**Question 52**
A 35yo man presents with bilateral gynaecomastia. He has a past history of viral orchitis. He has hypertension treated with spironolactone and admits to binge drinking of alcohol. Examination reveals normal body hair distribution and 20mL testicles bilaterally. He has moderate bilateral gynaecomastia.

Investigations show:

<table>
<thead>
<tr>
<th>Serum</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>normal</td>
</tr>
<tr>
<td>LH</td>
<td>&lt;1 [1-9]</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>250 [40-110]</td>
</tr>
<tr>
<td>Prolactin</td>
<td>350 [&lt;400]</td>
</tr>
<tr>
<td>DHEAS</td>
<td>10 [2-12]</td>
</tr>
</tbody>
</table>

Which of the following is the most important next step in management of his gynaecomastia?

A. Cease alcohol intake  
B. MRI scan of pituitary  
C. Testicular ultrasound  
D. Karyotype analysis  
E. Cease treatment with spironolactone

**GYNAECOMASTIA**

- Definition: histologically benign proliferation of the glandular tissue of the male breast and clinically by the presence of a rubbery or firm mass extending concentrically from the nipples  
- DDx: carcinoma (usually eccentrically located and unilateral), neurofibromas, lymphangiomas, haematomas, lipomas, dermoid cysts, pseudogynaecomosta = fat)

**Pathogenesis**

- Decreased androgen production, increased oestrogen production or increased availability of oestrogen precursors for peripheral conversion to oestrogen.  
- Other mechanism is androgen receptor blockade and increased binding of androgen to sex-hormone binding globulin (SHBG)  
- There is an imbalance between inhibitory effects of androgen and stimulatory effects of oestrogen

**Sites of sex hormone production in males**

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<table>
<thead>
<tr>
<th>Steroid producing organ</th>
<th>Blood</th>
<th>Extragenadal tissues</th>
<th>Blood</th>
<th>Target cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testes</td>
<td>E2</td>
<td>T</td>
<td>E2</td>
<td>E2 + ER</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T + AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ SHBG</td>
<td></td>
<td>DHT + AR</td>
</tr>
<tr>
<td>Adrenals</td>
<td>A</td>
<td>A</td>
<td>E1</td>
<td>E1 + ER</td>
</tr>
</tbody>
</table>

Sites of production and metabolism of sex steroid hormones in males.  
E2: estradiol; T: testosterone; E1: estrone; SHBG: sex hormone binding globulin; A: androstenedione; ER: estrogen receptor; AR: androgen receptor; DHT: dihydrotestosterone.
- In adult men, 95% of testosterone, 15% of oestradiol and <5% of oestrone secreted by the testes
- Androstenedione secreted by adrenal glands
- Most of oestradiol and oestrone converted from androstenedione in tissues
- Most androgens and oestrogens are bound to SHBG, androgens bind more strongly
- Any substance that displaces sex hormones from SHBG will tend to displace oestrogens more

**Specific conditions**

- Persistent pubertal gynaecomastia (25%)
- Drugs (10 – 25%)
- No detectable abnormality (25%)
- Cirrhosis or malnutrition (8%)
- Primary hypogonadism (8%)
- Testicular tumours (3%)
- Secondary hypogonadism (2%)
- Hyperthyroidism (1.5%)
- Chronic renal insufficiency (1%)

**Drugs associated with gynecomastia**

**Antiandrogens/inhibitors of androgen synthesis**
- Cyproterone acetate
- Flutamide
- Finasteride
- **Antibiotics**
- Ethionamide
- Isoniazid
- Ketoconazole
- Metronidazole
- **Antulcer drugs**
- Cimetidine
- Ranitidine
- Omprazole
- **Cancer chemotherapeutic drugs**
- Alkylating agents
- Methotrexate
- Vinca alkaloids
- Combination chemotherapy
- Imatinib
- **Cardiovascular drugs**
- Amiodarone
- Captopril
- Digiotin
- Diltiazem
- Enalapril
- Methyldopa
- Nifedipine
- Reserpine
- Spiromonolactone
- Verapamil

