Women taking pill get slightly more breast cancer

The worst reading of this Danish whole population study is that using hormonal contraception causes one extra breast cancer for every 7690 women per year. However, because this is an observational study, it is wrong to use the word “causes,” no matter how good the adjustment for known confounders. Oddly, the authors don’t concede this, instead asserting that: “A quantitative bias analysis showed that a hypothetical unmeasured confounder would need to have a 50% prevalence in the population, increase the risk of breast cancer by a factor of 3, and increase the chance of using hormonal contraception by 2.5 times in order to eliminate the observed relative risk with current or recent use of hormonal contraception.”

Walking in polluted air

In this study, 40 healthy volunteers, 40 people with chronic obstructive pulmonary disease, and 39 with ischaemic heart disease (all aged 60 or older) were monitored before they took a two hour walk down Oxford Street, or across Hyde Park, and for two days afterwards. Levels of air pollution were also measured. The Hyde Park constitutional did these individuals good, improving their lung function and pulse-wave velocity. Less improvement was obtained from walking down Oxford Street, which the authors blame on the buses and taxis belching carbon, nitrogen dioxide and ultrafine particles along that thoroughfare. But as a pedestrian of the same age, I find the main hazard is collision with people walking blindly with large bags of shopping while scanning their mobile phones. Not to mention being jostled by crowds of obstreperous French schoolchildren shouting at each other. It takes one’s breath away. The moral is always the same: avoid Oxford Street.

Starvation diet lowers glucose in “T2DM”

In crueler times, doctors would say to obese patients struggling with diets, “There were no fat people in Belsen.” I heard it with my own ears. In my experience, it is extraordinarily difficult for free living people to lose weight and keep it off. And there is plenty of evidence that on-and-off weight rebound is not a good thing. But here is a trial in which people with type 2 diabetes lost spectacular amounts of weight and kept it off for at least a year. About half of them became “non-diabetic” by current definitions and were able to give up oral medication. What was the intervention applied in primary care by Lean and his colleagues? A formula starvation diet of 825–853 kcal/day for 3–5 months, followed by phased reintroduction of food and continued support. The conclusion drawn is that “Remission of type 2 diabetes is a practical target for primary care.” Well yes. Preferably using an option grid to help people decide between this single one year trial and 10 year hard outcome data from bariatric surgery.

The most important primary care article in the world?

It’s received wisdom that good primary care is the basis for any successful medical system. Now consider a workforce of 1.7 million primary care doctors serving a population of 1.4 billion people. That sounds quite big and important, doesn’t it? This survey of the Chinese primary care system needs reading by anyone interested in the progress of medicine. It’s a superb work of scholarship and analysis. It tries to be positive, but the picture it paints is grim. Paid on average about £5000 per annum, primary care doctors in China have no specific training, no career structure, no standing in the profession, and no trusted position in the community. On the other hand, the Chinese government would like to rebuild the system and train up a new workforce of 400 000 doctors over 10 years. Quite a challenge—but if they succeed, it might create a model for the world. Exciting, if you’re an optimist.
Novel therapies for unresectable and metastatic melanoma

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Patricia McGettigan, clinical senior lecturer in clinical pharmacology, Queen Mary’s University, London. To suggest a topic, please email us at practice@bmj.com.

A 60 year old white woman who had a melanoma excised a year ago presents with multiple subcutaneous nodules along her left shin. Biopsy confirms the lesions as metastatic melanoma, with molecular analysis revealing a BRAF wild type genotype. Imaging also shows small nodules on her lungs. She is recommended to start systemic treatment with immunotherapy.

About 132 000 cases of melanoma are diagnosed globally a year.1 2 Surgical excision is the first line treatment for localised disease.3 A minority of patients present with increased tumour growth or ulceration, or with metastasis (see box, right). The prognosis varies by stage at diagnosis. US data show five year survival rates of 98% for local disease confined to site of origin, 63% for regional metastases with spread to surrounding lymph nodes or tissues, and 17% for distant metastases.4 5 Systemic chemotherapy with drugs such as dacarbazine has shown limited benefits in patients with metastatic melanoma, with median survival between six and 10 months.6 7 Over the past decade, understanding of molecular biology and immune regulation in melanoma has led to advancements in the treatment of unresectable and metastatic melanoma.

