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ORIGINAL ARTICLE

Scurvy and vitamin C deficiency in an Australian tertiary children's hospital

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Aim: We aimed to investigate the frequency of vitamin C deficiency scurvy in the Australian paediatric context, describe cohorts at risk, and identify factors associated with development of symptoms in children with vitamin C deficiency. We also aimed to propose a management guideline for children with features of scurvy.

Method: A retrospective study was done at a tertiary paediatric hospital in Australia over a three-year period, from August 2019 to July 2022. Children from birth to 18 years old, whose vitamin C levels were low (<23 μmol/L), were included. Data extracted from hospital medical records included demographics, weight, co-morbidities, eating disorder diagnoses, clinical features, investigations and treatment. Descriptive statistics and risk statistics were performed.

Results: In a cohort of 887 patients who had their vitamin C levels checked, we identified 272 (31%) who had a vitamin C level <23 μmol/L. Of these, 13 (5%) were symptomatic of vitamin C deficiency and 19 (7%) may have been symptomatic. In patients with vitamin C deficiency, 248 (91%) had comorbidities, neurodevelopmental disorders being most common, and 176 (65%) had restricted eating. When the asymptomatic and symptomatic groups were compared, in the symptomatic group, there was a significantly lower vitamin C level and disordered eating related to autism spectrum disorders was more common.

Conclusion: In order to avoid delayed diagnoses and unnecessary investigations, clinicians should be familiar with symptoms of scurvy and perform a dietary assessment, vitamin C assay, and commence empiric vitamin C supplementation where appropriate.

Key words: children; paediatrics; scurvy; vitamin C deficiency.

What is already known on this topic

1 Scurvy is more common in children with feeding disorders and restricted diets.
2 These restricted diets usually occur in children with comorbidities, most commonly neurodevelopmental disorders.
3 Unless there is clinical suspicion, the diagnosis of scurvy is often delayed.

What this study adds

1 Asymptomatic vitamin C deficiency and scurvy are not uncommon in patients tested for nutritional deficiencies in an Australian tertiary paediatric hospital.
2 Most patients with vitamin C deficiency have a normal weight and many have co-existing nutritional deficiencies.
3 Patients with symptoms of scurvy should have a dietary assessment, vitamin C assay and empiric commencement of vitamin C supplementation.

There has been an exponential rise in children with eating and feeding problems since the pandemic.[1] Although reasons for this are unclear, a range of factors are known to contribute to disordered eating including anatomical, gastro-intestinal, motor, sensory and psycho-social problems. Eating and feeding problems are more common in those with neurodevelopmental disorders, such as autism spectrum disorder (ASD).[2] Although restricted variety of food does not necessarily impact growth, limitations in either variety or amount of food can lead to micronutrient deficiencies.[3] Symptomatic vitamin C deficiency, known as scurvy, is one example of a micronutrient deficiency, which can result in significant morbidity, hospitalisation and invasive investigations. When it is recognised and treated, scurvy responds rapidly to vitamin C supplements.[4,5]

There is recent literature linking scurvy to children with feeding disorders and restricted diets. These restricted diets most

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frequently occur in the context of children with avoidant/restrictive food intake disorder (ARFID),[6] anorexia nervosa,[7] neurodevelopmental disorders in particular ASD,[6,8] cerebral palsy,[9,10] multiple food allergies[8] and those receiving chemotherapy.[11] Scurvy has also been documented in children without disorders, but is less common.[7,12,13] Despite the literature that is available, recent studies describing vitamin C deficiency and scurvy in Australian children are not available. The aim of this study was to investigate the frequency of vitamin C deficiency in Australian children, describe cohorts at risk, and identify factors associated with the development of symptoms in children with vitamin C deficiency. Based on our findings, we aimed to propose a management guideline for children with features of scurvy, in order to limit unnecessary hospitalisation and investigations.

Method

Study design

A retrospective study at a tertiary paediatric hospital in Australia over a three-year period, from August 2019 until July 2022.

Participants

Children, including inpatients and outpatients, from birth to 18 years old, whose vitamin C levels were low (<23 μmol/L), were included. Eligible patients were identified by screening all vitamin C assay results during the study period using the hospital electronic medical records (EMR) (Epic Hyperspace, Verona, WI, USA). Although the reference range for the assay used at our institution is 28–120 μmol/L, a vitamin C level of less than 23 μmol/L was used as a cutoff, consistent with previous literature.[8,11] Patients who were in the care of an external provider were excluded due to insufficient clinical information.