**Drugs of abuse**
- Alcohol
- Amphetamines
- Heroin
- Marijuana
- Methadone

**Hormones**
- Androgens
- Anabolic steroids
- Chorionic gonadotropin
- Estrogens
- Growth hormone

**Psychoactive drugs**
- Diazepam
- Haloperidol
- Phenothiazines
- Tricyclic antidepressants

**Other**
- Auranofin
- Diethylpropion
- Domperidone
- Etretinate
- Metclopramide
- Phenytoin
- Penicillamine
- Sulindac
- Theophylline
- Spironolactone can increase the aromatisation of testosterone to oestradiol, enhance the conversion of testosterone to androstenedione, decrease the testosterone production rate by the testes and displace testosterone from SHBG, thereby increasing its metabolic clearance rate. Can also act as an antiandrogen by binding to androgen receptors and displacing testosterone/dihydrotestosterone from the receptors.
- Spironolactone vs placebo: endocrine side effects 10% vs 3%
- Endocrine side effects were same as in placebo group for epleronone (more selective aldosterone antagonist)

**Cirrhosis:**
- Increased production rate of androstenedione from the adrenals
- Enhanced aromatisation of androstenedione to oestrone
- Increased conversion of oestrone to oestradiol
- Elevated serum SHBG → reduced free testosterone

**Malnutrition**
- Gonadotropin and testosterone levels probably lower during starvation
- Oestrogen levels normal (due to production from adrenal precursors)

**Male hypogonadism**
- Primary
  - Congenital (eg: Klinefelter’s or enzymatic defect in testosterone production)
  - Trauma
  - Infection
  - Infiltrative disorders
  - Vascular insufficiency
  - Ageing
- Leads to decreased serum testosterone concentration and a compensatory rise in LH release
- Excess LH results in enhanced Leydig cell stimulation with inhibition of enzymes and increased aromatisation of testosterone to oestradiol → increased oestradiol secretion
- Secondary
  - Due to hypothalamic or pituitary abnormalities
  - Production of LH is deficient → low testosterone production
  - Adrenal cortex continues to produce oestrogen precursors

**Testicular Neoplasms**
- Germ cell tumours 95% of testicular neoplasms
- 2.5-6% have gynaecomastia at presentation – poor prognostic sign
- Due to increased hCG
- Leydig cell tumours 2% of testicular neoplasms
- ~10% malignant
- 6-10yo precocious puberty
- 26-35yo testicular mass, gynaecomastia, impotence, loss of libido
- Secrete oestradiol, which also inhibits gonadotropin secretion leading to reduced testosterone production and secondary hypogonadism
- Sertoli cell tumours → excessive aromatase activity
Hyperthyroidism
- 10-40% of men with Grave's disease get gynaecomastia
- Increased concentration of SHBG → increased binding of testosterone relative to oestradiol
- Enhanced aromatisation

Chronic renal failure and dialysis
- 50% of haemodialysis pts
- Leydig cell dysfunction → low serum testosterone, appropriately elevated gonadotropins

Feminising adrenocortical tumours
- Rare
- Malignant in 75% of cases
- Median survival 1.5yrs
- Serum dehydroepiandrosterone sulfate, 17-hydroxyprogesterone and oestradiol increased
- Testosterone low

Ectopic production of hCG
- hCG-secreting hepatoblastomas → precocious puberty
- Large cell carcinoma of lung, gastric carcinoma, renal cell carcinoma, occasionally hepatoma

Androgen insensitivity syndromes
- Defect or absence of intracellular androgen receptor
- Variable clinical spectrum

Evaluation of gynecomastia

![Algorithm for interpretation of serum hormone levels and suggestions for further evaluation of patients with gynecomastia.](image)

Algorithm for interpretation of serum hormone levels and suggestions for further evaluation of patients with gynecomastia.
NL: normal; hCG: human chorionic gonadotropin; LH: luteinizing hormone; T: testosterone; E2: estradiol; CT: computed tomography; T4: thyroxine; TSH: thyroid-stimulating hormone; MRI: magnetic resonance imaging.