There is so much we don’t know in medicine that could make a difference, and often we focus on the big things, and the little things get forgotten. To highlight some smaller but important issues, we’ve put together a series of pearls that the Red Whale found at the bottom of the ocean of knowledge!

Acne

In this section I have drawn together information from multiple different sources, each of which I have referenced. There have been two good recent clinical reviews in the Lancet and BMJ and I have taken the best of both of these to form this section. First an overview of the different treatments available, then a rational approach to treatment.

Remember:
- Acne has four contributory factors:
  - Inflammation.
  - Proliferation of Propionibacterium acnes.
  - Comedones (black heads and white heads) due to abnormal keratin proliferation.
  - Androgen driven sebum production.
  Which are most dominant in your patient? Deciding this will help select the best treatment!
- All therapies for acne work on ‘tomorrow’s’ skin; improvement takes 3-6 weeks minimum and may take 3-6m for maximal effect to be seen.
- There have been very few head-to-head trials of acne treatments, and most studies have been small (most significantly fewer than 100 patients!)

Treatments for acne

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of action</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet and lifestyle</td>
<td>Varied</td>
<td>✷ Diet (including chocolate!) has not been shown to make any difference, although a recent systematic review suggests that a high dairy diet and those with ‘high glycaemic loads’ may be associated with more severe acne.</td>
</tr>
<tr>
<td>Soap, skin cleaners, abrasives</td>
<td>Varied</td>
<td>✷ Evidence of benefit as a first line agent in mild acne, but no additional benefit if used alongside prescribed therapies.</td>
</tr>
</tbody>
</table>
| Benzoil peroxide              | Anti-inflammatory and antimicrobial, mild comedolytic | ✷ Lower concentrations (2.5% or 5%) are equally effective as 10%, but cause less skin irritation.  
                                |                                                                            | ✷ Skin irritation improves over time and can be reduced by starting alternate days and gradually increasing to regular daily use.  
                                |                                                                            | ✷ Rapidly improves inflammatory lesions and reduces antibiotic resistance.  
                                |                                                                            | ✷ All topical retinoids (except adapalene) are unstable with benzoil peroxide. Apply at a different time of day. |
| **Topical retinoids** | Comedolytic | - Can be used in all types of acne, except where an oral retinoid is being taken.  
- **Women of child-bearing age should use contraception. Do not use in pregnancy/if breast-feeding.**  
- Improvement within weeks but maximum benefits at 3-4m.  
- Useful as maintenance treatment because prevents comedone formation.  
- Where inflammation is present, topical retinoids should be combined with either benzoyl peroxide (applied at the opposite end of the day) or a topical antibiotic.  
- All topical retinoids can cause initial skin irritation - start alternate or every third day and build up gradually over a few weeks.  
- Adapalene seems to be the best tolerated, but tazarotene may be the most effective. |
| **Topical azelaic acid** | Works against comedones and pustules | - Can cause hypopigmentation in darker skins so monitor for this.  
- Limited evidence of benefit! |
| **Topical antibiotics** | Antibacterial and anti-inflammatory | - Erythromycin and clindamycin are most commonly used.  
- Useful where inflammatory lesions dominate.  
- Bacterial resistance develops quickly so courses should be limited to 12w and they should be used with a topical retinoid (improves efficacy of antibiotics) and/or benzoyl peroxide which reduces resistance.  
- Don't use combined oral and topical antibiotics (no additional benefit, increased resistance). |
<table>
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<tr>
<th>Oral antibiotics</th>
<th>Antibacterial and anti-inflammatory</th>
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|                   | • For moderate to severe inflammatory acne.  
|                   | • Probably no more effective than topical antibiotics, but helpful where acne covers large areas, e.g. the back, and topicals difficult to apply.  
|                   | • No antibiotic has been shown to be more effective than any other - tetracycline, oxytetracycline, doxycycline, and erythromycin are most commonly used. Do NOT use minocycline (see below).  
|                   | • Once daily dosing of oxy/tetracycline is most cost-effective.  
|                   | • As with topical antibiotics, always use in conjunction with benzoyl peroxide or topical retinoid to minimise the risk of bacterial resistance.  
|                   | • Assess response at 6-8w and try to limit courses to 12w.  
|                   | • Tetracyclines should not be used in under 12s or women of child-bearing age who are not using contraception because of the risk of teeth discolouration and bone damage. |

