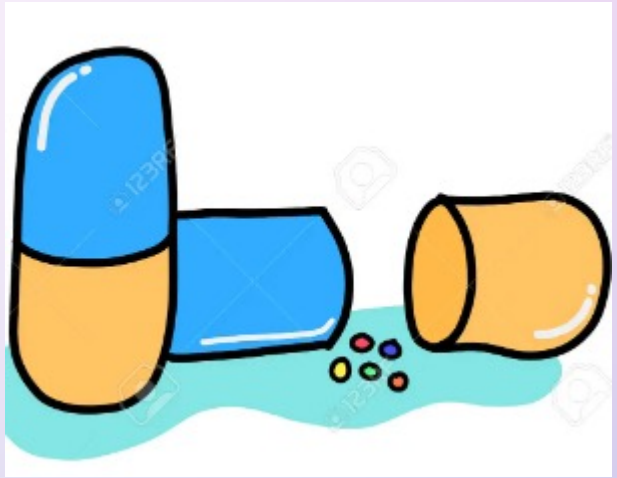
NAVIGATING THE WOBBLES OF LONG TERM ANTIFUNGAL THERAPY

DR ANNA WILD

SPR INFECTIOUS DISEASES/ MICROBIOLOGY

NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST

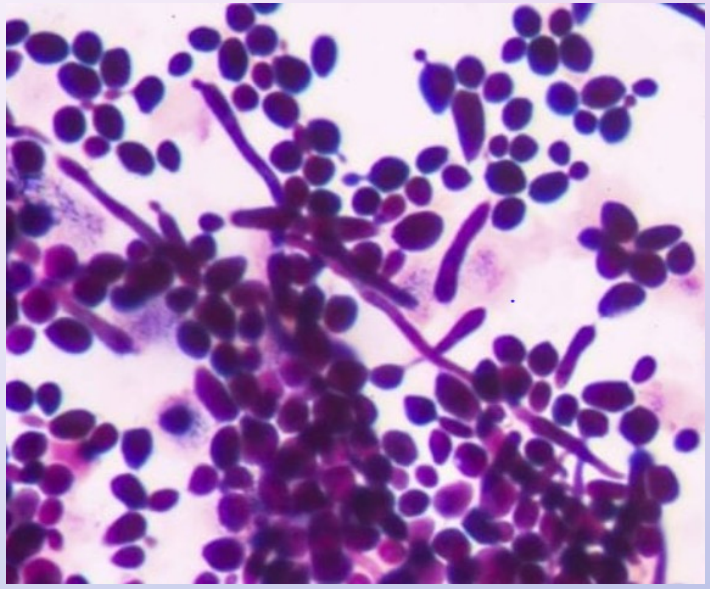
CONTEXT



- HOW MANY OF YOU HAVE PATIENTS ON ANTI-FUNGALS?
- CURRENTLY- 67 PATIENTS. 6 ON ANTIFUNGALS (9%)
- X3 FLUCONAZOLE
- X2 VORICONAZOLE
- X1 CASPOFUNGIN
- RANGING FROM 3/12 TO LIFELONG
- CONDITIONS- IE, SINUSITIS, CHRONIC CAVITATING ASPERGILLOSIS, CHRONIC OM MANDIBLE. NOE

FUNGI ARE HARD TO TREAT

- LIMITED AGENTS
- RESISTANCE
- PK/PD AND TISSUE PENETRATION
- SIDE EFFECTS AND TOLERABILITY



General side-e

Common or very con

Diarrhoea; gastrointestina

Uncommon

Dizziness; flatulence; hepa

Rare or very rare

Agranulocytosis; alopecia; interval prolongation; seve torsade de pointes

Specific side-effects:

Uncommon

With parenteral

Anaemia; appetite hyperhidrosis; insc

Rare or very ra

With parenteral

Angioedema; face

Frequency not

With oral use

Cardio-respiratory

General side-effects:

Common or very common

Acute kidr
bone marr
diarrhoea;
inflammat
hepatic di
leucopeni
pulmonary
syncope; t