Vitamin C assays

At our institution, samples taken for vitamin C assay are protected from light and transported promptly to the laboratory on ice (collection to received time >90% within 35 min, >97.5% within 1 h). Samples are immediately separated at 4°C and frozen at −80°C. Samples remain frozen until analysis at the referral laboratory. The collection service and receiving laboratory (at our institution) and referral laboratory are both accredited to ISO 15189, the international standard for medical laboratories.

Data collection

Data were extracted from the EMR and securely stored using Research Electronic Data Capture database software.[14] The data extracted included demographic data, weight, clinical features, comorbidities, dietary/feeding history, investigation results, treatment and response to treatment. Disordered eating was determined if patients had a diagnosis of ARFID, anorexia nervosa, bulimia nervosa, oral aversion or were reported to be fussy eaters. Clinical features of scurvy that were noted included bone pain, limp, bruising, folliculitis, bleeding gums and neurological symptoms, such as irritability, mood changes and lethargy. Patients were considered symptomatic of scurvy if there was no alternative cause for symptoms. Patients were considered indeterminate of scurvy if there were potential other causes for symptoms. The need for hospital admission, including the duration of the admission, was recorded. The study was reviewed by The Royal Children's Hospital Human Research Ethics Committee (HREC) (study number QA/89635/RCHM-2022).

Statistics

Stata 16 (Statacorp, College Station, TX, USA) was used for all analyses. For categorical variables, data were summarised as proportions and for continuous variables, data were summarised as medians with an interquartile range (IQR). Risk differences (RDs) with 90% confidence intervals (CI) were calculated. A P value <0.0017 was considered statistically significant after Bonferroni correction for multiple comparisons.

Results

During the 3-year study period, 887 patients had a vitamin C level measured. Of these, 272 (31%) patients fulfilled the study criteria of a low vitamin C level of less than 23 μmol/L. Of 272 patients with a low vitamin C level, 13 (5%) were clearly symptomatic of vitamin C deficiency with a diagnosis of scurvy (symptomatic group) and 19 (7%) may have been symptomatic (indeterminate group). The remaining 240 (88%) patients were asymptomatic (asymptomatic group) (Table 1) (Fig. 1).

Of the 272 patients with a low vitamin C level, the median vitamin C level was 8 μmol/L (IQR <5 to 14). The median age was 9.6 years (IQR 4.8 to 13.2), with 185 (68%) children age 6 years or older. There were 113 (42%) girls, 10 (4%) of Aboriginal or Torres Strait Islander background, and 65 (24%) from a non-English-speaking background. The median weight was on the 27th percentile (IQR 3 to 76), with 73 (27%) below the 5th percentile for weight. There were 248 (91%) patients with underlying comorbidities, most commonly neurodevelopmental disorders, reported in 145 (53%) patients. Seventy-four (27%) patients had a diagnosis of ASD and 51 (19%) patients had a diagnosis of global developmental delay or cognitive impairment. One hundred and seventy-six (65%) patients with a low vitamin C level were documented to have disordered eating. Seventy-two (26%) patients did not have a diagnosed eating disorder but were described by their parents as being fussy eaters. Thirty (11%) patients had disordered eating related to an ASD diagnosis.

Other nutritional investigations were documented in a high proportion of patients with a low vitamin C level (Table 2). There were 91/261 (35%) with a low haemoglobin level. Additionally, 116/230 (50%) had a low vitamin D level, while 129/194 (66%) had a low zinc level.

Symptomatic group

In the symptomatic group, the vitamin C level at diagnosis was <5 μmol/L for 11 of the 13 patients. For the two remaining patients, vitamin C levels were 5 and 10 μmol/L. The diagnosis of scurvy was based on clinical features combined with a low vitamin C level, and in eight cases, consistent imaging investigations. Of the 13 symptomatic patients, nine (61%) had a weight

Table 1 Demographics and clinical features of symptomatic and asymptomatic patients.