What are novel melanoma therapies?

Immunotherapy and targeted therapy are the two major classes of novel melanoma therapies. Table 1 lists individual drugs and approved indications.

Immunotherapy

Dysregulation of immune checkpoint proteins can cause tumour proliferation.8 9 Immunecheckpoint therapies block immune checkpoints such as CTLA-4 (ipilimumab) and PD-1 (pembrolizumab, nivolumab), thereby providing an anti-tumour immune response. Another novel immunotherapy employs a genetically modified herpes simplex virus known as talimogene laherparepvec (T-VEC). T-VEC preferentially invades and replicates within tumour cells, resulting in cell lysis (figure, p 33).10

Targeted therapy

These drugs act on mutations to proteins in the mitogen activated protein kinase (MAPK) pathway such as BRAF, MEK 1/2, and ERK, as well as on c-KIT which activates the MAPK pathway. These pathogenic mutations can cause uncontrolled transcription and tumour growth. About 50% of melanoma patients have a BRAF mutation and 5-6% of patients have a c-KIT mutation.11

How well do they work?

There is only limited moderate quality evidence from direct comparative clinical trials of immunotherapy and targeted therapy with chemotherapy in patients with advanced melanoma. Standard outcomes reported in melanoma therapeutic studies include median overall survival, progression-free survival, and response rate measured as the percentage of patients achieving partial or complete tumour shrinkage.12

Evidence from phase III randomised controlled trials (RCTs) of immunotherapy agents suggests better...
Mechanism of action
FDA and EU
Agency approval
MEK protein† inhibitor
FDA and EU
Not approved by EU or FDA
BRAF protein† inhibitor
FDA and EU or FDA and EU with BRAF V600E or V600K mutation
Table 1 | Classes of novel drugs, their targets, and approval status

Immunotherapy
Ipilimumab
Anti-CTLA-4 protein*
FDA and EU
Pembrolizumab, nivolumab
Anti-PD-1 protein*
FDA and EU regardless of BRAF gene status and prior therapies
T-VEC
Genetically modified herpes simplex virus
FDA and EU
Combination immunotherapy
Nivolumab + ipilimumab
Combination anti-PD-1 and anti-CTLA-4
FDA and EU with wild type BRAF genotype
Targeted therapy
Vemurafenib, dabrafenib
BRAF protein† inhibitor
FDA and EU with BRAF V600E or V600K mutation
Trametinib, cobimetinib
MEK protein† inhibitor
FDA and EU with BRAF V600E or V600K mutation
Cobimetinib
C-Raf protein† inhibitor
Not approved by EU or FDA
Combination targeted therapy
Dabrafenib (D) + trametinib (T), vemurafenib + cobimetinib
BRAF + MEK inhibitor
FDA and EU for advanced melanomas with BRAF V600E or K mutation
*Surface receptor proteins of T cells. †Transmembrane transcription signalling proteins. FDA = US Food and Drug Administration. EU = European Union.

response than that achieved by chemotherapy (26–60% vs 4–14%). Up to a third of patients may experience no recurrence or progression two to five years after start of treatment. However, it is not possible to estimate the actual gain in disease-free and overall survival because of variations in the outcomes, comparators, and quality of studies. Immunotherapies are slow to act, and it may take a few months to see a response.27

A quicker response is observed with targeted therapy, with median responses between six and seven weeks.28–31 Trials of single agent, BRAF targeted therapy report median survival in the range of 13–20 months (compared with 9–15 months for chemotherapy) with a response rate in the range of 22–57% (compared with 8–9% for chemotherapy). Long term remission is rare, however, and most patients experience disease progression 6–12 months after an initial response.

Studies show combination treatments have better response than single agents for either class of drugs. Most studies followed patients for at least 12 months up to four years. Long term follow-up data on survival are lacking. There have been no studies comparing immunotherapy with targeted therapy in these patients. Few studies have measured quality of life of patients taking these treatments.