Uncomr

Adrenal in
gallbladde
lymphade
pancreatit
enterocoli
adverse re

Rare or very rare

Angioedema; cardiac conduction disorders; disseminated intravascular coagulation; hyperthyroidism

Frequency not known

Cutaneous lupus erythematosus; periostitis (more common in transplant patients); squamous cell carcinoma (more common in presence of phototoxicity)

Specific side-effects:

Frequency not known

With intravenous use

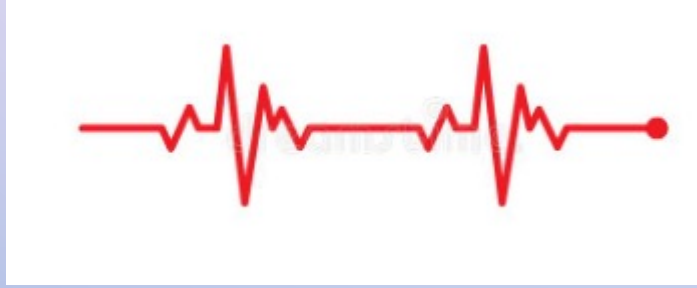
Infusion related reaction

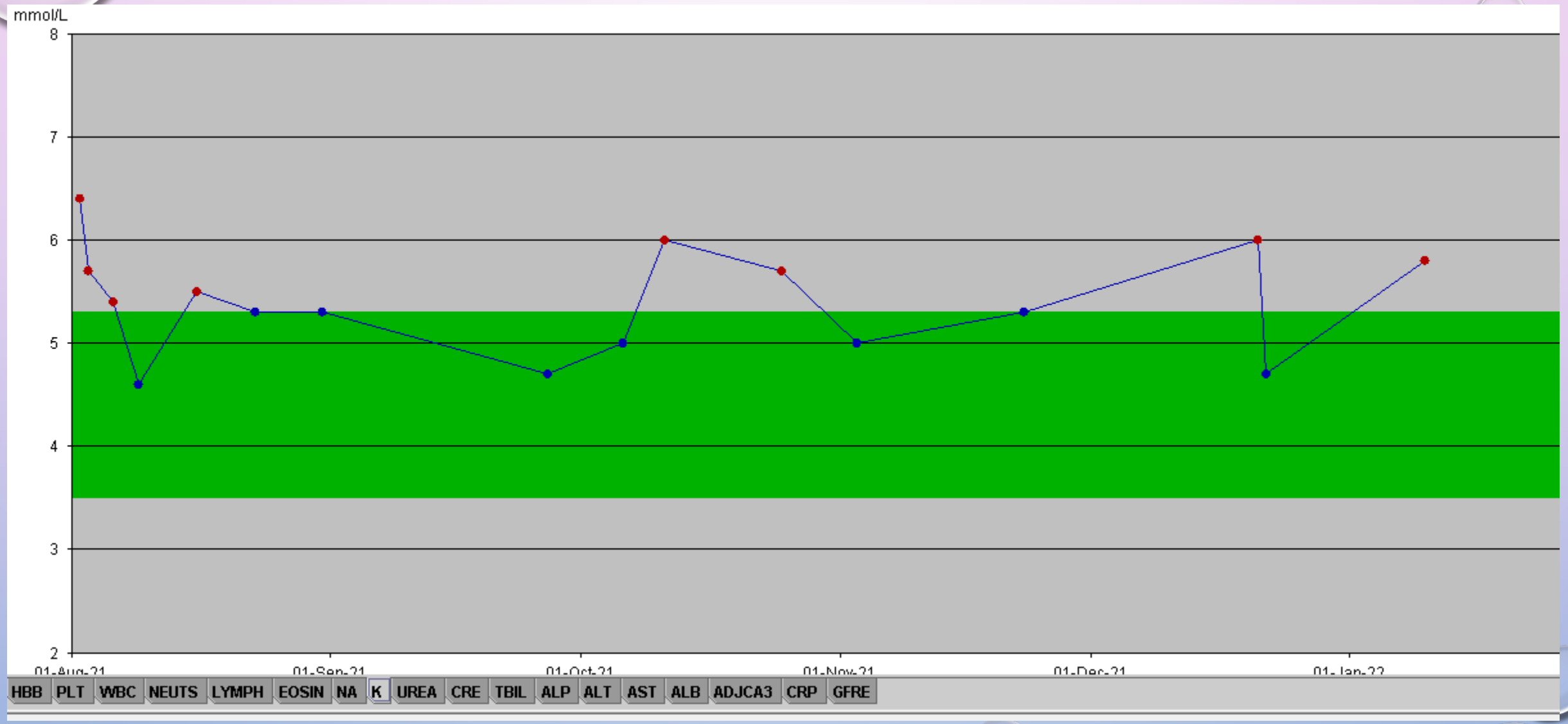
CASE

- FUNGAL IE – NOT SUITABLE FOR SURGERY
