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Variations in the management of acute illness in children with congenital adrenal hyperplasia: An audit of three paediatric hospitals

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Abstract

Objective: Episodes of acute adrenal insufficiency (AI)/adrenal crises (AC) are a serious consequence of congenital adrenal hyperplasia (CAH). This study aimed to assess morbidity from acute illness in CAH and identify factors associated with use of IV hydrocortisone, admission and diagnosis of an AC.

Method: An audit of acute illness presentations among children with CAH to paediatric hospitals in New South Wales, Australia, between 2000 and 2015.

Results: There were 321 acute presentations among 74 children with CAH. Two thirds (66.7%, n=214) of these resulted in admission and 49.2% (n=158) of the patients received intravenous (IV) hydrocortisone. An AC was diagnosed in (9.0%). Prior to presentation, 64.2% (n=206) had used oral stress dosing and 22.1% (n=71) had been given intramuscular (IM) hydrocortisone. Vomiting was recorded in 61.1% (n=196), 32.7% (n=64) of whom had used IM hydrocortisone. Admission, AC diagnosis, and use of stress dosing varied significantly between hospitals. IM use varied from 7.0% in one metropolitan hospital to 45.8% in the regional hospital. Children aged up to 12 months had the lowest levels of stress dosing and IV hydrocortisone administration. A higher number of prior hospital attendances for acute illness was associated with increased use of IM hydrocortisone.

Conclusion: Pre-hospital and in-hospital management of children with CAH can vary between health services. Children under 12 months have lower levels of stress dosing prior to hospital than other age groups. Experience with acute episodes improves self-management of CAH in the context of acute illness in educated patient populations.

Introduction

Congenital adrenal hyperplasia (CAH) is the most common cause of primary adrenal insufficiency (AI) in children (1-3). In Australia, the estimated CAH incidence is about one in 15,000, which is comparable to that in other countries (1-4). Approximately 95% of affected children have a deficiency of the enzyme 21-hydroxylase from the autosomal inheritance of inactivating mutations in both *CYP21A2* alleles. This results in an impaired biosynthesis and secretion of cortisol, with or without aldosterone deficiency, in addition to elevated levels of adrenal androgens (3,5-7). Treatment of CAH involves the administration of glucocorticoid, both as a replacement therapy and to suppress ACTH stimulation, thereby reducing excess adrenal androgen production (3,5,6). Fludrocortisone is also used to treat aldosterone deficiency.

All children with CAH are at higher risk of morbidity and mortality, some of which is attributable to potentially fatal adrenal crises (ACs) (5,6,8-10). These acute events have an estimated incidence of between 4.9 and 10 ACs per 100 patient years (10,11). ACs are characterised by hypotension, electrolyte abnormalities, hypoglycaemia, vomiting, abdominal pain and a reduced level of consciousness. They occur when the physiological requirement for cortisol is greater than the amount in the circulation, typically during periods of physiological stress, such as an infection (1,3,5,7). Children with the more severe salt-wasting phenotypes are at a heightened AC risk. Those with less severe forms are also vulnerable during stress due to glucocorticoid-related suppression of the hypothalamic-pituitary axis (12).

Cortisol dose escalation is regarded as the cornerstone of AC prevention in all forms of AI, including CAH (13-16). Parents and guardians are taught to increase their child's dose of oral glucocorticoid during intercurrent illness or to administer an intramuscular (IM) injection when oral glucocorticoid therapy cannot be taken or absorbed. However, efforts by health professionals to educate carers and patients about the importance of stress dosing have not resulted in the elimination of ACs (17-19). Indeed, recent studies have shown that AC events continue to occur, even among well-educated AI patients (17,18).

The reasons for the continued incidence of ACs in children with CAH are unknown. Various factors other than the effectiveness of AC prevention programs, such as psychosocial and cultural factors, health service availability, and clinical practices have been postulated but the basis for their continued occurrence remains unclear (9,17,20,21). The aim of this study was to investigate the frequency, causes, severity and management of acute illness in a large sample of patients with CAH who presented to hospital.

