Increased Infection Risk in Addison's Disease and Congenital Adrenal Hyperplasia

A Primary Care Database Cohort Study

Alberto S. Tresoldi,[1,2,3] Dana Sumilo,[4] Mary Perrins,[4] Konstantinos A. Toulis,[4] Alessandro Prete,[1,2] Narendra Reddy,[5] John A. H. Wass,[6] Wiebke Arlt,[1,2,7,*] and Krishnarajah Nirantharakumar[4,*]

[1]Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK; [2]Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK; [3]Endocrinology, Diabetology and Medical Andrology Unit, Humanitas Clinical and Research Hospital, Rozzano (Milan), Italy; [4]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK; [5]Department of Diabetes and Endocrinology, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK; [6]Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK; and [7]NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, UK

Primary adrenal insufficiency (PAI) is a severe and potentially life-threatening condition caused by the failure of the adrenal cortex to produce glucocorticoids and, in most cases, mineralocorticoids, which occurs in the setting of adrenal disease (1). The 2 most frequent causes of PAI are autoimmune adrenalitis, the most frequent cause of Addison's disease (AD) in Western countries, and congenital adrenal hyperplasia (CAH).

The prognosis of patients with PAI has improved considerably after life-saving glucocorticoid replacement therapy became available in the 1950s; however, an increased risk of death has been described in both AD and CAH patients even in recent years (2, 3). In patients with AD, this has been attributed to adrenal crisis- and infection-related mortality (4), while for both CAH and AD patients an increased cardiovascular-related mortality has been described (3, 4). Other studies have reported an increased use of antimicrobial agents and infection-related hospital admissions in patients with PAI (5, 6). Recent evidence suggests that the increased risk of infections in these patients could be explained by an impairment of natural killer cell function (7), which may be caused by the nonphysiological delivery of glucocorticoids by currently available preparations and an associated change in clock gene expression patterns in immune cells (7, 8).

No studies have estimated yet the overall risk of common infections in people with PAI, namely, infections that are primarily managed in the primary care setting and usually do not require hospital admission. However, such infections potentially expose PAI patients to significant risk of adrenal crisis. Therefore, this study aimed to assess the risk of common types of primary care–managed infections—namely, lower respiratory tract infections (LRTIs), urinary tract infections (UTIs), and gastrointestinal infections (GIIs)—and the use of antimicrobials in the primary care setting in patients with PAI, including both AD and CAH patients with and without glucocorticoid therapy.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 8 May 2019. Accepted 13 September 2019.
First Published Online 18 September 2019.

*Joint senior authors.

Materials and Methods

Study design and setting

We conducted a population-based, retrospective, open cohort study to determine the infection risk of patients with AD and CAH in the primary care setting. We assessed the risk of LRTIs, UTIs, and GIIs and the counts of antimicrobial prescriptions. We used data from The Health Improvement Network (THIN) database, comprising anonymized electronic medical records from UK general practitioner (GP) practices covering over 5% of the UK population. THIN holds data on demographic characteristics, clinical diagnoses, physical measurements, laboratory results and drug prescriptions recorded using a clinical Read code system. Patients registered in THIN have similar age and sex distributions to the general UK population, and, therefore, THIN data are well suited for epidemiological studies (9, 10).

Study population and period

Our study population consisted of 2 "exposed" cohorts, comprising adult patients (≥18 years old) diagnosed with AD or CAH according to selected Read codes (11, 12). (see supplementary materials (13)) We excluded patients who were at any time point coded with a code consistent with other causes of adrenal insufficiency. We could not retrieve data on 21-hydroxylase autoantibodies in the study participants, due to the nature of the study. Therefore, in this paper, we defined AD as PAI not caused by CAH. To ensure accuracy of case definition in the AD cohort, we only included patients who had at least 1 prescription of both glucocorticoids (accepting glucocorticoids commonly used in AD) and mineralocorticoids. We also performed a sensitivity analysis to include only patients who had at least 2 prescription of both glucocorticoids and mineralocorticoids. We subdivided the CAH cohort in two subcohorts: (i) patients who had at least 1 glucocorticoid prescription at any point (using the same glucocorticoid codes used for AD patients) and (ii) patients who were never prescribed with any glucocorticoid therapy, since patients with CAH do not always require glucocorticoid therapy. For every exposed patient, we randomly selected 2 individuals from a pool of patients matched for age, sex, and GP practice who did not have a Read code consistent with PAI at any point before or during the observation period.

The study period extended from January 1, 1995 to January 1, 2018. Patients were eligible for inclusion 1 year from the latest of the following dates: study start date, patient registration date with the GP practice, and practice eligibility date (the date when practices have implemented an electronic medical record and have passed the assessment for acceptable data quality). The 1-year lag period was applied to ensure there was enough time to document all information accurately after registration with the practice or after a practice was deemed eligible to take part. To ensure acceptable data quality, practices were required to have used the electronical health record system for at least 1 year and have acceptable mortality reporting (13).

The index date (ie, the date when follow-up commences) was defined as the date of diagnosis for newly diagnosed patients or, if they were already diagnosed with PAI, the date when they registered with an eligible GP practice. Patients were followed from index date up until the earliest of the following dates: outcome of interest (only for estimating the incidence of infections), patient transfer date from practice, patient death, practice's last data collection date, and study end date.

Outcomes

For the first outcome, the incidence of infections, we used the Read codes that identify cases of LRTIs, UTIs and GIIs (see supplementary materials (13)). These infections were chosen because they are the most common type of infections evidenced in general population and they are frequently diagnosed in primary care (14). We then calculated the occurrence of this outcome in the different cohorts.

For the second outcome, antimicrobial use, we used the codes for antibiotics and antifungals as classified in the British National Formulary. We then calculated the total number of prescriptions for every antimicrobial in each cohort.