	Vitamin C deficiency (total = 272), *n* (%)	Symptomatic and asymptomatic (total* = 253), *n* (%)	Symptomatic (total = 13), *n* (%)	Asymptomatic (total = 240), *n* (%)	Risk difference (95% CI)	*P* value
Age						
0 to 5 years	87 (32)	80 (32)	4 (31)	76 (32)	−0.01 (−0.07 to 0.05)	0.69
6 to 10 years	65 (24)	63 (25)	2 (15)	61 (25)	−0.03 (−0.09 to 0.03)	0.32
>10 years	120 (44)	110 (43)	7 (54)	103 (43)	Reference category	
Sex (female)	113 (42)	105 (42)	6 (46)	99 (41)	0.1 (−0.2 to 0.3)	0.7
Weight centiles						
<5th centile	73 (27)	67 (26)	3 (23)	64 (27)	−0.04 (−0.12 to 0.05)	0.4
5th to 85th centile	140 (51)	130 (51)	9 (69)	121 (50)	−0.05 (−0.15 to 0.03)	0.2
>85th centile	59 (22)	56 (22)	1 (8)	55 (23)	−0.05 (−0.13 to 0.04)	0.3
Comorbidities	248 (91)	232 (92)	9 (69)	223 (93)	−0.23 (−0.49 to 0.02)	0.003
Developmental comorbidities	146 (54)	137 (54)	8 (62)	129 (54)	0.08 (−0.19 to 0.35)	0.6
ASD	74 (27)	71 (28)	8 (62)	63 (26)	0.35 (0.08 to 0.62)	0.0058
Anxiety disorder	17 (6)	14 (6)	1 (8)	13 (5)	0.02 (−0.12 to 0.17)	0.7
GDD/Cognitive impairment	51 (19)	50 (20)	3 (23)	47 (20)	0.03 (−0.20 to 0.27)	0.8
Cerebral palsy	25 (9)	23 (9)	0	23 (10)	−0.10 (−0.13 to −0.05)	0.2
Other	29 (11)	26 (10)	1 (8)	25 (10)	−0.03 (−0.18 to 0.12)	0.7
Gastrointestinal	60 (22)	58 (23)	2 (15)	56 (23)	−0.02 (−0.17 to 0.13)	0.8
Neurological	52 (19)	49 (19)	1 (8)	48 (20)	−0.12 (−0.28 to 0.03)	22 (21)
Endocrine	14 (5)	13 (5)	1 (8)	12 (5)	0.03 (−0.12 to 0.17)	0.7
Respiratory	25 (9)	25 (10)	1 (8)	24 (10)	−0.02 (−0.17 to 0.13)	0.8
Cardiac	16 (6)	16 (6)	2 (15)	14 (6)	0.10 (−0.10 to 0.29)	5 (5)
Oncological	6 (2)	6 (2)	0	6 (3)	−0.02 (−0.04 to −0.01)	0.6
Disordered eating	169 (62)	158 (62)	12 (92)	146 (61)	0.31 (0.16 to 0.47)	0.02
Fussy eater†	72 (26)	67 (26)	5 (38)	62 (26)	0.13 (−0.14 to 0.40)	0.3
Disordered eating related to ASD	30 (11)	28 (11)	5 (38)	23 (10)	0.29 (0.02 to 0.56)	*0.0012*
ARFID	15 (6)	14 (6)	2 (15)	12 (5)	0.10 (−0.09 to 0.30)	0.1
Oral aversion	8 (3)	8 (3)	0	8 (3)	−0.03 (−0.05 to 0.01)	0.5
Anorexia nervosa	6 (2)	6 (2)	0	6 (3)	−0.03 (−0.04 to −0.01)	0.5
Bulimia nervosa	1 (0.4)	1 (0.4)	0	1 (0.4)	−0.00 (−0.12 to 0.00)	0.8
Other	45 (17)	42 (17)	0	42 (18)	−0.18 (−0.22 to −0.13)	0.1
Vit C, <5 μmol/L	86 (32)	80 (32)	10 (77)	70 (29)	0.48 (0.24 to 0.71)	*0.0003*
Vit C, 5 to 23 μmol/L	186 (68)	173 (68)	3 (23)	170 (71)	0.48 (0.24 to 0.71)	*0.0003*