Subjects and Methods

Three paediatric hospitals provide specialist healthcare to the 1.9 million children (22) in the state of New South Wales, Australia on a referral basis, in addition to providing general and specialist paediatric services to their local community. Two of these hospitals (A and B) are in metropolitan Sydney and the third (Hospital C) is in a large regional centre. Hospitals A and B have a practice guideline, which consists of a protocol for acute AI/AC management that includes instructions on the immediate administration of IM or IV hydrocortisone, fluid resuscitation and specific treatment of hypoglycaemia and abnormal electrolytes. By comparison, Hospital C uses a specific AI management sheet for each patient that is developed by their regular paediatric endocrinologist and paediatric endocrine nurse educator. Information on all episodes of care in these hospitals is stored according to the patient's medical record number (MRN) and includes demographic details; the principal diagnosis; whether the patient was treated in Accident and Emergency only or was admitted to hospital; and all comorbid diagnoses, which are coded according to the Australian modification of the International Statistical Classification of Diseases and Related Problems (ICD-10) (23).

The MRNs of all children in each hospital who had at least one admission in which there was a record of a principal or comorbid diagnosis coded under the rubric E25.0 *(*Adrenogenital disorders associated with enzyme deficiency) were identified (23). All attendances at Accident and Emergency and admissions to hospital between January 2000 and December 2015 for patients up to 18 years of age were included. Only those children who were on glucocorticoid replacement therapy and had an

acute medical (non-surgical) illness that resulted in an unplanned attendance at hospital were selected for this analysis.

All records were accessed electronically except for some of the earliest records for Hospital B, which were paper-based. Demographic information and data on the reason for attendance, type and length of stay, presenting symptoms and signs, diagnosis, use of stress dosing and management were collected.

Ethics approval was granted by the Human Research and Ethics Committees of the Sydney Children's Hospital Network (SCHN), John Hunter Children's Hospital, and The University of Notre Dame, Australia.

Data management

Some symptoms were not documented in some medical records, possibly through omission. Where this information was not found, it was assumed that the symptom was not part of that child's presenting problem and that symptom was classified as absent. Similarly, where there was no blood chemistry, it was assumed that this represented a clinical decision not to take blood as the child was relatively well and these records were coded as normal. Hypotension was classified as either a blood pressure that was lower than the appropriate age-related boundary or a capillary return time of greater than 3 seconds and, where these values were absent, it was considered that the blood pressure was normal. Hyperkalaemia was defined as a serum potassium of greater than 5.0mmol/L, hyponatraemia as a serum sodium lower than 135mmol/L and hypoglycaemia as a blood glucose of less than 3.5mmol/L (24). In this analysis, an AC, which is usually characterised by hypotension, reduced consciousness and electrolyte abnormalities, was classified as present when this diagnosis was made by the treating doctor and entered into the medical record (14). To add further information a variable representing the number of typical AC symptoms for each attendance was calculated. This score comprised a count for each of hypotension, vomiting, diarrhoea, hyperkalaemia, hyponatraemia, hypoglycaemia, and reduced consciousness for a possible score of 7 points.

Stress dosing (either oral or IM) in this analysis refers to any administration prior to arrival at hospital. Fifty (15.6%) records did not include any information about the use of stress dosing. The proportion of complete records differed between the hospitals, with satisfactory documentation for 96.3% (n=103) in Hospital C, 79.0% (n=124) for Hospital A and 77.2% (n=40) for Hospital B. Where these data were missing, that record was coded as not stress dosed. One record stated that stress dosing had been used but the type was not specified.

Statistical analysis

Chi square and independent t-tests were used to assess group differences. Stepwise logistic regression models were developed to identify predictors of: an AC diagnosis; hospital admission; the use of any form of stress dose; oral stress dose use only; IM hydrocortisone administration; and the use of IV hydrocortisone in hospital. Statistical tests were conducted using SPSS (IBM SPSS Statistics for Mac, Version 24.0, Armonk, NY, USA). A P-value of <0.05 was considered significant.