For each of the study groups, we analyzed age, sex, body mass index (BMI), smoking status, Townsend Deprivation Index (a measure of deprivation within a population) (15), Charlson Comorbidity Index (a method of classifying comorbidities to predict mortality in primary care) (16, 17), and type of glucocorticoids prescribed at baseline. For the AD cohort (in which most patients were likely to have autoimmune PAI), given the frequent association with other autoimmune conditions, we also evaluated the prevalence of associated autoimmune comorbidities.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics for the exposed and unexposed groups of patients. Categorical variables were investigated using Chi-square test and continuous variables were analyzed using a *t* test.

Adjusted incidence rate ratios (aIRRs) for specific infections and antimicrobial prescriptions were calculated after adjustment for age, sex, smoking status, BMI, Townsend Deprivation Index, and Charlson Comorbidity Index, using multivariate Poisson regression analysis. Statistical analyses were conducted using Stata version 14.2 (Stata Corp, College Station, Texas, US) and GraphPad Prism 7.04 (GraphPad Software Inc, San Diego, California, US).

Ethical approval

The THIN database obtained ethical approval from the South East Multicentre Research Ethics Committee in 2003. The present study was reviewed and approved (study reference: 18THIN063) by the THIN Scientific Review Committee in July 2018.

Results

Baseline characteristics of the AD cohort

In total, 1 580 patients fulfilled the AD criteria; these were matched with 3 158 unexposed individuals (Table 1). The mean age of AD patients was 51.7 years, and the majority were women (57.8%). Compared to unexposed individuals, AD patients had a lower median BMI, while the Townsend Deprivation Index did not differ significantly between the 2 groups. The Charlson Comorbidity Index showed that AD patients had an

increased burden of comorbidities compared to the matched population; this included a higher prevalence of autoimmune comorbidities, including autoimmune thyroid diseases, type 1 diabetes mellitus (T1DM), ulcerative colitis, celiac disease, and pernicious anemia (Table 1).

Baseline characteristics of the CAH cohort

In total, 602 patients fulfilled the CAH criteria and were subdivided into 254 glucocorticoid-treated patients (42.2%) and 348 patients not on glucocorticoids (57.8%). These were matched with 508 and 696 unexposed controls, respectively (Table 2).

The majority of CAH patients were female (72.3%), with a lower mean age in glucocorticoid-treated patients at cohort entry (33.4 vs. 36.9 years). CAH patients had a higher median BMI compared to controls, and this was evident for both glucocorticoid-treated subcohort and the CAH subcohort never treated with glucocorticoids. CAH patients were more frequently overweight or obese (60.3% vs. 44.2% in matched controls, $P < 0.001$), and this was observed both in glucocorticoid-treated and untreated CAH patients (59.1 and 61.1%, respectively). The Townsend Deprivation Index and the Charlson Comorbidity Index did not differ between CAH patients and controls.

Glucocorticoid prescriptions

The most commonly prescribed type of glucocorticoid in the AD cohort was hydrocortisone (1 296 patients, 82%), followed by prednisolone (187 patients, 11.8%). Only a minority of patients were prescribed cortisone acetate (91 patients, 5.8%, no longer available in the United Kingdom) and dexamethasone (6 patients, 0.4%).

In the glucocorticoid-treated CAH cohort, prednisolone was most commonly prescribed (127 patients, 50.0%), followed by hydrocortisone (96 patients, 37.8%), with a small minority receiving dexamethasone (15 patients, 5.9%) or cortisone acetate (11 patients, 4.3%). Only 5 CAH patients (2%) were prescribed a combination of short- and long-acting glucocorticoids.

Risk of infections

The risk of LRTIs, UTIs, and GIIs was significantly increased in the AD cohort compared to unexposed patients, with the highest relative risk observed for GIIs (aIRR 3.80 [95% CI 2.99–4.84]) followed by LRTIs (aIRR 2.11 [95% CI 1.64–2.69]) and UTIs (aIRR 1.51 [95% CI 1.29–1.77]) (Table 3; Fig. 1). These results were confirmed in the subanalysis of patients who had at least 2 prescriptions of both glucocorticoids and mineralocorticoids (94.5% of the total cohort (see supplementary materials (13)).

In the overall CAH cohort, there was a significantly increased risk of UTIs and LRTIs (aIRR 1.40 [95% CI 1.06–1.85] and 2.36 [95% CI 1.25–4.42], respectively), with no difference in gastrointestinal infections (Table 4; Fig. 1). However, when analyzing the population accordingly to glucocorticoid use, only patients exposed to glucocorticoids had an increased risk of infections, with the highest risk observed for LRTIs (aIRR 3.23 [95% CI 1.21–8.61]) followed by UTIs (aIRR 2.20 [95% CI 1.43–3.4]) and GIIs (aIRR 1.93 [95% CI 1.06–3.52]) (Table 4; Fig. 1). In contrast, infection risk in CAH patients not treated with glucocorticoids did not differ from that observed in the matched background population.

Antimicrobial prescriptions

Prescription rates of antibiotics and antifungals were increased in patients with AD (aIRR 1.73 [95% CI 1.69–1.77] and 1.89 [95% CI 1.74–2.05], respectively) (Table 5; Fig. 1). These results were confirmed in the subanalysis of patients who had at least 2 prescriptions of both glucocorticoids and mineralocorticoids (see supplementary materials (13)).

Similarly, we observed increased antimicrobial prescription rates in CAH patients, with a higher prescription rate in glucocorticoid-treated patients (antibiotics: aIRR 1.77 [95% CI 1.66–1.89]; antifungals: aIRR 1.91 [95% CI 1.50–2.43]) than in CAH patients not exposed to glucocorticoids (antibiotics: aIRR 1.15 [95% CI 1.08–1.23]; antifungals: aIRR 1.44 [95% CI 1.18–1.83]) (Table 6; Fig. 1).

Given the higher incidence of T1DM in our AD cohort (8% vs. 0.5% in matched controls) and given the potentially higher risk of infections in T1DM patients, we performed a subgroup analysis comparing AD patients with and without T1DM to a matched unexposed cohort. Findings were similar, although given the smaller number of T1DM patients group, some did not reach statistical significance (see supplementary materials (13)).