- POTENTIAL UROLOGICAL FUNGAL BALLS
- TREATED WITH IV ANIDULAFUNGIN 6 WEEKS + PO FLUCONAZOLE 2 WEEKS AS AN INPATIENT
- PLAN- LIFELONG SUPPRESSION FLUCONAZOLE
- COMMENCED 400MG OD
- BG- T2DM, ILEOSTOMY FOR PREVIOUS UC, CKD 3, HYPOTHYROID, CABG

OPAT MONITORING

- BLOODS- WEEKLY → TWO WEEKLY
- QTC MONITORING- ECG LEAST ONCE/MONTH




mmol/L
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01-Jan-22
HBB
PLT
WBC
NEUTS
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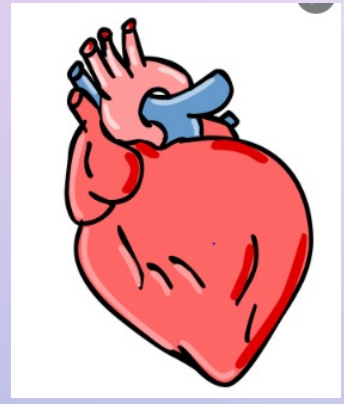
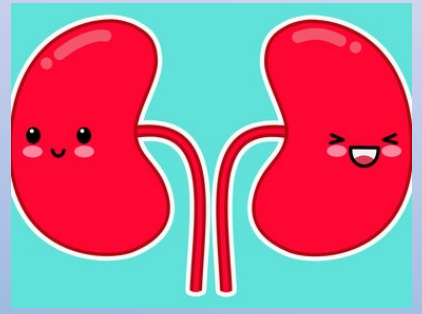
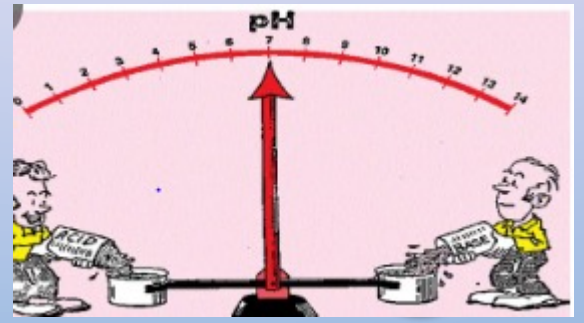
GFRE