Results

There were 321 presentations for treatment of an acute medical illness by 74 children with CAH during the study period, corresponding to a median of 3 (IQR 2-7) presentations per child. Fifty-nine (79.9%) of these children had salt-wasting CAH. Two-thirds (66.7%, n=214) of the presentations were to the metropolitan hospitals [157 (48.9%) to Hospital A and 57 (17.8%) to Hospital B] and the remainder (n=107, 33.3%) were to the regional hospital (C). Two-thirds (66.4%) of the attendances resulted in admission; IV hydrocortisone was administered to 158 (49.2%) patients; and the median length of stay was 2 (IQR 1-3) days. An AC was recorded in 29 (9.0%) cases. There were no in-hospital deaths; 8 (2.5%) children were admitted to an ICU; and one child developed a severe brain injury following hypoglycaemic seizure at home.

The median age of attendees was 3 (IQR 0-7) years. More than a third (39.3%, n=126) of the patients were in the age group 1-4 years (Table 1). An infection was diagnosed in 42.7% (n=137), with 52 (16.2%) having a diagnosis of gastroenteritis (Table 1). More infections were identified as viral (34.0%, n=109) than bacterial (5.3%, n=17). Hypotension was noted in 5.9% (n=19) and 11.8% (n=38) had reduced consciousness/unconsciousness. Hyponatraemia was more common than hyperkalaemia (12.8%, n=41 and 6.2%, n=20 respectively). Hypoglycaemia was identified in 27 (12.4%) of the patients and a seizure was reported in 13 (4.1%). The most common symptom was vomiting, which was reported in 196 (61.1%) of the attendances, while diarrhoea was recorded in 78 (24.3%) and a prodromal illness was noted in 189 (58.9%) (Table 1). The mean number of signs and symptoms per presentation to hospital was 1.21±0.94 and this did not differ significantly between the hospitals (Table 2). A diagnosis of AC was significantly associated with hypoglycaemia [24.1% (n=7) of those with an AC compared with 6.8% without (n=20), P<0.01]; a reduced level of consciousness/unconsciousness [36.8% (n=14) of patients with a reduced level consciousness were diagnosed with an AC compared with 5.3% (n=15) of those without (P<0.001)] and lethargy [62.1% (n=18) of AC patients were lethargic compared with 28.8% (n=84) of those who were not, P<0.001]. The mean number of signs and symptoms of AI was significantly higher in patients with an AC diagnosis than those without (1.93±1.00 vs. 1.14±0.90, p<0.001).

Stress dosing was used by 64.2% (n=206) of the patients; 41.7% (n=134) used oral glucocorticoid dose escalation only and 22.1% (n=71) used IM hydrocortisone with or without oral. Among patients with a prodromal illness, 68.8% (n=130) used stress doses, as did 74.0% (n=145) of those with a history of vomiting and 75.6% (n=59) of patients with diarrhoea (Table 3). One third (32.7%, n=64) of the children with vomiting were given IM hydrocortisone prior to hospital attendance, with 41.3% (n=81) using oral only (Table 3). Similarly, fewer patients with diarrhoea used IM hydrocortisone (24.4%, n=19) than oral (51.3%, n=40) (Table 3). IM hydrocortisone use was significantly associated with the diagnosis of an AC (18.3% (n=13) of patients using IM were classified as having an AC compared with 6.4% (n=16), p<0.01). By comparison, there was no

significant association between oral stress dose use or use of all types of stress dose and AC incidence (both $p>0.05$).

AC incidence did not differ by age group but use of stress dosing did ($P<0.02$), being used most commonly in children aged 1-4 years (73.0%, n=92). By comparison, both IM and IV hydrocortisone use varied significantly by age group ($p<0.04$ and <0.03, respectively), and were used more often in older patients (Table 1). Children aged 1-4 years had the highest levels of prodromal illness (67.5%, n=85) and the lowest proportion (58.7%, n=74) of admissions (Table 1). Hyperkalaemia was more common in children under 12 months (17.3%, n=14) (Table 1).