Discussion

In this population-based study we found that the risk of three common infections (LRTIs, UTIs, and GIIs) was increased in the primary care setting in patients with PAI, as compared to population-based matched controls. This was also supported by our finding of increased prescription rates of antimicrobials in in patients with PAI. Moreover, we found that CAH patients

Table 1. Baseline Characteristics of Patients With AD and Matched Unexposed Patients

	AD Patients (*n* = 1580)	Matched Unexposed Patients (*n* = 3158)
Age years, mean ± SD	51.7 ± 18.5	51.7 ± 18.5
Male sex, *n* (%)	666 (42.2)	1.330 (42.1)
BMI, total *N*	1227	2264
median (interquartile range)	24.3 (21.5–27.6)[a]	25.5 (22.6–28.9)
˂18.5 kg/m2, *n* (%)	87 (7.1)	51 (2.3)
18.5–25 kg/m^2, *n* (%)	606 (49.4)	973 (43.0)
25–30 kg/m^2, *n* (%)	362 (29.5)	791 (34.9)
≥30 kg/m^2, *n* (%)	172 (14.0)	449 (19.8)
Missing, *n*	353	894
Smoking status, total *N*	1384	2679
Nonsmoker, *n* (%)	882 (63.7)[a]	1548 (57.8)
Ex-smoker, *n* (%)	250 (18.1)	490 (18.3)
Smoker, *n* (%)	252 (18.2)[a]	641 (23.9)
Missing, *n*	196	479
Townsend Deprivation Index, total *N*	1373	2780
1 (least deprived), *n* (%)	350 (25.5)	743 (26.7)
2, *n* (%)	306 (22.3)	590 (21.2)
3, *n* (%)	290 (21.1)	607 (21.8)
4, *n* (%)	255 (18.6)	471 (16.9)
5 (most deprived), *n* (%)	172 (12.5)	369 (13.3)
Missing, *n*	207	378
Charlson Comorbidity Index		
0 (no comorbidities), *n* (%)	863 (54.6)[a]	2263 (71.7)
1, *n* (%)	377 (23.9)[a]	536 (17.0)
≥2 (more comorbidities), *n* (%)	340 (21.5)[a]	359 (11.4)
Associated autoimmune comorbidities		
Hyperthyroidism, *n* (%)	40 (2.5)[a]	16 (0.5)
Hypothyroidism, *n* (%)	457 (28.9)[a]	122 (3.9)
Rheumatoid arthritis, *n* (%)	25 (1.6)	37 (1.2)
Type 1 diabetes mellitus, *n* (%)	127 (8.0)[a]	15 (0.5)
Inflammatory bowel disease, *n* (%)	29 (1.8)[a]	22 (0.7)
Crohn's disease, *n* (%)	9 (0.6)	9 (0.3)
Ulcerative colitis, *n* (%)	20 (1.3)[a]	11 (0.4)
Coeliac disease, *n* (%)	25 (1.6)[a]	10 (0.3)
Multiple sclerosis, *n* (%)	<5	8 (0.3)
Pernicious anaemia, *n* (%)	41 (2.6)[a]	15 (0.5)
Systemic lupus erythematosus, *n* (%)	6 (0.4)	n < 5

[a]$P < 0.05$ for AD patients vs. unexposed cohort.

not receiving glucocorticoids did not have an increased risk of infections, indicating that glucocorticoid therapy might at least partly drive the increased infection risk observed in PAI. To our knowledge, our study is the first to analyze the risk of infection in PAI according to different etiologies and also the first to evaluate these outcomes in a primary care setting.

Previous studies have described an increased infection-related mortality in patients with AD (2, 4), but not in CAH patients (3). This was attributed to infections representing a possible trigger for a fatal adrenal crisis. Smans and colleagues (5) reported an increase of the use of antimicrobials and of infection-related hospital admissions in PAI; however, the authors focused on hospital-treated infections only, possibly overestimating the actual incidence of this complication due to a lower threshold for admission in PAI patients. In addition, information on the actual etiology of PAI was not available in this study, as PAI was diagnosed based on concomitant glucocorticoid and mineralocorticoid prescriptions, which did not allow for the differentiation between AD, CAH, and other causes of PAI.

Until recently, it was unclear whether the observed increase in infection episodes in patients with PAI is related to the underlying disease itself or to the nonphysiological delivery of glucocorticoid replacement by currently available glucocorticoid preparations. Autoimmune AD patients frequently also suffer from other autoimmune comorbidities (18), and this was confirmed in our study, with more prevalent autoimmune disease in our AD cohort, which can be safely assumed to consist of a large majority of patients with AD of autoimmune origin. However, in CAH patients, there is only marginal evidence of an imbalance of immune function (19), and as we found similar increases in infection risk in the CAH cohort, potential etiology-related immune function is unlikely to explain the increased susceptibility to infections we observed.

Table 2. Baseline Characteristics of the CAH Patients and Matched Unexposed Patients