* Nineteen patients (indeterminate group) excluded from analysis. † Documented as 'fussy eater' or restricted eating in absence of other conditions and without a physical disability, *P* value <0.0017 deemed statistically significant after Bonferroni correction for multiple comparisons. ARFID, avoidant/restrictive food intake disorder; ASD, autism spectrum disorder; CI, confidence interval; GDD, global developmental delay; Vit C, vitamin C.

percentile between the 5th and 85th percentile. Nine (69%) symptomatic patients had comorbidities, all of which were neurodevelopmental diagnoses associated with feeding problems,

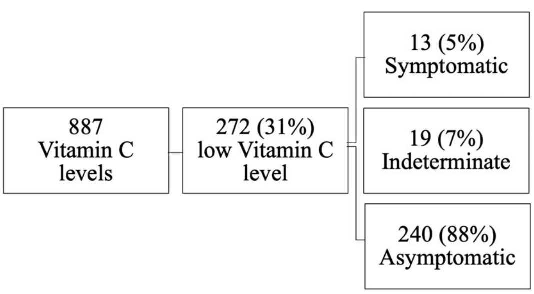

Fig. 1 Patient numbers.

and four (31%) symptomatic patients had no comorbidities but were documented to have disordered eating. The most commonly reported symptoms included bone pain, limp, bleeding gums and bruising. Twelve (92%) patients presented with bone pain or limp. Ten (77%) patients had multisystem features of scurvy including skeletal, soft tissue and neurological system involvement. Three (23%) patients appeared to have symptoms affecting a single system, which may have been related to failure to report or document other symptoms. Nine symptomatic patients required admission to hospital, with a median admission duration of 6 days (IQR 2 to 48 days). As part of the initial diagnostic assessment, the symptomatic group had a number of investigations. The erythrocyte sedimentation rate (ESR) was measured in nine patients and raised in eight of these; the median ESR level was 29 mm/h (IQR 22 to 44) (reference range 2–10 mm/h). The C-reactive protein (CRP) was measured in nine patients and

Table 2 Co-existing nutritional deficiencies.

Analysis of risk differences of asymptomatic and symptomatic* groups.

	Total, *n* (%)	Symptomatic, *n* (%)	Asymptomatic, *n* (%)	Risk difference (95% CI)	*P* value
Low haemoglobin Dependent on age (g/L)	86/244 (35)	9/13 (69)	77/231 (33)	0.36 (0.10 to 0.62)	0.008
Low vitamin B12 <38 pmol/L	11/213 (5)	1/12 (8)	10/201 (5)	0.03 (−0.13 to 0.19)	0.6
Low folate <1900 nmol/L	21/183 (11)	2/22 (9)	19/174 (11)	0.11 (−0.16 to 0.39)	0.3
Low vitamin D <50 nmol/L	106/214 (50)	5/13 (38)	101/200 (50)	−0.12 (−0.39 to 0.15)	0.4
Low ferritin <11 μg/L	19/220 (9)	2/13 (15)	17/207 (8)	0.07 (−0.12 to 0.27)	0.37
Low zinc <9.9 μmol/L	121/184 (66)	9/9 (100)	112/175 (64)	0.36 (0.29 to 0.43)	0.03
Low vitamin A <0.6 μmol/L	15/147 (10)	4/7 (57)	11/140 (8)	0.49 (0.12 to 0.86)	<0.001

* Nineteen patients (indeterminate group) excluded from analysis, *P* value <0.0017 deemed statistically significant after Bonferroni correction for multiple comparisons, denominator varied due to varying numbers of patients tested for co-existing nutritional deficiencies. CI, confidence interval.

raised in four; the median CRP was 14 mg/L (IQR 9 to 18) (reference range <5 mg/L). Eleven (85%) symptomatic patients had imaging investigations; eight (62%) patients had MRI scans and four (31%) patients had bone scans, all of which were abnormal. Scurvy was raised as a differential diagnosis by the reporting radiologist in six of the eight MRI scans, with an additional MRI report suggesting the possibility of a metabolic diagnosis in view of the diffuse infiltrative marrow process. Three patients had bone marrow aspirates and one patient had a bone biopsy. In the symptomatic group, five patients were treated with intravenous vitamin C supplements and subsequently oral supplements; eight patients were initially treated with oral vitamin C supplements. Several patients were given dietary supplemental preparations in addition to vitamin C supplements. In patients treated with intravenous vitamin C supplements, there was wide variability in the dose and number of doses prescribed, ranging from two to seven doses. Similarly, prescribing practices for oral vitamin C were variable with different doses (between 375 mg and 1.5 g daily) and frequency of doses (once or three times daily) prescribed. In most symptomatic cases, the response to treatment was not clearly documented, but five patients improved within 1 week, two patients in 2 weeks, and one patient in 3 weeks. In five patients, the response to treatment was not documented.