Admission for acute illness and use of stress dosing varied significantly by hospital ($p<0.001$ and $p<0.01$, respectively). Hospital C admitted the largest proportion (80.4%, n=86) of patients and had the highest proportion of patients using stress doses (75.7%, n=81) (Table 2). Patients who were admitted had a significantly higher mean number of signs and symptoms of AI than those who were treated as outpatients only (1.35±0.92 vs. 0.93±0.92,$p<0.001$) (Table 4). There were also substantial differences between the hospitals in the use of IM hydrocortisone ($p<0.001$), with 45.8% (n=49) of the patients at Hospital C using IM hydrocortisone compared with 7.0% (n=11) of the patients in Hospital A (Table 2). This difference was maintained even when only those records in which there was a definitive note of stress dosing were included (47.6% compared to 8.8%, $p<0.01$). ACs were most commonly recorded in patients attending Hospital C (15.9%, n=17) ($p<0.01$) and this hospital had the highest use of IV hydrocortisone (69.2%, n=74) ($p<0.001$).

Predictors of AC and CAH management

Logistic regression analysis showed that an AC diagnosis was significantly associated with two factors: the treating hospital [Hospital B vs A: OR (95% CI) 4.42 (1.25-15.65)] and Hospital C vs A: OR (95% CI) 4.63 (1.65-12.94)] and with the presence of a reduced level of consciousness/unconsciousness [OR (95% CI) 11.27 (4.57-27.80)] but not the number of AC signs

and symptoms (Table 5). Admission was also significantly associated with the treating hospital; number of signs and symptoms [OR (95% CI) 1.64 (1.24-2.17)]; and patient age (Table 5).

The use of any type of stress management strategy (either oral or IM) prior to hospital attendance was associated with the treating hospital; vomiting [OR (95% CI); 2.50 (1.52-4.10)]; and a diagnosis of gastroenteritis [OR (95% CI): 2.67 (1.17-6.09)] (Table 5). By comparison, oral stress dosing was associated with a prodromal illness [OR (95% CI) of 2.43 (1.49-3.96)] and hospital, with hospitals B and C having a lower likelihood of oral stress dosed patients than hospital A (Table 5).

IM hydrocortisone use was related to the number of previous attendances for an acute illness [(OR (95% CI) for each additional presentation: 1.11 (1.03-1.20)] but not the child's age. It was also predicted by a history of vomiting and gastroenteritis but was negatively associated with a history of prodromal illness (Table 4). The treating hospital was also predictive of IM hydrocortisone use, with the regional hospital having an OR of 9.65 (95% CI 4.43-21.00) relative to Hospital A (Table 5).

Hospital was also associated with IV hydrocortisone use [OR of 2.47 (95% CI: 1.39-4.37) for Hospital C compared with A]. In addition, vomiting was associated with IV hydrocortisone administration, as was the increased number of signs and symptoms of acute AI (Table 5). Increasing age was also associated with IV hydrocortisone treatment [OR for each year of age of 1.10 (95% CI 1.04-1.16)] (Table 5).

Discussion

The results of this comprehensive study of morbidity in paediatric CAH demonstrate that affected children experience significant illness episodes and that AC events still occur, being diagnosed in 9% of the hospital attendees. Two-thirds of the presentations resulted in admission and IV hydrocortisone was administered to half the children who attended hospital. Overall, glucocorticoid stress management of any kind was used by 64.2% of the patients, with exclusively oral dose escalation employed by 41.7% and parenteral hydrocortisone used by 22.1%. While there were some differences

in presentation and treatment according to the age of the child, greater variation was found between the hospitals with regards to both pre-hospital management and in-hospital care. Use of IM hydrocortisone was positively associated with the number of previous hospital attendances for acute care. Treatment in hospital was successful, as there were no in-hospital deaths, although one child sustained a neurological injury.