WHAT YOU NEED TO KNOW

WHAT YOU NEED TO KNOW

Immunotherapy and targeted therapy against BRAF gene mutations are newer treatments for advanced (unresectable or metastatic) melanoma
These treatments have shown better response and survival rates than chemotherapy in advanced melanoma, but evidence on long term benefit is lacking
Refer any patient with recurrence of melanoma, change in size or appearance of lesions, or symptoms suggestive of spread of disease to specialist cancer physicians for staging the disease, genetic analysis, and planning the appropriate treatment

What are the harms?
Immunotherapies can cause immune related adverse events such as pruritus, rash, vitiligo, diarrhoea, colitis, and, less commonly, hepatotoxicity, pneumonitis, and endocrinopathies. A systematic review and meta-analysis (81 studies, 1265 patients) found adverse events occurred in 72% of patients receiving anti-CTLA-4 therapy, with severe, life threatening events or death in 24% of patients.30 The most common adverse events were dermatological (such as pruritus, rash, and vitiligo: 44%, 95% CI 38% to 49.5%) and gastrointestinal (such as diarrhoea and colitis: 35%, 95% CI 29% to 41%). Instances of colonic perforation have been reported in patients treated with ipilimumab.31 A phase III trial of combined anti-CTLA-4 and anti-PD-1 therapy reported much higher toxicity, with severe or life threatening adverse events noted in 172/313 patients (55%).32

Common toxicities with targeted therapies include arthralgia, fatigue, rash, pyrexia, and gastrointestinal complaints such as nausea and diarrhoea.33–39 Skin toxicity and pyrexia are class side effects of BRAF inhibitors. Specifically for the BRAF inhibitor vemurafenib, the most common severe toxicities include early cutaneous squamous cell carcinoma and keratoacanthomas, raised liver enzymes, and papulo-pustular skin rash.30 Cutaneous squamous cell carcinoma was the most common cutaneous side effect observed with dabrafenib, affecting nearly 10% of patients in a trial with 250 patients.38

How are they given and monitored?
While evidence on long term benefit is still awaited, these therapies are recommended because of their

Fig 2 | A 67 year old man with stage IVa melanoma. (A) Multiple cutaneous in-transit metastases of buttocks before starting intra-lesional T-VEC (arrows). (B) Near complete resolution of lesions after eight cycles of T-VEC
Recommended treatment approach for patients with melanoma based on disease stage

<table>
<thead>
<tr>
<th>Melanoma stage</th>
<th>Recommended treatment approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>First clinical presentation</td>
<td>Excisional biopsy</td>
</tr>
<tr>
<td>Low risk tumour (no ulceration, thickness &lt;1 mm)</td>
<td>Wide local excision only</td>
</tr>
<tr>
<td>Increased risk (tumour thickness &gt;1 mm, ulceration)</td>
<td>Wide local excision ± sentinel lymph node biopsy ± adjuvant immunotherapy</td>
</tr>
<tr>
<td>Clinical or pathological lymph node involvement</td>
<td>Systemic therapy: immunotherapy or targeted therapy</td>
</tr>
<tr>
<td>Metastatic disease with molecular target</td>
<td>Systematic therapy: immunotherapy or targeted therapy</td>
</tr>
<tr>
<td>Metastatic disease without molecular target</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>Second line treatment, clinical trials, or chemotherapy</td>
</tr>
</tbody>
</table>

Table 2

Testing and monitoring recommended for targeted therapy and immunotherapy

- **BRAF inhibitors**—Baseline blood counts, glucose, renal function, liver enzymes, skin exam, and electrocardiogram; repeat assessments every two months
- **MEK inhibitors**—Baseline retinal exam and evaluation of cardiac ejection fraction; repeat evaluation every 3 months
- **Anti-CTLA-4 and anti-PD-1 drugs**—Baseline blood counts, renal function, liver enzymes, and thyroid tests; repeat testing every 3-4 weeks