	CAH Cohort (*n* = 602)	Matched Unexposed Cohort (*n* = 1204)	CAH Cohort on Glucocorticoids (*n* = 254)	Matched Unexposed Cohort (*n* = 508)	CAH Cohort Not on Glucocorticoids (*n* = 348)	Matched Unexposed Cohort (*n* = 696)
Age, years, mean ± SD	35.4 ± 16.3	35.5 ± 16.2	33.4 ± 15.1	33.5 ± 15.0	36.9 ± 17.0[b]	37.0 ± 16.9
Male sex, *n* (%)	167 (27.7)	334 (27.7)	80 (31.5)	160 (31.5)	87 (25.0)	174 (25.0)
BMI, total *N*	438	835	186	340	252	495
Median (interquartile range)	26.9 (23.2–31.2)[a]	24.0 (21.0–28.0)	27.0 (23.2–32.0)[a]	24.0 (21.3–27.9)	26.9 (23.2–30.9)[a]	24.4 (21.8–28.3)
<18.5, *n* (%)	12 (2.7)	35 (4.2)	8 (4.3)	9 (2.6)	4 (1.6)	26 (5.2)
18.5–25, *n* (%)	162 (37.0)	431 (51.6)	68 (36.6)	187 (55.0)	94 (37.3)	244 (49.3)
25–30, *n* (%)	133 (30.4)	224 (26.8)	52 (28.0)	90 (26.5)	81 (32.1)	134 (27.1)
≥30, *n* (%)	131 (29.9)	145 (17.4)	58 (31.2)	54 (15.9)	73 (29.0)	91 (18.4)
Missing, *n*	164	369	68	168	96	201
Smoking status, total *N*	524	1048	212	423	312	625
Non-smoker, *n* (%)	349 (66.6)	670 (63.9)	138 (65.1)	277 (65.5)	211 (67.6)	393 (62.9)
Ex-smoker, *n* (%)	71 (13.6)	142 (13.6)	28 (13.2)	50 (11.8)	43 (13.8)	92 (14.7)
Smoker, *n* (%)	104 (19.9)	236 (22.5)	46 (21.7)	96 (22.7)	58 (18.6)	140 (22.4)
Missing, *n*	78	156	42	85	36	71
Townsend Deprivation Index, total *N*	516	1057	223	459	293	598
1 (least deprived), *n* (%)	123 (23.8)	235 (22.2)	52 (23.3)	107 (23.3)	71 (24.2)	128 (21.4)
2, *n* (%)	107 (20.7)	222 (21.0)	46 (20.6)	92 (20.0)	61 (20.8)	130 (21.7)
3, *n* (%)	114 (22.1)	232 (22.0)	51 (22.9)	99 (21.6)	63 (21.5)	133 (22.2)
4, *n* (%)	104 (20.2)	225 (21.3)	44 (19.7)	98 (21.4)	60 (20.5)	127 (21.2)
5 (most deprived), *n* (%)	68 (13.2)	143 (13.5)	30 (13.5)	63 (13.7)	38 (13.0)	80 (13.4)
Missing, *n*	86	147	31	49	55	98
Charlson Comorbidity Index						
0 (no comorbidities), *n* (%)	457 (75.9)	907 (75.3)	187 (73.6)	394 (77.6)	270 (77.6)	513 (73.7)
1, *n* (%)	103 (17.1)	242 (20.1)	50 (19.7)	96 (18.9)	53 (15.2)	146 (21.0)
≥2 (more comorbidities), *n* (%)	42 (7.0)	55 (4.6)	17 (6.7)	18 (3.5)	25 (7.2)	37 (5.3)

[a] $P < 0.05$ for CAH patients vs. unexposed cohort.
[b] $P < 0.05$ for CAH patients on glucocorticoids vs. CAH patients not on glucocorticoids.

Table 3. Absolute and relative risk of infections in AD patients and matched cohort

	AD Cohort (*n* = 1580)		Matched Unexposed Cohort (*n* = 3158)
Lower respiratory tract infections			
Outcome events, *n* (%)	130 (8.2)		137 (4.3)
Person-years, *n*	10 337		22 836
Crude incidence rate/1000-person years	12.58		6.00
Follow-up years, median (interquartile range)	4.87 (1.78–10.20)		5.78 (2.37–11.12)
Unadjusted incidence rate ratio (95% CI)		2.10 (1.65–2.66)	
P-value		0.001	
Adjusted incidence rate ratio (95% CI)[a]		2.11 (1.64–2.69)	
P-value		0.001	
Urinary tract infections			
Outcome events, *n* (%)	282 (17.9)		396 (12.5)
Person-years, *n*	9 248		21 003
Crude incidence rate/1000-person years	30.49		18.85
Follow-up years, median (interquartile range)	4.09 (1.44–9.14)		5.08 (2.11–10.26)
Unadjusted incidence rate ratio (95% CI)		1.62 (1.39–1.88)	
P-value		0.001	
Adjusted incidence rate ratio (95% CI)[a]		1.51 (1.29–1.77)	
P-value		0.001	
Gastro-intestinal infections			
Outcome events, *n* (%)	194 (12.3)		110 (3.5)
Person-years, *n*	9 598		22 662
Crude incidence rate/1000-person years	20.21		4.85
Follow-up years, median (interquartile range)	4.49 (1.67–9.31)		5.63 (2.37–11.03)
Unadjusted incidence rate ratio (95% CI)		4.16 (3.30–5.26)	
P-value		0.001	
Adjusted incidence rate ratio (95% CI)[a]		3.80 (2.99–4.84)	
P-value		0.001	

[a]Adjusted for age, gender, smoking status, BMI, Townsend Deprivation Index and Charlson Comorbidity Index.

Supraphysiological glucocorticoid doses, as usually administered in the context of chronic inflammatory disease, is well known to cause changes in the immune system, with consequently increased risk of bacterial and fungal infections (20). However, this has not been demonstrated for the physiological replacement doses generally used in patients with PAI. Still, currently available glucocorticoid replacement therapy does not provide a physiological substitution, with significant peaks and troughs of cortisol availability during the day following oral intake of immediate release glucocorticoid preparations. In addition, significant heterogeneity exists in the management of glucocorticoid replacement in clinical practice; a recent paper recorded 25 different regimens with which glucocorticoid therapy is administered in AD patients receiving a daily hydrocortisone of 20 mg (21). Therefore, it would come as no surprise that physiological dose glucocorticoid therapy is not free of side effects, if administered in a nonphysiological delivery pattern. An improvement in metabolic outcomes after switching from standard cortisol replacement to more physiological cortisol replacement via continuous subcutaneous hydrocortisone was previously demonstrated in both AD and CAH patients (22, 23).

Some recent papers have indeed suggested that adverse changes in immune function might occur with glucocorticoid replacement in PAI. A recent paper documented significantly decreased natural killer cytotoxicity in patients with PAI (7), which was present in both patients with autoimmune adrenalitis and those with PAI following bilateral adrenalectomy, indicating that the underlying etiology did not play a role in these changes in immune function. A recent randomized control trial including patients with primary and secondary adrenal insufficiency reported a reduction in respiratory tract infections with modified-release hydrocortisone (8). However, this was a secondary outcome, based on self-reported questionnaires on infections and not verified against medical records, thereby providing only limited evidence. A study on immune function in the same cohort reported dysregulation of circadian gene expression in peripheral blood mononuclear cells in the PAI patients at baseline, which attenuated after the switch to modified-release hydrocortisone therapy (24). The findings of our study, including both patients with AD and CAH, suggest that exogenous glucocorticoid is at least a contributory factor to the increased infection risk we observed, given that no significant increase in infection risk was observed in the CAH patients not receiving glucocorticoid therapy.