<table>
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<tr>
<th>Contraceptive pills</th>
<th>Reduce sebum production</th>
</tr>
</thead>
</table>
|                     | • For women with moderate to severe acne, especially if lesions confined to lower face and jaw (anecdotally seems to correspond to hormonal acne) who require contraception.  
|                     | • Are certain pills better than others? NO! Evidence on varying effectiveness of different progesterones may have been overplayed in the past. A recent Cochrane review agreed and identified no differences in efficacy between different COCP preparations including cyproterone acetate (Dianette) (Cochrane 2012;7:CD004425). Remember though that progesterone-based contraceptives may make skin worse.  
|                     | • Most women with acne have normal androgen levels. |
Treatment options by severity

So, here is a flow chart to apply some of that knowledge (Lancet 2012;379:361). BZP = benzoyl peroxidase:
MILD

Mainly pustules?

BZP 2.5%

Mainly comedones?

Topical retinoids

Mixed comedones and pustules?

Either

BZP + topical antibiotics

or

BZP + topical retinoids

Start alternate days, review response at 6w, if insufficient, step up to:

Add in to the above, one of the following that is not already being used:

- Topical retinoids
- Topical antibiotic
- BZP
- Azelaic acid

Start alternate days, review response at 6w, if insufficient, manage as for moderate acne.

MODERATE

Need contraception?

YES

COCP

Assess at 6w, if insufficient, offer any of the following:

- Oral antibiotics plus BZP
- Oral antibiotics plus topical retinoids.
  (Do NOT use oral and topical antibiotics together)

If oral antibiotic combination beneficial:

- continue for 4–6m, then stop. Use 2.5%
  BZP for 2w to reduce resistance, then use a
  topical preparation until acne flares, when oral
  antibiotics can be restarted.

If initial benefit lost within 2–6m:

- STOP oral antibiotics, use BZP for 2w to reduce
  resistance and START alternative oral antibiotic.
  If still insufficient, treat as for severe acne.

SEVERE

If after 2 x 8w of oral antibiotics there is insufficient benefit proceed to retinoids.

Do not wait for scarring!
**IMPORTANT SAFETY INFORMATION: MINOCYCLINE**

DTB reminds us (DTB 2013;51:48):

- There is no role for minocycline in the treatment of acne.
- Other tetracyclines are equally effective and do not carry the same risks of SLE, autoimmune hepatitis and slate grey skin pigmentation.
- NICE have recommended 'review and revise prescribing as appropriate in light of potential harms'.
- The DTB recommend more urgent action and suggest that minocycline should be removed from local formularies and prescribers justify each prescription individually.

Whilst prescribing has fallen, there are still 100 000 scripts per year - how many are yours?

**DRUG DILEMMA: Cyproterone acetate with ethinylestradiol (co-cyprindiol)(Dianette)**

The MHRA issued a new safety and licensing update following a Europe-wide review which suggests that the balance of benefits to risks are favourable for specific groups of women (Drug Safety Update 2013;6(11):A3):

- Licensed for use in women of reproductive age for the treatment of:
  - androgen-sensitive skin conditions, e.g. severe acne
  - hirsutism.
  - It should only be used when topical treatment and systemic antibiotics have failed.
- It is an effective contraceptive but should not be used solely as a contraceptive.
- It should not be co-prescribed with another COCP.
- The risk of VTE is low but we should remain vigilant - it is 1.5-2 times more likely to cause VTE than levonorgestrel containing pills, but similar to desogestrel, gestodene and drospirenone containing pills.

**DRUG DILEMMA: Oral retinoids and pregnancy prevention**

The MHRA issued a reminder about the importance of pregnancy prevention in women taking oral retinoids - it is relevant to us as GPs because we are likely to be prescribing the contraception (Drug Safety Update 2013;6(11):H1):

- Pregnancy should be excluded before starting retinoids with a sensitive HCG test.
- Women should be on at least one, and ideally two, forms of complementary contraception, e.g. hormonal and barrier.
- Women should continue contraception for:
  - At least 1m after completing isoretinoin or acitretin.
  - At least 2y after completing acitretin (used for severe psoriasis).
- There is no evidence that maternal exposure to semen from patients taking an oral retinoid is associated with any teratogenic effect.