*Tips for Patients*

- Visit your GP or dermatologist for evaluation of suspicious changes in the colour, size, borders, or symptoms (such as itching, bleeding, or pain) of moles
- Seek medical attention if you have a history of melanoma and develop any new skin lesions, lymph gland swelling, sudden loss of appetite or unintentional weight loss (>10%), shortness of breath, headaches, or fainting
- If recurrence or spread of disease is suspected, your doctor will refer you to a physician specialising in melanoma or anticancer treatments
- Over the past decade, new treatments for unresectable or metastatic melanoma have become available, including drugs that directly target cancer genes (BRAF and MEK inhibitors) and drugs that boost your immune system to fight cancer (immunotherapy)
- Your doctor will discuss treatment options with you based on genetic analysis of the tumour tissue, your symptoms, and possible adverse effects from these treatments
- Although response to BRAF and MEK inhibitors is fast, about half of patients stop responding after about 12 months of therapy, and lesions can recur. With immunotherapy, the response is slower and may take months. The available evidence suggests that 20-30% of patients will sustain a durable response for 3-5 years with no recurrence or progression of disease
- BRAF and MEK inhibitors are taken orally as tablets, and immunotherapies are injected intravenously
- Your doctor will inform you of potential side effects to watch for such as:
  - With BRAF inhibitors: rashes, fever, chills, photosensitivity, and the development of non-melanoma skin cancers
  - With MEK inhibitors: rash, shortness of breath, swelling legs, and blurred vision
  - With immune checkpoint inhibitors: rashes, fatigue, diarrhoea, and abdominal pain suggestive of colitis (inflammation of the colon)

Potential to offer some benefit in patients with an otherwise poor prognosis. Table 2 lists treatment approaches based on disease stage. There is no consensus on the treatment sequence for offering targeted therapy or immunotherapy in patients with advanced melanoma. The choice of therapy depends on mutational status, tumour burden, disease related symptoms, costs, and patient preferences.

The National Institute for Health and Care Excellence (NICE) and the National Comprehensive Cancer Network (NCCN) of the US recommend immunotherapy as first line therapy in advanced melanoma regardless of mutational status. Genetic analysis of tumour tissue is not routinely recommended for primary localised melanoma. However, it is advised in patients with unresectable or metastatic melanoma being considered for targeted therapy. In adult patients with BRAF V600 mutation, BRAF inhibitors may be offered as single agents or in combination with MEK inhibitors (see table 1).

These drugs are prescribed only under the supervision of specialised physicians. Immunotherapies are administered intravenously every two to three weeks. Targeted therapies are taken as a pill daily. Treatment may be continued until response is achieved or adverse effects limit use. If disease progresses or no response is seen with one therapy, the alternative therapy may be offered.

These therapies are contraindicated in patients with hypersensitivity to the drugs. Immunotherapies are avoided in patients with congenital or acquired immune suppression or a history of life threatening autoimmune conditions. The box above lists the monitoring recommended during treatment.

How cost effective are they?

These treatments are expensive and impose a substantial healthcare burden. In an abstract presented by Klint et al at the 2016 Society of Melanoma Research, the median cost per dose for single agent anti-PD1 agents was $10 991 (£8223) and for anti-CTLA4 therapy was $19 544. The median monthly cost for BRAF + MEK inhibitor combination was $16 214. Chemotherapeutic agents are much cheaper. In a recent cost effectiveness analysis, the total cost of the drug and of managing toxicity accrued over the patients’ remaining lifetime was $15 221 for dacarbazine compared with $49 938 for vemurafenib. In the UK, these drugs have a discounted price under the patient access scheme.

How do they compare with other treatments?

Drugs such as dacarbazine and temozolomide are no longer routinely recommended for melanoma. Guidelines from NICE and NCCN recommend chemotherapy only as a last resort in patients who have failed to respond to targeted therapy or immunotherapy.

While novel therapies have shown better response and survival than chemotherapy, data on long term benefits are still awaited. It is expected the guidelines will change as new evidence emerges. There is also a need for research to establish the treatment sequence for immunotherapy and targeted therapy, and the effectiveness of combining these drugs with chemotherapy.

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Acute rotator cuff tears

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, professor of primary care, Department of Primary Care Health Sciences, University of Oxford, and Dr Kevin Barraclough, School of Social and Community Medicine, University of Bristol. To suggest a topic for this series, please email us at practice@bmj.com.

A 45 year old woman falls on ice and injures her shoulder. Assessment at her local hospital reveals bruising only and no bony injury on plain radiographs. Despite ongoing reassurance and participation in a physiotherapy programme for three months, she continues to complain of pain, weakness, and inability to raise her arm. Eventually she is referred to a specialist shoulder clinic, where an ultrasound scan confirms she has suffered an acute full thickness tear of her supraspinatus tendon.

