatient care during the study period. Eight patients because they lacked the motivation or capacity to achieve medical stabilisation at home. Only one patient was admitted purely because of medical risk due to severe hypokalaemia.

Table 3
Change in risk profile variables during further treatment period.

Risk profile variable[a]	Days 1–30 within service (N = 65)[b]	Days 31–60 within service (N = 60)[b]	*p*-value[c]
Lowest heart rate (60–100 bpm)	**49 (13)**	60 (17)	<0.001
Lowest systolic BP (90–140 mmHg)	**80 (21)**	**82.5 (20)**	=0.002
Lowest sodium (135–145 mmol/L)	136 (5)	138 (5)	=0.002
Lowest potassium (3.6–5 mmol/L)	3.8 (.6)	3.9 (.5)	<0.001
Lowest bircarb (22–30 mmol/L)	27.4 ± 3	27.9 ± 4	<0.47
Highest bicarb (22–30 mmol/L)	29.1 ± 4.1	29.9 ± 5.6	=0.008
Lowest creatinine (60–120 μmol/L)	**51.75 ± 11.17**	**52.9 ± 11.2**	<0.07
Highest creatinine (60–120 μmol/L)	64 (16)	57 (2.20)	<0.001
Lowest urea (2.5–6.6 mmol/L)	3.5 (1.5)	4 ± 1.2	<0.001
Highest urea (2.5–6.6 mmol/L)	5 (2.4)	5 ± 1.6	<0.37
Lowest calcium (2.1–2.6 mmol/L)	2.3 ± 0.1	2.4 ± 0.14	=0.001
Lowest phosphate (0.8–1.4 mmol/L)	1.04 (.3)	1.2 (.2)	<0.001
Lowest magnesium (0.7–1.00 mmol/L)	0.85 ± 0.08	0.88 ± 0.08	=0.001
Highest ALT (10–50 U/L)	33.5 (54)	26.5 (22)	<0.03
Highest Alk Phos (40–125 U/L)	65 (27)	66.5 (24)	<0.62
Highest bilirubin (3–21 μmol/L)	10 (6)	9 (4)	<0.001
Highest GGT (0–51 U/L)	30 (18)	27 (131)	<0.35
Highest CK (30–135 U/L)	99 (118)	108 (86)	<0.07
Lowest albumin (30–45 g/L)	43 (7)	45 (6)	<0.02
Lowest glucose (4.4–6.1 mmol/L)	**3.3 (1.47)**	**3.9 (1.3)**	=0.31
Lowest WCC (4–11 × 10^9/L)	**3.1 (1.75)**	**3.9 (1.75)**	<0.001
Highest WCC (4–11 × 10^9/L)	4.6 (2)	4.6 (2.55)	<0.43
Lowest neutrophil (2–7.5 × 10^9/L)	**1.81 (1.28)**	2.2 (1.25)	<0.001
Highest neutrophil (2–7.5 × 10^9/L)	2.9 (1.63)	2.9 (1.77)	<0.60
Lowest Hb (F 115–165 g/L)	117 (15)	120 (21)	=0.004
Lowest free T4 (9–21 mmol/L)	12 (5)	13 (6)	<0.32
Lowest daily intake	**1039 (0)**	**1502 (601)**	<0.001
Vegan	7 (10.8%)	6 (10%)	=1
Binge-purge behaviour	9 (13.8%)	8 (20.5%)	=1
Alcohol use	0	1 (1.7%)	=1
Illegal substances use	0	0	N/A
Diabetes	0	0	N/A
Sufficient dietary phosphate estimate	51 (78.5%)	49 (81.7%)	=1

Averages out of normal range highlighted in **bold**.
[a] Normal reference range shown in parentheses.
[b] Mean ± standard deviation for normally distributed variable. Median (interquartile range) for non-normally distributed variables. Frequency (percentage) for categorical variables.
[c] Paired samples t test for normal distributions, Wilcoxon signed rank test for non-normal distributions. McNemar's test for categorical variables.

4. Discussion

The common perception amongst health professionals and the lay public, is that anorexia nervosa is a condition almost invariably associated with high medical risk. Our population of patients with severe AN in this study represent approximately 30% of a secondary care population of patients with AN [21]. It is undeniable that AN is a *potentially* fatal illness. However there is a distinction to be drawn between the physical risks associated with a severe form of the illness and the majority of cases. Terminology such as 'life threatening' or 'critically ill' are regularly used about the AN population as a whole in academic publications, in the media and in discussions with patients or carers. In this study at least, the objective physical risks are modest amongst this severe AN population, in the context of good multi-disciplinary community or inpatient treatment. This study and other published objective evidence do not in our view support the prevailing portrayal of universally high medical risk associated with AN.