105

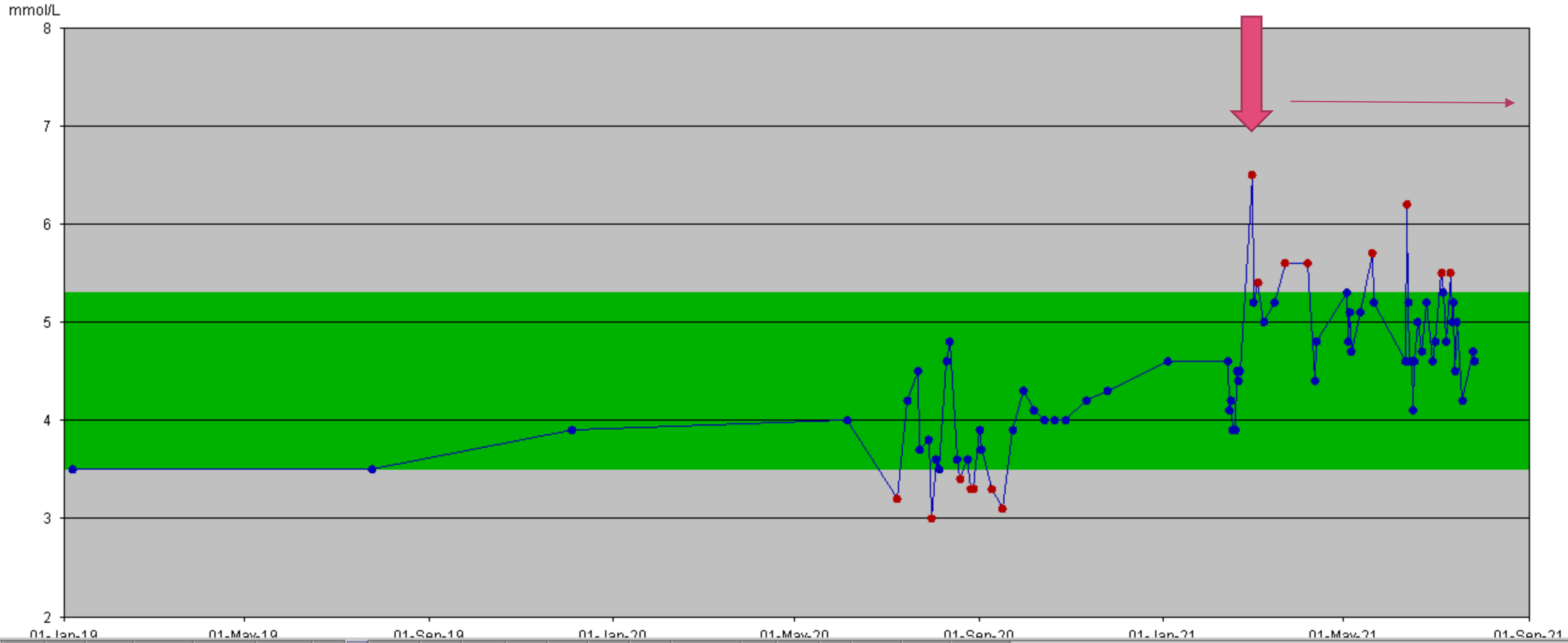





pH

HOW WOULD YOU MANAGE THIS?

- MDT APPROACH- LETTERS TO GASTRO, DIETICIAN, DIABETES, CARDIOLOGY, RENAL
- DEC 21- UNWELL, PH 7.18, K 6.0, WBK 6.1, VBG K 6.0
- ADMITTED- IV SODIUM BICARBONATE AND DISCHARGED
- FOLLOWING WEEK K 5.8.
- MEDS – AMLODIPINE HELD. NIL ELSE
- 13/1- INCREASED ORAL SODIUM BICARBONATE 1G TDS
- SST ALREADY DONE JULY/AUG- CORTISOL NORMAL
- RPT K 18/1 ON HIGHER DOSE = K 5.9
- WHAT NOW?- DM BEING MANAGED, DIETICIAN INPUT LOW K DIET, GAINING WEIGHT (45KG), BICARBONATE INCREASED, CKD STABLE


mmol/L
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01-Sep-20
01-Jan-21
01-May-21
01-Sep-21

PHONE A FRIEND

- MYCOLOGY REF LAB BRISTOL
- RARE SE FLUCONAZOLE- RENAL TUBULAR ACIDOSIS
- NOT IN BNF
- EMC-

lymphocutaneous sporotrichosis and histoplasmosis is limited, which prevents specific dosing recommendations.

Renal system

Fluconazole capsule should be administered with caution to patients with renal dysfunction (see section 4.2).

Adrenal insufficiency

Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely seen be applicable to fluconazole. Adrenal insufficiency relating to concomitant treatment with Prednisone is described in section 4.5, 'The effect of fluconazole on other medicinal products'

*Fluconazole and Renal tubular acidosis, a phase IV clinical study of FDA data - eHealthMe

LITERATURE SEARCH

Fluconazole and Renal tubular acidosis - a phase IV clinical study of FDA data

Summary:

Renal tubular acidosis is found among people who take Fluconazole, especially for people who are male, 50-59 old, have been taking the drug for 1 - 6 months.