Indeterminate group

There were 19 (7%) patients with a low vitamin C level, who may have had symptoms attributable to vitamin C deficiency. In these cases, it was possible that the symptoms were consistent with scurvy or secondary to the patients' comorbidities. In the indeterminate group, the median vitamin C level at diagnosis was 8 μmol/L (IQR <5 to 15).

Comparison between with symptomatic and asymptomatic groups

The symptomatic and asymptomatic groups were compared to determine if there were factors associated with the development of symptoms in children with vitamin C deficiency. There was no significant difference in patient groups in terms of demographics or weight. There was a significant difference in the vitamin C levels, which were lower in the symptomatic group (symptomatic group vitamin C median <5 μmol/L (IQR <5 to <5); asymptomatic group vitamin C median 8 μmol/L (IQR <5 to 15) (*P* value 0.001)). There was also a significant difference between the symptomatic and asymptomatic groups, in disordered eating related to ASD, which was more common in the symptomatic group (symptomatic group 5/13 (38%); asymptomatic group 23/240 (10%) (*P* value 0.0012)). The vitamin A level was lower in the symptomatic group, but the significance of this is unclear due to few samples.

Discussion

Our study highlights how common a low vitamin C level is among children presenting to a tertiary hospital, both in the outpatient and inpatient clinical service. During the 3-year study period, almost a third of the children who had their vitamin C level tested, had a low vitamin C level. Of these, up to 12% were symptomatic of scurvy.

Most of the previous literature describing paediatric scurvy is limited to case reports and case series, with a few larger retrospective studies.[8,11,15] One study reported that 32/151 (21.2%) vitamin C levels measured at their institution between 2011 and 2015 were low (≤23 μmol/L),[11] which is lower than the prevalence in our study population. An earlier American nationwide report documented that the prevalence of vitamin C deficiency was <2% in children aged 6–11 years and <4% in adolescents.[16] While there may be multiple factors contributing to this apparent increase in prevalence, it may reflect the rise in paediatric feeding and eating disorders, with resulting micronutrient deficiencies such as scurvy. Our cohort consisted of children with complex medical and developmental disorders, with associated dietary restrictions, accounting for a high prevalence of nutritional deficiencies, including vitamin C deficiency. Although vitamin C is unstable and measurement requires careful handling and appropriate analysis to ensure accuracy of results,[17] our receiving and referral laboratories follow clear processes (as stated in methods), in order to reduce inaccurate measurements. In a retrospective study of a largely adult population in Sydney, New South Wales, over a 4-year period, 7040/12934 (54%) were found to have low vitamin C, although this study did not differentiate between those with symptoms and those without. Similar to our study, the authors observed that vitamin C deficiency is likely to be under-recognised by care providers.[18]

Consistent with previous literature, our study demonstrates that the majority of children with vitamin C deficiency have co-existing neurodevelopmental diagnoses, in particular ASD.[6,15,19] In addition, paediatric patients with vitamin C deficiency commonly have a background of feeding or eating disorders, and a restricted diet.[19] Despite this correlation between scurvy and disordered eating, our research showed that most patients with vitamin C deficiency had a normal weight, which is consistent with previous studies.[6,19] Yule *et al*. reported that most patients with ARFID are not underweight and would benefit from screening for adequacy of micronutrient intake.[19] This emphasises the importance of assessment of dietary variety, regardless of a patient's weight, particularly in patients with neurodevelopmental disorders.

At least two thirds of patients in our cohort with a low vitamin C level had co-existing nutritional deficiencies. Yule *et al*. similarly noted that a significant proportion of their cohort of 53 children with scurvy and ASD had concurrent vitamin A, thiamine, vitamin B12, vitamin D, calcium, folate or iron deficiencies.[19] This finding emphasises the need to screen for additional nutritional deficiencies when one deficiency is present. This is important, as different nutritional deficiencies can manifest with similar clinical features.