In exploring change in a set of prospectively defined risk variables before and during treatment, we found few markedly abnormal results at intake and only minor haemodynamic and blood test changes in the crucial first 30 days of re-feeding and stabilisation. These results attest to the physical resilience of most patients with sAN and their physiological adaptation to starvation. The overall direction of changes during the initial re-feeding period, was of deterioration amongst markers of risk. As we gathered data on risk and complications for a 30 day period prior to re-feeding, we can clarify the likely processes underlying the development of significant medical complications. Our data suggest the increased incidence of medical complications during the first 30 days of re-feeding, compared with the 30 days prior to treatment, is accounted for less by the starvation process per se, and more by a transient process of physiological adaptation to increased nutrition after starvation. However, we have shown that such change is not of great clinical significance with the rates of re-feeding and other treatment used in our services. These change in risk indicators may be of greater significance in services using higher rates of re-feeding. As one would expect of risks largely due to a transient period of physiological adaptation to initial re-feeding, they improved during the second month of treatment.

Similarly, a rise in the incidence of significant medical complications (as defined) did occur during the initial 30 day treatment phase, compared with intake and the second phase of treatment. Again this reinforces the hypothesis that such complications arise, at least in part, as a response to the treatment of re-feeding. We must emphasise however that 74% of this sample developed no significant medical complications. Furthermore, many of the incidences of SMC's we have described may not be regarded by clinicians in the field as 'serious', such as LFT rises or transient hypoglycaemia. Perhaps our most important finding is that all the medical complications that arose were temporary, largely resolving within 2 months with initial weight gain of just 4 kg on average over 60 days. We believe integrated multi-disciplinary treatment is a crucial component in achieving such safe outcomes.

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There is much debate about appropriate rates of re-feeding for patients with sAN. There is concern about under-feeding in some quarters [31] and about the high rates of re-feeding advocated by others [8]. Although existing published data in this area varies in both methodology and severity of sample, we reviewed available studies. Five published studies of medical complications amongst patients with AN and average initial BMI's <15, describe sufficient data for comparisons of the starting rate of re-feeding, the rate of weight gain and the prevalence of hypophosphatemia (Table 5) [8,11,13,24,28]. There is an apparent association between higher prevalence of hypophosphatemia and higher rates of re-feeding. It is important to note that all of these studies report low rates of serious medical complications, and mild hypophosphatemia is in itself not of great concern, but many regard hypophosphatemia as an important potential harbinger of re-feeding related risks [11]. A potential confounding factor limiting the comparability of these studies is the use of phosphate supplementation. This may be used prophylactically or in response to low serum levels. Prophylactic use is likely to alter the prevalence of hypophosphatemia. Unfortunately the details of phosphate and other supplementary treatments are not adequately reported in all of these studies for direct comparison. In the present study oral phosphate supplementation was used in only 9% of the sample, largely in response to low serum levels and only prophylactically in a small number of cases in community treatment when dietary phosphate intake was assessed as markedly deficient. Thiamine and multi-vitamin supplements were also used with most patients in our sample.

We can draw more detailed comparisons with the three studies with sufficient comparable data, similar average intake BMI's and presumably therefore similar severity of illness to this study [11,13,24]. Gaudiani et al. [13] described a population with a similar severity of illness, with an average BMI of 13.1 (n = 25) treated as inpatients with a mean duration of stay of 19 days. Their rate of re-feeding increased from initial average intake of 990 kcal/day to 2000 kcal/day by discharge this resulted in an average weight gain of 0.48 BMI points per week, compared with only 0.18 BMI points per week in our study. They described the development of hypophosphatemia in 45% of their sample, compared with 6.5% in this study. Similarly they found 44% of their sample developed LFT's greater than three times the normal range, compared with only 15.4% in the first month of treatment amongst our sample. Neither study used naso-gastric feeding. Both studies used multi-vitamin and thiamine supplementation and neither routinely used prophylactic phosphate supplementation. The clearest difference in treatment delivered between these studies is the rate of re-feeding. Brown and colleagues [11], from the same treatment centre, have recently published an analysis specifically of the predictors of developing hypophosphatemia amongst a larger data set (n = 123), with an average BMI at intake of 13.0. They report higher haemoglobin, and lower BMI, potassium or prealbumin, as independent risk factors associated with the development of hypophosphatemia. Whilst these may be important risk factors predicting potential risk, we suggest these risk factors may not be independent, but instead dependent on the rate of re-feeding delivered. To establish the independence of these risk factors would require a study incorporating varying rates of re-feeding and clear reporting of supplementation treatment as a confounding factor. The hypophosphatemia prevalence of 33% reported by Brown and colleagues is substantially higher than the prevalence rates in studies with slower rates of re-feeding that we present here alongside our data (Table 5). For example, Hofer and colleagues [24], investigating a population with a slightly higher mean initial BMI of 13.7, described very similar rates of re-feeding and weight gain to our study and only 4.7% prevalence of hypophosphatemia. The rates of significant medical complications are low. Two further studies, lacked fully comparable data, with no reported rate of weight gain. Vignaud and colleagues reviewed outcomes for 68 patients with a mean BMI at intake of 12.0, treated in non-specialist medical intensive care units [18]. Seven patients developed re-feeding syndrome. Patients who did not develop re-feeding syndrome had re-feeding initiated at an average rate of 14.1 kcal/kg/day compared with 23.2 kcal/kg/day for those who did then develop re-feeding syndrome. Although other factors such as prompt detection and supplementation for hypophosphatemia may have influenced the prevalence of re-feeding syndrome in this study, this analysis nonetheless supports concerns about faster rates of re-feeding.