In this study, the incidence of ACs differed significantly between the hospitals. This variation may be due to patient factors, severity of illness, or more probably reflects differences between clinicians in the classification of AI-related illness as an AC. Disparities between clinicians appears in this study to be more likely given that the symptom scores did not differ between the hospitals, although differences in severity of individual symptoms were not assessed. The definition of an AC has been shown to vary substantially between studies in both adult and paediatric patients, encompassing the classification of relatively mild illness as an AC to the inclusion of only severe episodes (9,14-16). Cardiovascular compromise, manifest by hypotension or other features of circulatory collapse in children, is generally agreed to be the key physiological feature of an AC (14-16,25). However, in this study, hypotension was not significantly associated with an AC diagnosis and was reported in fewer than 6% of the patients. Electrolyte abnormalities and hypoglycaemia are also common features of an AC in children (15) but there was a relatively low incidence of those in this study. Although hypoglycaemia was found to be associated with an AC on bivariate analysis, it was not a significant predictor of AC in multivariate logistic regression models due to its association with reduced consciousness/unconsciousness, which was the only predictor, other than the treating hospital, of an AC diagnosis.

Patient age was associated with the management of symptomatic AI in this study, with stress management strategies used less commonly by parents of children under 12 months than those with older children. Similarly, IV hydrocortisone was given less often to children in the youngest age group than to older patients. This suggests that parents are less able to manage intercurrent illness in their very young children and are more reliant on assistance from a health service than parents of older children. These results are consistent with research by Fleming *et al*. (21), which demonstrated

that the parent's confidence and their ability to assess the severity of their child's illness were integral to their capacity to manage an acute illness episode. Improvement in the child's ability to articulate their symptoms with increasing age was also found to assist the family's management of the illness (21). Paradoxically, there were higher rates of IV hydrocortisone use in adolescents in this study, which may reflect non-adherence to their glucocorticoid regimens, as older children with CAH attempt to take a greater role in managing their own treatment (2,26).

While gastroenteritis was formally diagnosed in 16.2% of the children, vomiting which is also a symptom of symptomatic AI or an AC, was present in a substantially more (61.1%) patients and was significantly associated with hospital admission. Previous reviews have emphasised the importance of parenteral glucocorticoids in the context of vomiting, as this symptom can preclude or impair the absorption of oral therapy (15-17,26). Although vomiting was a predictor of both IM and IV hydrocortisone use in the present study, only a third (32.7%) of the children with this symptom were given parenteral hydrocortisone prior to presentation and approximately 40% were given oral hydrocortisone only, with some parents making repeated unsuccessful attempts at its administration. In this analysis, a record of a prodromal illness was associated with an increased use of oral stress dosing and a decreased use of parenteral therapy. As most of these illnesses were viral respiratory tract infections, this is consistent with recommended practice (3,15,16,19, 27). While the estimates of stress dosing cannot be used to infer the appropriateness of the decision in each circumstance in this study, the lower than expected use of IM hydrocortisone in the presence of vomiting suggests that there may be opportunities for improvement in pre-hospital management of ill children with CAH.

There were differences between the three health services with regards to the pre-hospital use of both forms of stress dosing, particularly the use of IM hydrocortisone, in which there was a six-fold variation in usage from 7.0% to 45.8% of the presentations. Disparities between the health services were also observed in the use of IV hydrocortisone and the rates of hospital admission. Possible reasons for these differences include patients presenting at different stages at each hospital or differences in clinical practice between the hospitals. Variations in the distribution of other patient characteristics, such as ethnicity and socioeconomic status, between the hospitals may also have

influenced both pre-hospital management and in-hospital care but these could not be assessed in this analysis. Previous studies have shown differences in outcomes according to ethnicity (9), and AC events have been found to occur even among well-educated patients (17,28). Patients at each hospital in this study had all been given education on stress management, which typically involves instruction on stress dosing by the treating specialist, reinforcement of the steps in AC prevention at each clinic visit and education sessions with a specialist paediatric endocrine nurse when required. Given this, the effect of repeated experience of attendance at the same hospital for acute care on the use of IM hydrocortisone suggests that experience may have a positive and independent influence on management strategies used by parents who have been given education about AC prevention. Other health service factors, such as delays in access to definitive treatment, were not found in this study but have been identified in other populations as barriers to the implementation of effective treatment of acute illness in AI (14,28,29).