The phase IV clinical study analyzes which people take Fluconazole and have Renal tubular acidosis. It is created by eHealthMe based on reports of 53,330 people who have side effects when taking Fluconazole from the FDA, and is updated regularly. You can use the study as a second opinion to make health care decisions.

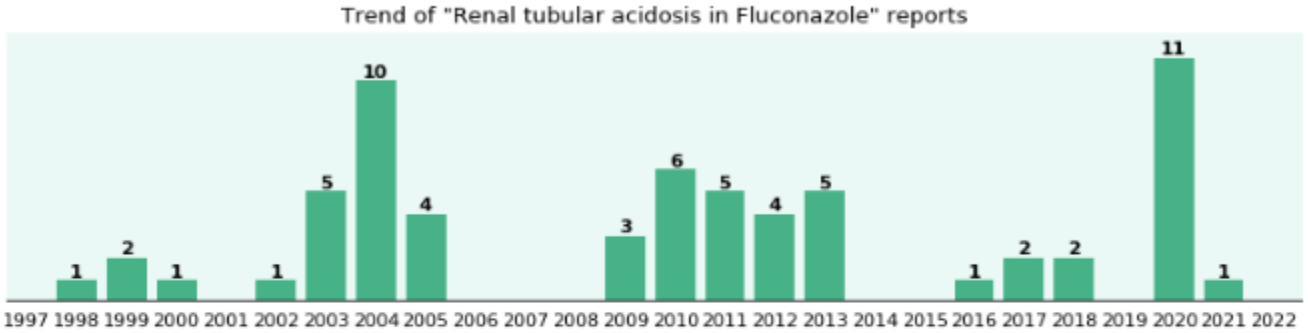
With medical big data and AI algorithms, eHealthMe enables **everyone to run phase IV clinical trial** to detect adverse drug outcomes and monitor effectiveness. Our original studies have been referenced on 600+ peer-reviewed medical publications including The Lancet, Mayo Clinic Proceedings, and Nature. Most recently, phase IV clinial trails for COVID 19 vaccines have been added, check here.

On May, 13, 2022

53,330 people reported to have side effects when taking Fluconazole.

Among them, 64 people (0.12%) have Renal tubular acidosis.

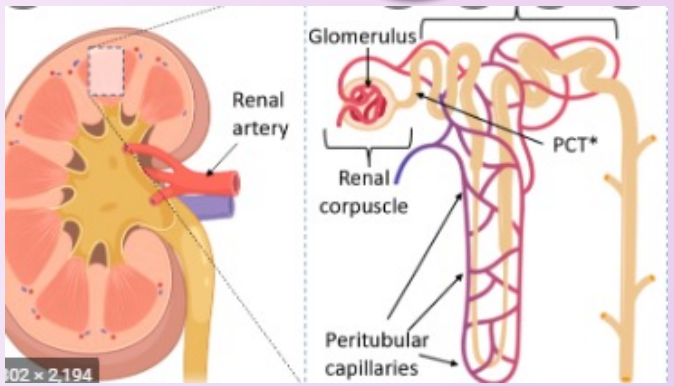
Number of Fluconazole and Renal tubular acidosis reports submitted per year:



Time on Fluconazole when people have Renal tubular acidosis *:

- < 1 month: 33.33 %
- 1 - 6 months: 50.0 %
- 6 - 12 months: 0.0 %
- 1 - 2 years: 0.0 %
- 2 - 5 years: 16.67 %
- 5 - 10 years: 0.0 %
- 10+ years: 0.0 %