The European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines [5] for the management of re-feeding syndrome recommend a rate of initiation of re-feeding of 10 kcals/kg/day, increasing to 15 kcals/kg/day by day 3. These guidelines have been tested by Hofer and colleagues [24] as described above, in a population of patients with sAN, demonstrating low rates of hypophosphatemia and other adverse outcomes. The MARSIPAN guidelines [4], established due to concerns related to both over and under-feeding in non-specialist medical settings in the UK, advocate a rate of initiation for re-feeding of 5–10 kcals/kg/day. Although anecdotal accounts of death or serious complications due to underfeeding have been described by the MARSIPAN group [31], it is not clear at what level of feeding intake these may occur. There is no published outcome data testing the MARSIPAN guidance, but the evidence from Hofer and colleagues [24] would suggest this is likely

Table 4
Period prevalence of significant medical complications (SMCs).

	Prevalence of SMCs in the 30 days before entry to service (N = 65)[a]	Prevalence of SMCs in days 1–30 within service (N = 65)[a]	Prevalence of SMCs in days 31–60 within service (N = 60)[a]
Severe hypophosphatemia (phosphate <0.45 mmol/L)	1 (1.5%)	0	0
Loss of consciousness	0	2 (3.1%)	0
Pneumonia	0	1 (1.5%)	0
Renal failure	1 (1.5%)	2 (3.1)	0
Significant hepatic dysfunction (LFTs >3× normal)	5 (7.7%)	10 (15.4%)	3 (5%)
Severe hyponatraemia (sodium <120 mmol/L)	1 (1.5%)	0	0
Severe hypokalaemia (potassium <2.5 mmol/L)	1 (1.5%)	0	1 (1.7%)
Severe low bircarbonate (bircarbonate <15 mmol/L)	1 (1.5%)	0	0
Severe hypoglycaemia (glucose <2.2 mmol/L)	4 (6.2%)	2 (3.1%)	1 (1.7%)
Total number of SMC's[b]	14	18	5

Note: SMCs that did not occur are not shown on this table.
[a] Data expressed in frequencies and percentages of the population in the sample.
[b] Total number of serious medical complications across all patients.

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Table 5
Comparison of re-feeding rates and hypophosphatemia.

Study	Sample Size	Average BMI at intake	Starting rate of re-feeding[a,b]	Rate of weight gain[c,d]	Prevalence of hypophosphatemia in sample
Davies et al.	n = 65	12.8	20–30 kcal/kg/day[a] 953 kcal/day[b]	0.47 kg/week[c] 0.18 BMI points/week[d]	6.5%
Gaudiani et al. (2012)	n = 25	13.1	*Not reported* 990 kcal/day[b]	*Not reported* 0.48 BMI points/week[d]	45%
Brown et al. (2015)	n = 123	13	*Not reported* 1200–1400 kcal/day[b]	*Not reported* 0.48 BMI points/week[d]	33%
Hofer et al. (2014)	n = 86	13.7	10–15 kcal/kg/day[a] 379–569 kcal/day[b]	0.5 kg/week[c] 0.18 BMI points/week[d]	4.7%
Redgrave et al. (2015)	n = 135	<15	*Not reported* 1200–1500 kcal/day[b]	1.36–1.98 kg/week[c] *Not reported*	32.4%
Rigaud et al. (2012)	n = 41	10.1	12–35 kcal/kg/day[a] *Not reported*	1.15 kg/week[c] 0.5 BMI point/week[d]	9%

[a] Starting rate of refeeding calculated in kcal intake per kilogram of body weight per day.
[b] Starting rate of refeeding calculated in total kcal intake per day.
[c] Rate of weight gain calculated in kilograms per week.
[d] Rate of weight gain calculated in BMI points per week.

to be a safe approach assuming feeding is judiciously increased during days 2–3 of re-feeding.