This study reviewed the records of all patients with at least one treatment episode in a referral hospital over a large geographic area. Importantly, it included all attendances at Accident and Emergency as well as all hospital admissions. This enabled the examination of variation in outcomes and management between patient subgroups and between different health services. It is possible that there were some presentations of children to other non-specialist hospitals during the time frame of this study that could not be included in the study sample. However, it is likely that children who were very unwell would have been more likely to present to a specialist service or be transferred there for treatment and, therefore, would have been included in this dataset. In addition, the number of patients with less severe disease or those who managed episodes of illness successfully at home could not be determined. The AC classification used in this study was based on the clinical impression of the attending physician and this may have introduced some measurement error into the estimate of AC incidence. Further, although the data extracted from the record was validated in this study, not all records were complete and this differed between the hospitals. Information regarding timeframes of readmission was not included in this study but is important and worthy of further investigation.

In conclusion, prevention of symptomatic AI/AC remains an issue in the management of patients with CAH. Importantly, the results of this investigation demonstrate that patient factors alone are not the sole determinants of health outcomes in CAH, and that parental experience with the management of illness influences the use of stress dosing even among well-educated patients. Finally, these results demonstrate the value of inter-hospital comparison studies for chronic diseases, such as CAH and emphasise the importance of the consistent, guideline based application of AC prevention strategies and optimal hospital management.

Declaration of interests

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contributions

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Table 1 Signs, Symptoms and Treatment of AI by Age Group for all Presentations to Paediatric Referral Hospitals in NSW, 2000-2015

Category	Total (N=321)	Age Group (Yrs) N (%)				P value
		<1	1-4	5-9	10-18	
		(N=81)	(N=126)	(N=56)	(N=58)	
Males	178 (55.5)	57 (70.4)	60 (47.6)	27 (48.2)	34 (58.6)	<0.01
Admitted	213 (66.4)	55 (67.9)	74 (58.7)	38 (67.8)	46 (79.3)	NS
Diagnosis						
Any Infection	137 (42.7)	33 (40.7)	62 (49.2)	24 (42.9)	18 (31.0)	NS
Gastroenteritis	52 (16.2)	13 (16.0)	17 (13.5)	14 (25.0)	8 (13.8)	NS
Signs and symptoms						
Diarrhoea	78 (24.3)	21 (25.9)	25 (19.8)	16 (28.6)	16 (27.6)	NS
Vomiting	196 (61.1)	40 (49.4)	86 (68.3)	39 (69.6)	31 (53.4)	<0.05
Prodromal illness	189 (58.9)	46 (56.8)	85 (67.5)	26 (46.4)	32 (55.2)	0.05
Fever	108 (33.6)	22 (27.2)	52 (41.3)	22 (39.3)	12 (20.7)	<0.05
Hypotension	19 (5.9)	3 (3.7)	4 (3.2)	7 (12.5)	5 (8.6)	NS
Dehydration	35 (10.9)	6 (7.4)	13 (10.3)	8 (14.3)	8 (13.8)	NS
Reduced level of consciousness	38 (11.8)	3 (3.7)	23 (18.3)	6 (10.7)	5 (14.3)	<0.05
Lethargy	102 (31.8)	20 (24.7)	52 (41.3)	14 (25.0)	16 (27.6)	<0.05
Hyponatreamia	41 (12.8)	13 (16.0)	16 (12.7)	7 (12.5)	5 (8.6)	NS
Hyperkalaemia	20 (6.2)	14 (17.3)	4 (3.2)	2 (3.6)	0 (0.0)	<0.01
Hypoglycaemia	27 (8.4)	5 (6.2)	14 (11.1)	5 (8.9)	3 (5.2)	NS
AC Recorded	29 (9.0)	7 (8.6)	14 (11.1)	4 (7.1)	4 (6.9)	NS
Management						
PO Stress Dosing	134 (41.7)	30 (37.0)	67 (53.2)	19 (33.9)	18 (31.0)	<0.01
IM Hydrocortisone	71 (22.1)	12 (14.8)	24 (19.0)	16 (28.6)	19 (32.8)	<0.05
Any form of Stress Dosing	206 (64.2)	42 (51.9)	92 (73.0)	35 (62.5)	37 (63.8)	<0.05
IV Hydrocortisone	158 (49.2)	31 (38.3)	60 (47.6)	30 (53.6)	37 (63.8)	<0.05