Failing to identify an acute full thickness rotator cuff tear is a common problem, and this article is aimed at raising awareness of the condition and its correct management. The article is directed to all clinicians, but especially emergency department clinicians, trauma clinic clinicians, and general practitioners, who tend to see such cases.

### What is an acute rotator cuff tear?

The rotator cuff comprises four important muscles (supraspinatus, infraspinatus, teres minor, and subscapularis) which attach close to the humeral head via tendons and are critically involved in stability and function of the shoulder. A rotator cuff tear is when one or more of these tendons tears or detaches from the humerus (fig 1). These tears can vary in size and be acute or chronic. Chronic full and partial thickness tears are due to tendon degeneration and attrition, and these patients are not always referred to hospital unless they are having substantial problems—these are not the focus of this article. However, a direct or indirect shoulder injury from trauma can result in an acute full thickness tear, and this is a different problem that necessitates an urgent patient referral for a surgical opinion.

### How common is it?

The estimated incidence of acute full thickness cuff tear is reported at 2.5 per 10 000 patients aged 40-75 years.1 In studies of patients with “red flag” features for an acute cuff tear after an injury, with normal radiographs and no pre-existing shoulder problems:

- Of 104 patients aged 19-75 years, 60 had some degree of cuff tear on ultrasound assessment within six weeks of injury, including 33 with a full thickness tear.2
- Of 259 patients aged 18-75 years, 60 had full thickness acute rotator cuff tears, including 15% with involvement of subscapularis.1

Acute cuff tear after shoulder dislocation is particularly common in older patients. Two studies have identified high rates of acute cuff tears in these patients: 47 (54%) of 87 patients aged 40-87 years,3 and 33 (49%) of 67 patients aged 60-89 years.4

### Why is it missed?

The importance of early diagnosis and treatment of acute traumatic rotator cuff tears is easily overlooked at presentation because many clinicians focus on excluding dislocations and bony injuries and do not consider...
tendon ruptures. A clinician’s index of suspicion is often further lowered if apparently adequate emergency treatment has taken place elsewhere. The injury is commonly missed after a dislocated shoulder has been reduced in an emergency department and post-reduction radiographs seem normal. Two related studies have shown that pain limits the assessment for specific clinical features of a rotator cuff tear, and clinical examination alone will underdiagnose full thickness rotator cuff tears unless they are very large, and so ultrasound or magnetic resonance imaging (MRI) are needed to fully assess. In a prospective series of 104 patients with soft tissue injuries assessed with ultrasound imaging, a third had a full thickness cuff tear. This patient group will typically receive no formal follow-up in most regions of the UK, and so those who fail to improve inevitably present much later to general practice when successful treatment options are limited. A recent service evaluation of 30 patients from a large NHS hospital found that the subsequent mean delay from routine referral to treatment was an additional 115 days.

Why does this matter?
Patients with symptomatic rotator cuff tears typically have pain and weakness that can have profound, cascading effects on sleep, work, leisure, and psychosocial functioning, including depression and anxiety. Early diagnosis of acute tears is essential to facilitate prompt surgical treatment and the improved outcome scores and satisfaction seen after early surgical repair. In a study of younger patients aged 26-49 years with acute cuff tears, 95% returned to their usual occupation after rotator cuff repair. Surgical repair of acute rotator cuff tears results in a significant improvement in pain and function. A 2013 systematic review of 15 studies that included a total of 371 patients undergoing surgery after injury demonstrated significantly improved outcome scores with an earlier time to surgery. While the included studies were predominantly small case series and high level evidence in this area is limited, surgical repair is difficult if it is delayed and often impossible if acute tears are ignored for many months or years. Patient are then left unable to raise their arm above shoulder height and are at risk of developing earlier joint arthritis problems.

In a study of patients aged 26-49 years with acute cuff tears, 95% returned to their usual occupation after rotator cuff repair.
How is it diagnosed?

Clinical
The following key clinical features constitute “red flags” for a possible acute rotator cuff tear:
- Recent trauma
- Pain from the shoulder and/or lateral aspect of the arm
- Inability to raise arm in abduction above shoulder level, especially if not limited by pain.

The presence of these features together mandates urgent assessment and plain radiography to exclude a fracture. If the problems still persist two weeks after injury, the patient should be referred urgently to an appropriate fracture clinic or shoulder clinic with ready access to soft tissue imaging.