The re-feeding debate often gives little consideration to the psychological impact of re-feeding. Both services in this study combine psychological treatment with medical stabilisation and re-feeding. As such we are aware that overly rapid weight gain can be intolerable and counter-productive for some patients. Patients are often told that risk of death or serious complications necessitates urgent weight gain only to lose weight further without developing serious complications. This can undermine trust and reinforce misguided patient beliefs about infallibility, potentially increasing the risks. Should further research confirm that slower re-feeding is safer or safe enough, as our results suggest, we suggest there is a strong case for slower rates of re-feeding if this facilitates the crucial process of building trust between patient and clinical teams, in preparation for further psychological treatment.

We suggest there is a need for a definitive prospective multi-centre observational cohort study, to gather a data set sufficient to fully investigate risks factors, medical outcomes and the effects of treatments amongst people with sAN. This would have the potential to elucidate the relationships between risk markers, or aggregated groups of risk markers, treatment interventions and adverse outcomes. There is a possibility that current practice in some specialist services result in avoidable medical complications. Services for patients with severe AN may be determined too much by prevailing cultures of care and idiosyncratic local circumstances because health service providers currently lack sufficient robust evidence to plan safe evidence-based services for patients with severe AN.

The strengths of this study are in the systematic definitions of risk factors and significant medical complications, applied to analyse outcomes for a clearly defined and representative population of patients with severe anorexia nervosa. The collection and analysis of data from prior to and during the course of re-feeding treatment allowed for more robust conclusions about the likely causation of changes that arose. The central limitation of this study is that we had insufficient power to explore the relationship between the risk factor variables and the significant medical complications that arose, as the prevalence of complications was low. Our data was also gathered retrospectively which may have introduced greater risk of error.

We have established definitions of risk profile variables and serious medical complications relevant in sAN and tested a methodology for gathering such data. We have shown that within a crucial 60 day period after initiation of intensive treatment in specialist inpatient or community settings, that patients with sAN can be safely medically stabilised with very few significant medical complications.

Statement of authorship

All authors contributed to the methodology and design of the study. Data collection was contributed to by all. Analysis was led by JED & CM, with contributions from all. Writing this article was led by CM, with revisions and final approval of submission version by all authors.

Conflict of interest

The authors report no conflict of interests relevant to the content of this article.

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Appendix A. Definitions of risk profile variables (RPVs)

1. *Weight* = Weight in kilograms as recorded at closest point, on entry to service, 30 & 60 days
2. *Initial weight loss trajectory* = average weekly weight loss (Kg), over 30 days preceding entry to service.
3. *Initial body mass index* = lowest BMI during preceding 30 days recorded at entry, to one decimal place (normal range = 18.5–25)
4. *Estimated lowest daily kcal intake* = best estimate of lowest daily kcal intake at entry to service, in preceding 30 days (Estimate by Dietitian).
5. *Estimated average daily kcal intake* = best estimate of average daily kcal intake in preceding 5 days, at entry, 30 & 60 days. (Estimate by Dietitian).
6. *Dietary phosphate intake* = whether or not the patient was assessed to be consuming sufficient phosphate (with or without supplementation) intake in preceding 30 days. (Estimate by Dietitian).
7. *Heart rate* = lowest heart rate, beats per minute, during preceding 30 days (normal range = 60–100 bpm)
8. *Systolic BP* = lowest systolic BP (sitting, standing or lying) mmHg, during preceding 30 days (normal range = 90–140 mmHg)
9. *Sodium* = lowest sodium level, during preceding 30 days (normal range = 135–145 mmol/L)