RENAL TUBULAR ACIDOSIS



- TYPE 1- DISTAL -LOW HCO3, LOW K→ E.G. SLE, SJORGENS SYNDROME
- TYPE 2- PROXIMAL– LOW HCO3 , LOW K→ E.G. HIV MEDS, PART OF FANCONI SYNDROME
- TYPE 3- MIXTURE OF 1&2
- TYPE 4- LOW HCO3, HIGH K → UNABLE TO REMOVE K FROM TUBULES- SECONDARY TO LOW ALDOSTERONE/ KIDNEYS NOT RESPOND TO ALDOSTERONE OR DISEASES THAT AFFECT HOW THE KIDNEYS WORK E.G. OBSTRUCTION

nOtes | last vAlue

Point Of Care

Taken: 21-DEC-2021

PATIENT TEMPERATURE	36.4			
PH(T) (POC) TEMP CORRECT	7.180		[7.350 - 7.450]	
PCO2(T) (POC) TEMP CORRE	5.36	kPa	[4.67 - 6.40]	
PO2(T) (POC) TEMP CORREC	4.37	kPa	[11.10 - 14.40]	
CHCO3-(P.ST)(POINT OF CA	14.0	mmol/L	[19.0 - 28.0]	
CHCO3-(P) (POINT OF CARE	15.1	mmol/L		
CBASE(ECF) (POINT OF CAR	-13.3			
PSO2 (POINT OF CARE)	56.2	kPa	[95.0 - 100.0]	
HAEMATOCRIT (POINT OF CA	37.4	%	[40.0 - 54.0]	
PO2HB	55.4	%	[94.0 - 98.0]	
COHB (POINT OF CARE)	1.4	%	[0.5 - 1.5]	
METHAEMOGLOBIN (POINT OF	0.1	%	[0.0 - 1.5]	

TYING IT ALL TOGETHER

- NEVER TESTED ALDOSTERONE
- HOWEVER POORLY CONTROLLED DM WITH DIABETIC CKD CAN CAUSE CHRONIC LOW ALDOSTERONISM
- HOWEVER …. BEEN DM FOR LONG TIME … K FINE UNTIL MARCH/APRIL- ANTI-FUNGALS GIVEN
- DID THE FLUCONAZOLE TIP THE APPLE CART?
- KETOCONAZOLE, VORICONAZOLE LISTED TO CAUSE ADRENAL INSUFFICIENCY- CAN RESULT LOW ALDOSTERONE (AFFECTING RAAS) , LOW CORTISOL
- ?CLASS EFFECT WITH FLUCONAZOLE AFFECTS ALDOSTERONE PATHWAY IN ADRENALS ??DOES IT SPARE CORTISOL ?

Specific side-effects:

Common or very common

With oral use

Adrenal insufficiency; diarrhoea; gastrointestinal discomfort; nausea; vomiting

Uncommon

With oral use

Allergic conditions; asthenia; dizziness; drowsiness; headache; thrombocytopenia

With topical use

Excessive tearing; folliculitis; hair changes

Uncommon

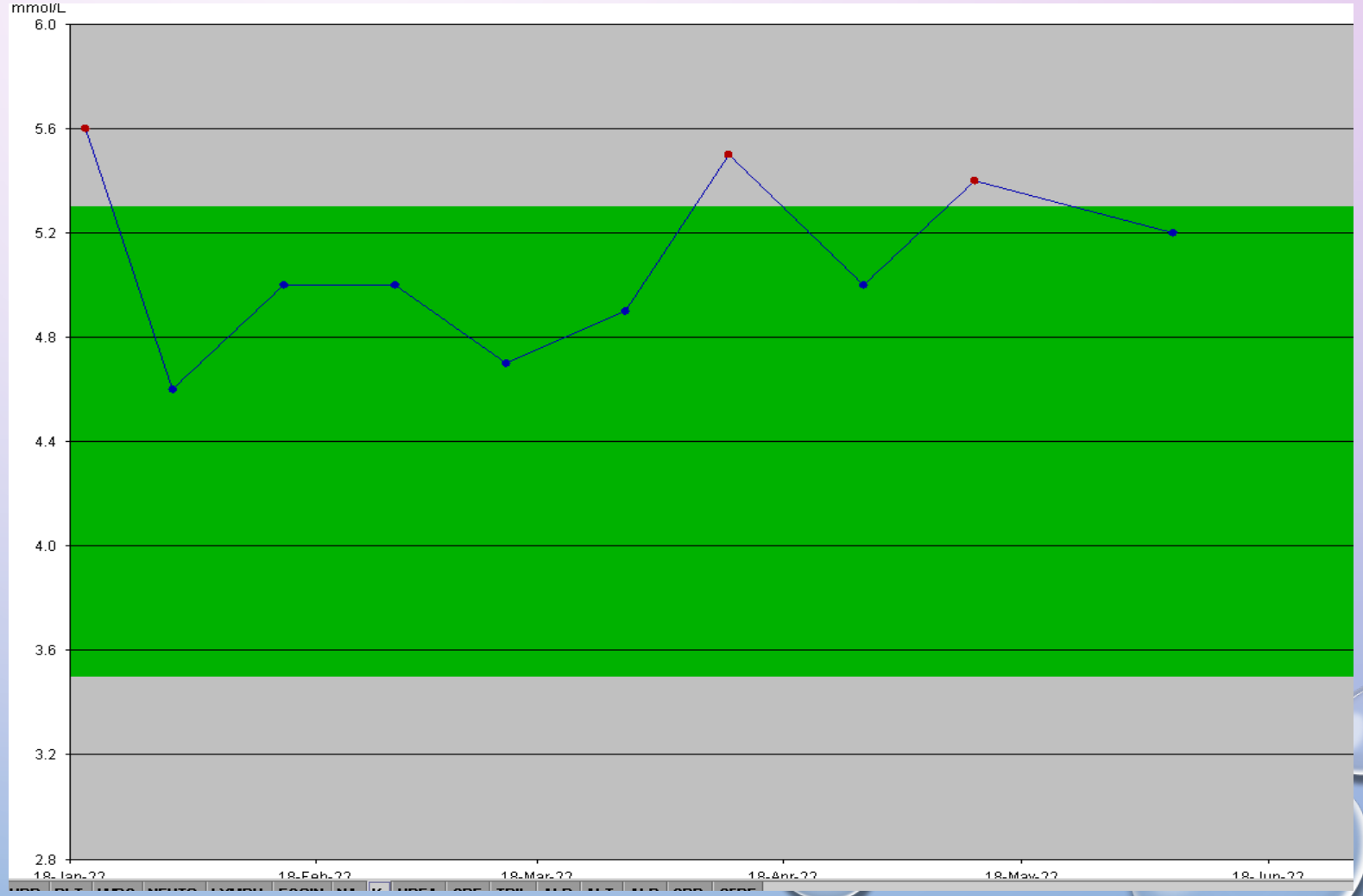
Adrenal insufficiency; arth
gallbladder disorders; hear
lymphadenopathy; lympha
pancreatitis; parkinsonism
enterocolitis; QT interval p
adverse reactions (SCARs)

Rare or very rare

Angioedema; cardiac cond
hyperthyroidism

OUTCOME

- ADVISED TO SPLIT FLUCONAZOLE 400MG OD → 200MG BD
- MIRACULOUSLY WORKED!
- K BEEN <5.6 EVER SINCE



TAKE HOME MESSAGES

- ANTIFUNGALS NEED CLOSE MONITORING IN LONG-TERM USE
- CONSIDER THE SPECIFIC SIDE EFFECTS LISTED IN BNF IN ADDITION TO THE GENERAL
- CONSIDER RTA WITH FLUCONAZOLE IF FITS – LOW HCO3, HIGH K- CHECK ALDOSTERONE
- SPLITTING THE DOSE MAY HELP

THANK YOU

- REFERENCES

- *FLUCONAZOLE AND RENAL TUBULAR ACIDOSIS, A PHASE IV CLINICAL STUDY OF FDA DATA - EHEALTHME
- VORICONAZOLE | DRUGS | BNF | NICE
- FLUCONAZOLE | DRUGS | BNF | NICE
- FLUCONAZOLE 150MG CAPSULES - SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) - (EMC) (MEDICINES.ORG.UK)
- RENAL TUBULAR ACIDOSIS | NIDDK (NIH.GOV)