Both our AD and CAH populations had increased prescription rates for antibiotics and antifungals. Interestingly, increased prescription rates were also

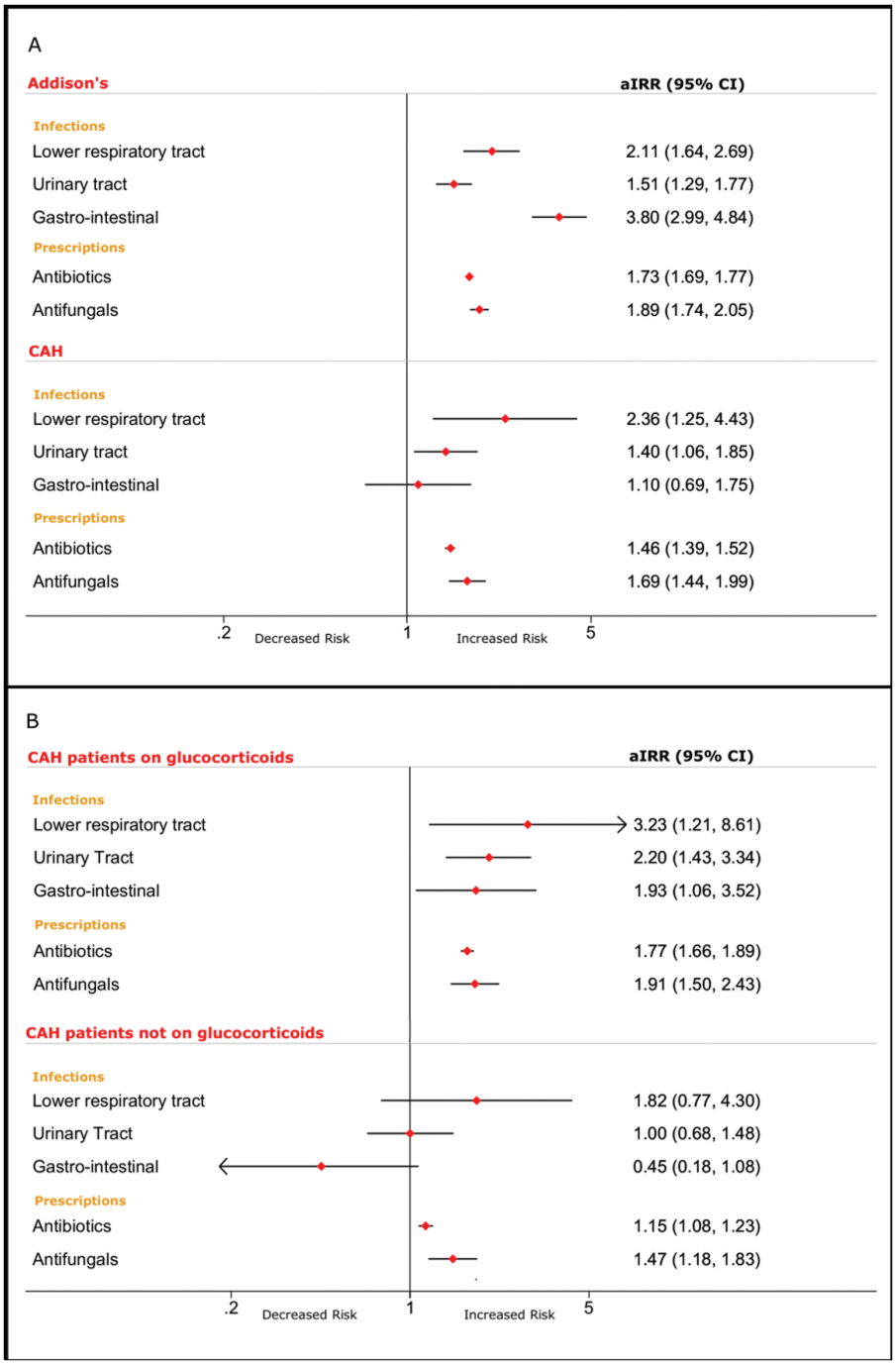

Figure 1. Forest plot of outcomes. Panel A: Adjusted incidence rate ratio (aIRR) for infections and antimicrobial prescriptions in Addison's disease (AD) and congenital adrenal hyperplasia (CAH) cohorts. Panel B: aIRR for infections and antimicrobial prescriptions in CAH patients separately for patients with and without chronic glucocorticoid treatment.

noted in the CAH patients not receiving glucocorticoid treatment, albeit to a much lower extent. This could possibly be explained by a lower threshold for prescribing antimicrobials due to the perceived risk of adrenal crisis in CAH patients; in fact, up to 60% of nonclassic CAH patients, who usually do not receive chronic glucocorticoid replacement, have been reported to have at least partial glucocorticoid deficiency as assessed by cosyntropin testing (25).