Table 2 Demographic characteristics, signs, symptoms and treatment of AI by hospital for all Presentations to Paediatric Referral Hospitals in NSW, 2000-2015

Category	Hospital N (%)			P Value
	Hospital A (N=157)	Hospital B (N=57)	Hospital C (N=107)	
Admissions	90 (57.3)	37 (64.9)	86 (80.4)	<0.001
Diagnosis				
Any infection	63 (40.1)	26 (45.6)	48 (44.9)	NS
Gastroenteritis	20 (12.7)	8 (14.0)	24 (22.4)	NS
Signs and Symptoms				
Diarrhoea	39 (24.8)	8 (14.0)	31 (29.0)	NS
Vomiting	84 (53.5)	34 (59.6)	78 (72.9)	<0.01
Prodromal illness	101 (64.3)	25 (43.9)	63 (58.9)	<0.05
Fever	58 (36.9)	18 (31.6)	32 (29.9)	NS
Hypotension	11 (7.0)	1 (1.8)	7 (6.5)	NS
Dehydration	9 (5.7)	10 (17.5)	16 (15.0)	<0.05
Reduced level of consciousness	17 (10.8)	3 (5.3)	18 (16.8)	NS
Hyperkalaemia (>5.0mmol/L)	9 (5.7)	5 (8.8)	6 (5.6)	NS
Hyponatraemia (<135mmol/L)	19 (12.1)	12 (21.1)	10 (9.3)	NS
Hypoglycaemia (<3.5mmol/L)	18 (11.5)	5 (8.8)	4 (3.7)	NS
AC Recorded	6 (3.8)	6 (10.5)	17 (15.9)	<0.01
Mean AC Signs and Symptoms (SD)	1.15 (0.96)	1.14 (0.90)	1.35 (0.93)	NS
Management				
PO Stress dosing	85 (54.1)	17 (29.8)	32 (29.9)	<0.001
IM Hydrocortisone	11 (7.0)	11 (19.3)	49 (45.8)	<0.001
Any form of Stress Dosing	96 (61.1)	29 (50.9)	81 (75.7)	<0.01
IV Hydrocortisone	62 (39.5)	22 (38.6)	74 (69.2)	<0.001

Table 3 Signs, Symptoms and Treatment of AI by Method of Stress Dosing for all Presentations to Paediatric Referral Hospitals in NSW, 2000-2015

Category	**Method of Stress Dosing N (%)**		
	Total	**PO Route**	**IM Injection**
Males	178	63 (35.4)	39 (21.9)
Admitted	133	79 (37.1)	53 (24.9)
Diagnosis			
Any Infection	137	59 (44.0)	39 (54.9)
Gastroenteritis	52	22 (42.3)	22 (42.3)
Signs and Symptoms			
Diarrhoea	78	40 (51.3)	19 (24.4)
Vomiting	196	81 (41.3)	64 (32.7)
Lethargy	102*	48 (47.1)	28 (27.5)
Hypotension	19	9 (47.4)	7 (36.8)
Fever	108*	50 (46.3)	25 (23.1)
Prodromal Illness	189*	96 (50.8)	33 (17.5)
Reduced Consciousness	38	15 (39.5)	15 (39.5)
Dehydration	35	14 (40.0)	16 (45.7)
Hyperkalaemia	20	5 (25.0)	4 (20.0)
Hyponatraemia	41	19 (46.3)	9 (22.0)
Hypoglycaemia	27	11 (40.7)	7 (25.9)
AC Recorded	29	10 (34.5)	13 (44.8)
Management			
IV Hydrocortisone	158*	65 (41.1)	50 (31.6)

*One patient had a record of stress dosing without a specification about the type of administration. Therefore, the number of patients reporting any form of stress dosing do not correspond to the sum of the other variables.