**Isotretinoin and suicide**

There has always been a concern about isotretinoin (Roaccutane) and suicide. This cohort study involved almost every person in Sweden prescribed isotretinoin over a 10y period (5700 patients) (BMJ 2010;341:c5812). The researchers were able to identify suicide attempts before, during and after treatment and then adjust the rates according to the expected suicide rate for that age and sex in that calendar year in Sweden. The data showed that although there is an increased risk of suicide that risk is small and may be attributed not just to the drug, but also to the acne itself. The accompanying editorial calculated the NNH (number needed to harm): for a 6m course of isotretinoin the NNH (first suicide attempt) is 2300 (BMJ 2010;341:c5866).

**Isotretinoin and LASIK eye treatment**

A letter in the BMJ reminds us that LASIK (laser refractive eye surgery) is contraindicated in the 6 months before and after isotretinoin because the dry eyes that may occur after both isotretinoin and LASIK can result in corneal ulceration, infection and visual loss (BMJ 2011;342:d3353).
<table>
<thead>
<tr>
<th>Acne</th>
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<tbody>
<tr>
<td>• Topical retinoids prevent comedone formation and can be used in all types of acne - women should use adequate contraception, if co-prescribed with benzoyl peroxide they should be applied at opposite ends of the day.</td>
</tr>
<tr>
<td>• Benzoyl peroxide at 5% is often as effective as 10% and causes less irritation.</td>
</tr>
<tr>
<td>• Beware significant resistance with topical antibiotics - use for 12w maximum duration and always with benzoyl peroxide.</td>
</tr>
<tr>
<td>• Use oral antibiotics for widespread moderate to severe inflammatory acne - choose single daily dose of oxy/tetracycline first line. Try to limit courses to 12w and always use with benzoyl peroxide or topical retinoid to reduce resistance and improve efficacy, respectively.</td>
</tr>
<tr>
<td>• Stop prescribing minocycline.</td>
</tr>
<tr>
<td>• The COCP reduces sebum production and is an effective acne treatment for women with hormonal acne - there is no evidence that any particular COCP (including Dianette) is more effective - start with the one with the lowest VTE risk!</td>
</tr>
<tr>
<td>• Refer severe scarring acne and moderate acne that is treatment-resistant for consideration of oral retinoid treatment - check LFT and lipid profile whilst waiting for appointment.</td>
</tr>
</tbody>
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We make every effort to ensure the information in these pages is accurate and correct at the date of publication, but it is of necessity of a brief and general nature, and this should not replace your own good clinical judgement, or be regarded as a substitute for taking professional advice in appropriate circumstances. In particular check drug doses, side effects and interactions with the British National Formulary. Save insofar as any such liability cannot be excluded at law, we do not accept any liability for loss of any type caused by reliance on the information in these pages.

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March 2016
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The Women’s Health Update Course
From the pill to pelvic pain, periods and prolapses, this one day women’s health update is a comprehensive guide to understanding and managing common gynaecological problems in general practice.

The course covers the latest evidence and guidelines as well as simple ideas which we as GPs have found helpful in our consultations. The subjects are covered in a much greater depth than is possible on the general GP Update course and the day is designed for all GPs and GP STs - not just those with a special interest!

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The Cancer Update Course
Since 2012, Red Whale | GP Update has joined forces with Macmillan Cancer Support to provide this course to give all GPs the knowledge and inspiration they need when dealing with cancer. This course covers the latest evidence and guidelines around cancer prevention, screening, diagnosis, treatment and palliative care, as well as simple ideas which we as GPs have found helpful in our consultations.

2015 has seen the biggest shake up in cancer in the last 10 years with the publication of the updated NICE guidelines on suspected cancer. If, like many of us in England & Wales, you are still finding your way around them, then this course will definitely help!

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