When we compared patient groups with symptomatic and asymptomatic vitamin C deficiency, we demonstrated that the vitamin C level was significantly lower in the symptomatic group. Unfortunately, the duration of vitamin C deficiency was unknown in all cases, meaning that we were not able to compare duration of vitamin C deficiency in symptomatic and asymptomatic patient groups. A longer duration of vitamin C deficiency is considered a risk factor for the development of symptoms, as vitamin C is water soluble and little is stored in the body.[19] Depending on body stores, signs can appear within 1 month of little or no vitamin C intake (below 10 mg/day).[20]

Similar to previous reports, many of our symptomatic cohort had multiple subspeciality consultations and investigations, due to diagnostic uncertainty.[8,21–23] Symptomatic patients were consulted by orthopaedic, rheumatology, infectious diseases and oncology teams, and some had costly and invasive investigations including MRI scans, bone marrow aspirates or bone biopsies. In some symptomatic patients, consideration of the diagnosis and a trial of treatment, could have precluded further investigations and shortened hospital admissions, particularly in light of the rapid response of scurvy to treatment with vitamin C supplementation.[21,22] In order to avoid diagnostic delays in at-risk patients with clinical features consistent with scurvy, where appropriate, we propose an initial trial of vitamin C supplementation and close follow-up, prior to invasive investigations (Fig. 2). The literature is reassuring that vitamin C has low toxicity and that high levels should not result in significant adverse side effects.[20,23]

Our study has a number of limitations. This study was conducted at a single tertiary level healthcare institution in a developed country, limiting generalisability. In addition, there were few symptomatic patients identified retrospectively over the 3-year study period. Symptoms were potentially not documented or under-reported due to developmental disabilities. Lastly, there remains a possibility that the proportion with asymptomatic vitamin C deficiency is over-estimated due to fragility of vitamin C assays, despite measures being taken to reduce this risk. A prospective study on vitamin C deficiency and scurvy is needed to understand if duration of vitamin C deficiency impacts the

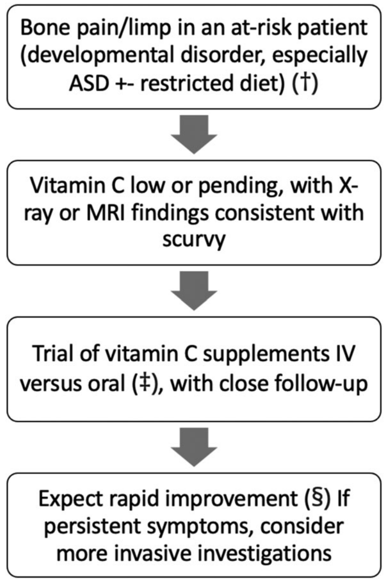

Fig. 2 Proposed management guideline for at-risk patients with clinical features consistent with scurvy. †Investigations for diagnoses that require urgent treatment should not be delayed. ‡Vitamin C supplemental dose recommendations: Infants, children and adolescents: Limited data: Oral, IM, IV: Initial: 100 to 300 mg/day in divided doses for 1 week followed by 100 mg/day until normalisation of tissue saturation (~1 to 3 months).[24] Manufacturer's labelling: Ascor: Infants ≥5 months: IV: 50 mg daily for 1 week. Children <11 years: IV: 100 mg daily for 1 week. Children ≥11 years: IV: 200 mg daily for 1 week.[25] §Response to vitamin C supplements: All symptoms usually resolve in 3–5 days, and most signs, including bruising, perifollicular haemorrhages and gingival bleeding usually improve within resolve in 1–2 weeks. Complete recovery should be anticipated after approximately 3 months of regular vitamin C supplementation.[21,22]

development of symptoms and to determine how rapidly symptoms resolve with vitamin C supplementation.

Our study highlights that asymptomatic vitamin C deficiency and scurvy are not uncommon and need to be considered in patients with neurodevelopmental disorders and restricted diets regardless of their weight percentiles. In order to avoid unnecessary invasive investigations and delayed treatment, clinicians should be familiar with the symptoms of scurvy and perform a dietary assessment, vitamin C assay and be prepared to commence empiric vitamin C supplementation where appropriate.

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