The highest increase in risk of infection in our AD cohort was seen in GIIs, while for the CAH cohort on glucocorticoids the most significant increase in risk was seen in LRTIs and UTIs; however, the differences between the 3 infection groups was not statistically significant. This may be explained by the age difference between AD and CAH patients, with mean ages of 51.7 and 35.4 years, respectively. Indeed, LRTIs and UTIs are more frequently diagnosed in older patients (26, 27),

Table 4. Absolute and Relative Risk of Infections in CAH Patients and Matched Control Cohort

	CAH Cohort (*n* = 602)	Matched Unexposed Cohort (*n* = 1204)	CAH cohort on Glucocorticoids (*n* = 254)	Matched Unexposed Cohort (*n* = 508)	CAH Cohort Not on Glucocorticoids (*n* = 348)	Matched Unexposed Cohort (*n* = 696)
Lower respiratory tract infections						
Outcome events, *n* (%)	22 (3.7)	19 (1.6)	12 (4.7)	7 (1.4)	10 (2.9)	12 (1.7)
Person-years, *n*	3843	7842	1924	3567	1919	4275
Crude incidence rate/1000-person years	5.72	2.42	6.24	1.96	5.21	2.81
Follow-up years, median (interquartile range)	4.83 (1.92–9.54)	5.10 (2.04–9.80)	6.00 (2.60–12.06)	5.17 (2.45–10.77)	4.07 (1.54–8.00)	4.93 (1.86–9.37)
Unadjusted incidence rate ratio (95% CI)	2.36 (1.28–4.36)		3.18 (1.25–8.07)		1.86 (0.80–4.30)	
P-value	*P* = 0.01		*P* = 0.02		*P* = 0.15	
Adjusted incidence rate ratio (95% CI)[a]	2.36 (1.25–4.43)		3.23 (1.21–8.61)		1.82 (0.77–4.30)	
P-value	*P* = 0.01		*P* = 0.02		*P* = 0.17	
Urinary tract infections						
Outcome events, *n* (%)	83 (13.8)	130 (10.8)	45 (17.7)	43 (8.5)	38 (10.9)	87 (12.5)
Person-years, *n*	3478	7217	1709	3374	1769	3843
Crude incidence rate/1000-person years	23.87	18.01	26.33	12.75	21.48	22.64
Follow-up years, median (interquartile range)	4.15 (1.59–8.80)	4.64 (1.83–8.80)	4.97 (2.09–9.77)	4.84 (2.22–9.77)	3.42 (1.24–7.53)	4.18 (1.69–7.90)
Unadjusted incidence rate ratio (95% CI)	1.32 (1.01–1.74)		2.07 (1.36–3.14)		0.95 (0.65–1.39)	
P-value	*P* = 0.05		*P* < 0.001		*P* = 0.79	
Adjusted incidence rate ratio (95% CI)[a]	1.40 (1.06–1.85)		2.20 (1.43–3.34)		1.00 (0.68–1.48)	
P-value	*P* = 0.02		*P* < 0.001		*P* = 0.99	
Gastro-intestinal infections						
Outcome events, *n* (%)	29 (4.8)	52 (4.3)	23 (9.1)	23 (4.5)	6 (1.7)	29 (4.2)
Person-years.	3773	7678	1825	3486	1948	4192
Crude incidence rate/1000-person years	7.69	6.77	12.60	6.60	3.08	6.92
Follow-up years, median (interquartile range)	4.70 (1.83–9.63)	4.94 (2.04–9.69)	5.82 (2.12–11.38)	5.14 (2.47–10.38)	4.09 (1.50–8.11)	4.79 (1.86–9.13)
Unadjusted incidence rate ratio (95% CI)	1.13 (0.72–1.79)		1.91 (1.07–3.40)		0.45 (0.18–1.07)	
P-value	*P* = 0.59		*P* = 0.03		*P* = 0.07	
Adjusted incidence rate ratio (95% CI)[a]	1.10 (0.69–1.75)		1.93 (1.06–3.52)		0.45 (0.18–1.08)	
P-value	*P* = 0.70		*P* = 0.03		*P* = 0.07	

[a]Adjusted for age, gender, smoking status, BMI, Townsend Deprivation Index and Charlson Comorbidity Index.

Table 5. Antimicrobial Prescriptions Counts in AD Patients Compared to the Matched Control Cohort

	AD Cohort (*n* = 1580)		Matched Unexposed Cohort (*n* = 3158)
Antibiotic prescriptions			
Count of prescriptions, *n*	13 286		15 884
Person-years, *n*	10 767		23 308
Count rates (per 1000 years)	1234		681
Follow-up years, median (interquartile range)	5.12 (1.95–10.77)		5.90 (2.54–11.33)
Unadjusted incidence rate ratio (95% CI)		1.81 (1.77–1.85)	
P-value		0.001	
Adjusted incidence rate ratio (95% CI)[a]		1.73 (1.69–1.77)	
P-value		0.001	
Antifungal prescriptions			
Count of prescriptions, *n*	1191		1213
Person-years, *n*	10 767		23 308
Count rates (per 1000 years)	111		52
Follow-up years, median (interquartile range)	5.12 (1.95–10.77)		5.90 (2.54–11.33)
Unadjusted incidence rate ratio (95% CI)		2.13 (1.96–2.30)	
P-value		0.001	
Adjusted incidence rate ratio (95% CI)[a]		1.89 (1.74–2.05)	
P-value		0.001	

[a]Adjusted for age, gender, smoking status, BMI, Townsend Deprivation Index and Charlson Comorbidity Index.

and this was noted in our matched populations as well (population matched for AD: LRTIs 4.3%, UTIs 12.5%; population matched for CAH patients on glucocorticoids: LRTIs 1.4%, UTIs 8.5%). Therefore, the higher aIRR of LRTIs and UTIs in CAH patients is probably related to a difference in age-related background risk.

Our AD cohort had an age and sex distribution similar to the one reported in other papers (2, 5), and the types of prescribed glucocorticoid preparations at baseline in this cohort were not different from the ones reported in a recent worldwide survey (28). Our CAH cohort was younger that the AD cohort, consistent with the different etiology of these 2 diseases, and the types of glucocorticoids prescribed was similar to those reported in the cross-sectional UK CaHASE study (29), with the possible exception of lower numbers of dexamethasone users in our study. Taking this into account, our results can be assumed to be representative of the UK AD and CAH populations.