Table 4 Signs, Symptoms and Treatment of AI by Admission Status for all Presentations to Paediatric Referral Hospitals in NSW, 2000-2015

Category	Admission N (%)	ED Attendance Only N (%)	P Value
Diagnosis			
Any infection	81 (62.80)	48 (37.20)	NS
Gastroenteritis	32 (62.70)	19 (37.30)	NS
Signs and Symptoms			
Diarrhoea	51 (65.40)	27 (34.60)	NS
Vomiting	140 (71.40)	56 (28.60)	<0.02
Prodromal illness	126 (66.70)	63 (33.30)	NS
Fever	75 (69.40)	33 (30.60)	NS
Hypotension	12 (63.20)	7 (36.80)	NS
Dehydration	27 (77.10)	8 (22.90)	NS
Reduced level of consciousness	32 (84.20)	6 (15.80)	0.01
Hyperkalaemia (>5.0mmol/L)	14 (100.00)	0 (0.00)	<0.01
Hyponatraemia (<135mmol/L)	33 (80.50)	8 (19.50)	0.04
Hypoglycaemia (<3.5mmol/L)	22 (81.50)	5 (18.50)	NS
AC Recorded	28 (96.60)	1 (3.4)	<0.01
Mean AC Signs and Symptoms (SD)	1.35 (0.92)	0.93 (0.92)	<0.001
Management			
IV Hydrocortisone	143 (90.50)	15 (9.50)	<0.01
PO Stress dosing	79 (59.00)	55 (41.00)	<0.02
IM Hydrocortisone	53 (74.60)	18 (25.40)	NS
Any form of Stress Dosing	133 (64.60)	73 (35.40)	NS

Table 5 Odds ratios for use of Oral and IM stress dosing, IV hydrocortisone and Admission.

Variable	Wald statistic	OR	95% CI	P value
PO Use				
Hospital	16.53			<0.001
A (referent)	-	-	-	-
B	6.77	0.41	0.21-0.80	<0.01
C	14.02	0.36	0.21-0.62	<0.001
Prodromal Illness	12.74	2.43	1.49-3.96	<0.001
IM Use				
Vomiting	18.60	7.48	3.00-18.67	<0.001
Hospital	34.08			<0.001
A (referent)	-	-	-	-
B	4.31	2.80	1.06-7.41	<0.05
C	32.63	9.65	4.43-21.00	<0.001
Prodromal Illness	7.20	0.41	0.21-0.78	<0.01
Gastroenteritis	4.71	2.34	1.09-5.03	<0.01
Number of Attendances	7.47	1.11	1.03-1.20	<0.01
Any Form of Stress Dosing				
Vomiting	13.16	2.50	1.52-4.10	<0.001
Hospital	7.56			<0.05
A (referent)	-	-	-	-
B	2.63	0.59	0.31-1.12	NS
C	2.51	1.59	0.90-2.81	NS
Gastroenteritis	5.49	2.67	1.17-6.09	<0.05
IV Hydrocortisone Use				
Number of AC Signs and Symptoms	14.89	2.02	1.46-2.90	<0.001
Hospital	13.51			0.001
A (referent)	-	-	-	-
B	0.03	0.94	0.48-1.87	NS
C	11.74	2.73	1.54-4.86	0.001
Age (years)	12.105	1.11	1.05-1.17	0.001

Vomiting	4.51	1.97	1.05-3.69	0.034
Admission				
Number of AC Signs and Symptoms	12.01	1.64	1.24-2.17	0.001
Hospital	10.06			<0.01
A (referent)	-	-	-	-
B	1.23	1.44	0.76-2.75	NS
C	10.00	2.60	1.44-4.70	<0.01
Age (years)	4.10	1.10	1.00-1.128	<0.05