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10. *Potassium* = lowest potassium level, during preceding 30 days (normal range = 3.6–5 mmol/L)
11. *Lowest Bicarbonate* = lowest bicarbonate level, during preceding 30 days (normal range = 22–30 mmol/L)
12. *Highest bicarbonate* = highest bicarbonate level, during preceding 30 days (normal range = 22–30 mmol/L)
13. *Lowest creatinine* = lowest creatinine level, during preceding 30 days (normal range = 60–120 μmol/L)
14. *Highest creatinine* = highest Creatinine level, during preceding 30 days (normal range = 60–120 μmol/L)
15. *Lowest urea* = lowest urea level, during preceding 30 days (normal range = 2.5–6.6 mmol/L)
16. *Highest urea* = highest urea level, during preceding 30 days (normal range = 2.5–6.6 mmol/L)
17. *Calcium* = lowest calcium level, during preceding 30 days (normal range = 2.1–2.6 mmol/L)
18. *Phosphate* = lowest Phosphate level, during preceding 30 days (normal range = 0.8–1.4 mmol/L)
19. *Magnesium* = lowest magnesium level, during preceding 30 days (normal range = 0.7–1.00 mmol/L)
20. *ALT* = highest ALT level, during preceding 30 days (normal range = 10–50 U/L)
21. *Alk Phos* = highest Alk Phos level, during preceding 30 days (normal range = 40–125 U/L)
22. *Bilirubin* = highest bilirubin level, during preceding 30 days (normal range = 3–21 μmol/L)
23. *Gamma GT* = highest gamma GT level, during preceding 30 days (normal range = 0–51 U/L)
24. *Creatine Kinase* (*CK*) = highest CK level, during preceding 30 days (normal range = 30–135 U/L)
25. *Albumin* = lowest albumin level, during preceding 30 days (normal range = 30–45 g/L)
26. *Random glucose level* = lowest random glucose level in preceding 30 days (normal range 4.4–6.1 mmol/L)
27. Lowest WCC/WBC = lowest WBC level, during preceding 30 days (normal range = 4–11 $\times$ 10^9/L)
28. Highest WCC/WBC = highest WBC level, during preceding 30 days (normal range = 4–11 $\times$ 10^9/L)
29. Lowest neutrophils = lowest or highest neutrophil level, during preceding 30 days (normal range = 2–7.5 $\times$ 10^9/L)
30. Highest neutrophils = lowest or highest neutrophil level, during preceding 30 days (normal range = 2–7.5 $\times$ 10^9/L)
31. Hb = lowest Hb level, during preceding 30 days (normal range = F 115–165 g/L)
32. Free T4 = lowest T4 level, during preceding 30 days (normal range = 9–21 mmol/L)
33. *DEXA T-score spine* = T-score spine, at *T1* ± 1 year
34. *Vegan diet* = vegan diet (no meat, fish or dairy products), during preceding 30 days.
35. *Bing-purge behaviour* = evidence of any binge-purge behaviour in preceding 30 days.
36. *Alcohol use* = evidence of alcohol use in excess of 14 units per week, during the preceding 30 days.
37. *Illegal substance use* = evidence of any use of illegal substances during the preceding 30 days.
38. *Diabetes* = a diagnosis of insulin dependent diabetes.

Appendix B. Definitions of significant medical complications (SMCs)

1. *SMC1 hypophosphataemia* = any serum phosphate level below 0.45 mmol/L
2. *SMC2 loss of consciousness* = any witnessed objectively verified loss of consciousness for any reason
3. *SMC3 cardiac failure* = clinical diagnosis by doctor
4. *SMC4 arrhythmia* = arrhythmia diagnosed (atrial fibrillation, atrial flutter, AV-nodal re-entrant tachycardia, ventricular tachycardia) with objective evidence on ECG
5. *SMC5 cardiac arrest* = cardiac arrest, with objective evidence
6. *SMC6 myocardial infarction* = MI diagnosed with objective evidence
7. *SMC7 pneumothorax* = diagnosis with radiological evidence
8. *SMC8 pneumonia* = clinical diagnosis with radiological confirmation
9. *SMC9 sepsis syndrome* = generalised infection involving >1 organ system and with positive blood cultures
10. *SMC10 renal failure* = clinical diagnosis with associated blood test abnormalities
11. *SMC11 significant hepatic dysfunction* = any raised LFTs >3× normal
12. *SMC12 gastro-oesophageal perforation* = diagnosis with radiological evidence
13. *SMC13 bowel obstruction* = diagnosis with radiological evidence
14. *SM14 hypothermia* = body temp below 34°C on two consecutive occasions
15. *SMC15 severe hyponatraemia* = <120 mmol/L
16. *SMC16 severe hypokalaemia* = <2.5 mmol/L
17. SMC17 *severe low bicarbonate* = <15 mmol/L
18. *SMC18 severe hypoglycaemia* = <2.2 mmol/L
19. *SMC19 severe emaciation* = BMI <10
20. *SMC20 fracture* = radiological evidence of fracture (excluding stress fractures)
21. SMC21 *death*

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