Our study has several strengths. We used a large population-based sample of patients of both sexes, across all adult age groups, with very strict inclusion and exclusion criteria, allowing us to include only patients with a true diagnosis of AD and CAH. Using the cohort study design allowed us to look at longitudinal occurrence of infections and antimicrobial use. There are also some limitations to our study. First, all data rely on the accurate recording of diagnoses by GPs and this could have resulted in some degree of misclassification of the exposed cohorts and of the different episodes of infection. Although GPs document reasons for consultations in the electronic medical records, it is possible that when a patient presented with 2 or more conditions, this may have not been accurately coded; however, all prescriptions are electronically documented and therefore are captured accurately. Second, the threshold for visiting GP might be lower in patients with PAI who receive regular education on the importance of treating infections promptly to avoid adrenal crisis. This may be a factor resulting in a degree of overestimation of the difference in the infection rates we found between these cohorts. However, since patients with PAI are generally more medicalized, it is also possible that they own a higher knowledge of diseases and might decide to treat themselves without consulting the GP. Third, we could not evaluate the influence of different doses or types of glucocorticoid on the outcomes of interest due to the methodology used and due to the small number of infection events when further subdividing our populations according to type of glucocorticoid. Furthermore, even though we tried to assess the impact of associated comorbidities by adjusting for Charlson Comorbidity Index, this does not exclude the possibility that some other confounders not accounted for in our analyses might have influenced our results. Last, although there is some evidence of an immunemodulatory effect of androgens (30), we could not take this into account in our population as we had no data on dehydroepiandrosterone (DHEA) replacement therapy in AD patients, since this is a hospital-prescribed drug in the United Kingdom; similarly, we did not have data on biochemical control of androgen excess in the CAH patients.

doi:10.1210/clinem/dgz006

Table 6. Antimicrobial Prescription Counts in CAH Patients Compared to the Matched control Cohort

	CAH Cohort (*n* = 602)	Matched Unexposed Cohort (*n* = 1204)	CAH Cohort on Glucocorticoids (*n* = 254)	Matched Unexposed Cohort (*n* = 508)	CAH Cohort Not on Glucocorticoids (*n* = 348)	Matched Unexposed Cohort (*n* = 696)
Antibiotics prescriptions						
Count of prescriptions, *n*	3543	4930	2134	2088	1409	2842
Person-years, *n*	3941	7957	1974	3611	1967	4346
Count rates (per 1000 years)	899	619	1081	578	716	654
Follow-up years, median (interquartile range)	4.85 (1.95–10.32)	5.23 (2.09–9.90)	6.12 (2.67–12.48)	5.32 (2.54–10.87)	4.12 (1.54–8.30)	5.20 (1.88–9.62)
Unadjusted incidence rate ratio (95% CI)	1.45 (1.39–1.51)		1.87 (1.76–1.99)		1.10 (1.03–1.17)	
P-value	0.001		0.001		0.01	
Adjusted incidence rate ratio (95% CI)[a]	1.46 (1.39–1.52)		1.77 (1.66–1.89)		1.15 (1.08–1.23)	
P-value	0.001		0.001		0.001	
Antifungals prescriptions						
Count of prescriptions, *n*	302	330	159	130	143	200
Person-years, *n*	3941	7957	1974	3611	1967	4346
Count rates (per 1000 years)	77	41	81	36	73	46
Follow-up years, median (interquartile range)	4.85 (1.95–10.32)	5.23 (2.09–9.90)	6.12 (2.67–12.48)	5.32 (2.54–10.87)	4.12 (1.54–8.30)	5.20 (1.88–9.62)
Unadjusted incidence rate ratio (95% CI)	1.85 (1.58–2.16)		2.24 (1.77–2.82)		1.58 (1.27–1.96)	
P-value	0.001		0.001		0.001	
Adjusted incidence rate ratio (95% CI)[a]	1.69 (1.44–1.99)		1.91 (1.50–2.43)		1.47 (1.18–1.83)	
P-value	0.001		0.001		0.001	

[a]Adjusted for age, gender, smoking status, BMI, Townsend Deprivation Index and Charlson Comorbidity Index.

Our findings have several practical implications. First, given the confirmation of a higher risk of infections in patients with PAI due to AD and CAH, all health care professionals involved in the care of PAI patients should have a heightened alertness for the possibility of infections in these patients. This may also provide a case for recommending a vaccination strategy in PAI (eg, against *Streptococcus pneumoniae*, the leading cause of LRTIs in adults) (31) to reduce the risk of these infections and related morbidity and mortality. Second, our paper provides additional evidence that nonphysiological delivery of glucocorticoid replacement by currently available preparations represents a risk factor for the development of infections. This supports the case for a therapeutic shift toward more physiological replacement therapy options in these patients (32). Future studies will have to clarify whether achieving a more physiological delivery of glucocorticoid replacement will decrease the risk of infections in PAI, with the potential to result in reduced morbidity and mortality in these patients.

Acknowledgments

Financial Support: This work was supported by the Medical Research Council UK (Program Grant 0900567, to W.A.). K.N. is a UK Research and Innovation (UKRI)/Health Data Research (HDR) UK Innovation Clinical Fellow. W.A. receives support from the National Institute of Health Research (NIHR) Birmingham Biomedical Research Centre. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care UK.

Additional Information

Correspondence and Reprint Requests: Wiebke Arlt, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Medical School IBR Tower, Rm 236, Birmingham, B15 2TT, United Kingdom. E-mail: w.arlt@bham.ac.uk

Disclosure Summary: W.A. serves as scientific consultant to Diurnal Ltd. and Spruce Biosciences, Inc. All other authors have no conflicts to declare.

Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

References

1. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol*. 2015;**3**(3):216–226.
2. Erichsen MM, Lovas K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, Berg JP, Mella B, Husebye ES. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. *Eur J Endocrinol*. 2009;**160**(2):233–237.
3. Falhammar H, Frisén L, Norrby C, Hirschberg AL, Almqvist C, Nordenskjöld A, Nordenström A. Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2014;**99**(12):E2715–E2721.
4. Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, Johannsson G. Premature mortality in patients with Addison's disease: a population-based study. *J Clin Endocrinol Metab*. 2006;**91**(12):4849–4853.
5. Smans LC, Souverein PC, Leufkens HG, Hoepelman AI, Zelissen PM. Increased use of antimicrobial agents and hospital admission for infections in patients with primary adrenal insufficiency: a cohort study. *Eur J Endocrinol*. 2013;**168**(4):609–614.
6. Bjornsdottir S, Sundstrom A, Ludvigsson JF, Blomqvist P, Kampe O, Bensing S. Drug prescription patterns in patients with Addison's disease: a Swedish population-based cohort study. *J Clin Endocrinol Metab*. 2013;**98**(5):2009–2018.
7. Bancos I, Hazeldine J, Chortis V, Hampson P, Taylor AE, Lord JM, Arlt W. Primary adrenal insufficiency is associated with impaired natural killer cell function: a potential link to increased mortality. *Eur J Endocrinol*. 2017;**176**(4):471–480.
8. Isidori AM, Venneri MA, Graziadio C, Simeoli C, Fiore D, Hasenmajer V, Sbardella E, Gianfrilli D, Pozza C, Pasqualetti P, Morrone S, Santoni A, Naro F, Colao A, Pivonello R, Lenzi A. Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2018;**6**(3):173–185.
9. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf*. 2007;**16**(4):393–401.
10. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Informatics Primary Care*. 2011;**19**(4):251–255.
11. Iqbal K, Halsby K, Murray RD, Carroll PV, Petermann R. Glucocorticoid management of adrenal insufficiency in the United Kingdom: assessment using real-world data. *Endocr Connect*. 2018;**8**(1):20–31.
12. Jenkins-Jones S, Parviainen L, Porter J, Withe M, Whitaker MJ, Holden SE, Morgan CL, Currie CJ, Ross RJM. Poor compliance and increased mortality, depression and healthcare costs in patients with congenital adrenal hyperplasia. *Eur J Endocrinol*. 2018;**178**(4):309–320.
13. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Saf*. 2009;**18**(1):76–83. https://www.biorxiv.org/content/10.1101/628156v2.supplementary-material
14. Fleming DM, Cross KW, Barley MA. Recent changes in the prevalence of diseases presenting for health care. *Br J Gen Pract*. 2005;**55**(517):589–595.
15. UK Data Service Census. https://census.ukdataservice.ac.uk/get-data/related/deprivation.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;**40**(5):373–383.
17. Crooks CJ, West J, Card TR. A comparison of the recording of comorbidity in primary and secondary care by using the Charlson Index to predict short-term and long-term survival in a routine linked data cohort. *BMJ Open*. 2015;**5**(6):e007974.

18. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev.* 2002;**23**(3):327–364.
19. Parlato F, Pisano G, Brillante M, Ferrone R, Cavalcanti MR, Cosentini E, Misiano G, Brai M, Bellastella A. Immunological pattern in patients with 21-hydroxylase deficiency. *J Endocrinol Invest*. 1994;**17**(8):635–639.
20. Fardet L, Petersen I, Nazareth I. Common infections in patients prescribed systemic glucocorticoids in primary care: a population-based cohort study. *PLoS Med*. 2016;**13**(5):e1002024.
21. Murray RD, Ekman B, Uddin S, Marelli C, Quinkler M, Zelissen PM; EUAIRI. Management of glucocorticoid replacement in adrenal insufficiency shows notable heterogeneity: data from the EU-AIR. *Clin Endocrinol*. 2017;**86**(3):340–346.
22. Gagliardi L, Nenke MA, Thynne TR, von der Borch J, Rankin WA, Henley DE, Sorbello J, Inder WJ, Torpy DJ. Continuous subcutaneous hydrocortisone infusion therapy in Addison's disease: a randomized, placebo-controlled clinical trial. *J Clin Endocrinol Metab*. 2014;**99**(11):4149–4157.
23. Mallappa A, Nella AA, Sinaii N, Rao H, Gounden V, Perritt AF, Kumar P, Ling A, Liu CY, Soldin SJ, Merke DP. Long-term use of continuous subcutaneous hydrocortisone infusion therapy in patients with congenital adrenal hyperplasia. *Clin Endocrinol*. Ref;89(4):399–407.
24. Muller L, Quinkler M. Adrenal disease: imitating the cortisol profile improves the immune system. *Nat Rev Endocrinol*. 2018;**14**(3):137–139.
25. Stoupa A, Gonzalez-Briceno L, Pinto G, Samara-Boustani D, Thalassinos C, Flechtner I, Beltrand J, Bidet M, Simon A, Piketty M, Laborde K, Morel Y, Bellanne-Chantelot C, Touraine P, Polak M. Inadequate cortisol response to the tetracosactide (Synacthen®) test in nonclassic congenital adrenal hyperplasia: an exception to the rule? *Horm Res Paediat*. 2015;**83**(4):262–267.
26. Ahmed H, Farewell D, Jones HM, Francis NA, Paranjothy S, Butler CC. Incidence and antibiotic prescribing for clinically diagnosed urinary tract infection in older adults in UK primary care, 2004–2014. *PLoS One*. 2018;**13**(1):e0190521.
27. Hak E, Rovers MM, Kuyvenhoven MM, Schellevis FG, Verheij TJ. Incidence of GP-diagnosed respiratory tract infections according to age, gender and high-risk co-morbidity: the Second Dutch National Survey of General Practice. *Fam Pract*. 2006;**23**(3):291–294.
28. Forss M, Batcheller G, Skrtic S, Johannsson G. Current practice of glucocorticoid replacement therapy and patient-perceived health outcomes in adrenal insufficiency - a worldwide patient survey. *BMC Endocr Disord*. 2012;**12**:8.
29. Arlt W, Willis DS, Wild SH, Krone N, Doherty EJ, Hahner S, Han TS, Carroll PV, Conway GS, Rees DA, Stimson RH, Walker BR, Connell JM, Ross RJ. Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. *J Clin Endocrinol Metab*. 2010;**95**(11):5110–5121.
30. Trigunaite A, Dimo J, Jorgensen TN. Suppressive effects of androgens on the immune system. *Cell Immunol*. 2015;**294**(2):87–94.
31. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;**61**(40):816–819. https://www.ncbi.nlm.nih.gov/pubmed/23051612/
32. Whitaker M, Debono M, Huatan H, Merke D, Arlt W, Ross RJ. An oral multiparticulate, modified-release, hydrocortisone replacement therapy that provides physiological cortisol exposure. *Clin Endocrinol*. 2014;**80**(4):554–561.