While a thorough clinical assessment and documentation of power in the individual rotator cuff muscles is desirable, there are many clinical tests for shoulder problems described in the literature and the clinical utility of each in isolation is limited.

As a minimum, the function of the axillary nerve should be checked by testing sensation over the “regimental badge patch,” and the patient should be checked for any additional associated injuries, particularly of the cervical spine and the affected limb.

Investigations
Plain radiographs of the glenohumeral joint in two planes should be performed on the day of presentation for patients with “red flag” features. The radiographs should identify significant fractures, avulsions, or dislocations which may require immediate treatment.

Those patients with persistent symptoms at two weeks post-injury may be offered an ultrasound scan or MRI to assess for a torn rotator cuff through a specialist shoulder clinic. Because of the high incidence of rotator cuff tear after glenohumeral dislocation in patients aged over 40 years, this group should routinely undergo either urgent ultrasound scanning or MRI to comply with best practice national guidelines produced by the British Elbow and Shoulder Society and British Orthopaedic Association. The imaging modality chosen may depend on local availability: MRI and ultrasound are both reliable tests for assessing full thickness tears, with sensitivities of 98% and 91% respectively and specificities of 79% and 85%.

Differential diagnosis
Alternative explanations for a presentation of pain and limited function following shoulder injury include:
- Occult or missed fracture
- Persistent or recurrent glenohumeral subluxation or dislocation
- Acromioclavicular joint injury
- Referred pain from cervical spine injury or radiculopathy
- Brachial plexus injury.

How is it managed?
Shared treatment decisions should be made between a patient and the treating shoulder surgeon. Early surgical repair is usually recommended to patients with full thickness acute tears causing significant pain or disability. In patients with only a partial thickness tear or individuals not suited to surgical intervention, a course of conservative management would be recommended initially, including the use of adequate analgesia, activity modification, and physiotherapy.

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Letting my daughter go

Stephanie Nimmo’s daughter, Daisy, was born with a life limiting condition and died in January 2017. On the anniversary of her loss, Stephanie reflects on how working with health professionals enabled Daisy to enjoy her life and have a peaceful, dignified death.

I always knew Daisy would die before reaching adulthood. She was my fourth child, born prematurely in December 2004 with a severe form of a rare genetic condition called Costello syndrome.

Daisy required complex care, but every decision about her care was made on the basis of improving the quality of her life, which meant helping her do the things she loved, such as being at home with her family, going to school, and playing with friends.

Staying out of hospital
I was trained to undertake most of her care, including setting up her parenteral nutrition and additional fluids, administering multiple daily intravenous infusions, and inserting catheters into her Mitrofanoff stoma. When possible, outpatient appointments were conducted by phone or without Daisy present. To minimise emergency hospital admissions and stays, the emergency department and children’s ward had protocols specially written for her. A member of the palliative care team had access to her notes 24/7 and Daisy’s main consultant wrote a letter confirming that I was competent to manage her care at home once she was stable.
EDUCATION INTO PRACTICE

• How might you talk to families of children who are life limited about the care they want for the child after death? What do you need to know, and what does the family need to know?
• How can communication between teams be coordinated to lift the burden from parents?
• Routinely offer a cold cot or a cold blanket within four to six hours of death. Consider how the child might be transported from the ward to their home or children’s hospice after death, rather than via the mortuary.

USEFUL RESOURCES

• The charity Together For Short Lives has a comprehensive guide to end of life care, including advance care directives and the use of cooling blankets.
• A guide to end of life care. www.togetherforshortlives.org.uk/assets/0000/1855/TFLS_A_Guide_to_End_of_Life_Care_5_FINAL_VERSION.pdf
• Children’s palliative care definitions. www.togetherforshortlives.org.uk/families/information_for_families/2454_childrens_palliative_care_definitions

Working together

Daisy had been under hospice care since she was six months old, and was referred to the paediatric palliative care team for symptom management when she was seven.

For children living with unpredictable complex conditions there has to be a good and early relationship with palliative care services to make plans and be able to change plans.

Her palliative consultant was able to help join up care between teams, and would often attend outpatient appointments with me. This was important because, although I was Daisy’s advocate and an expert on her daily care, I also needed precious time to be her mum.

Letting Daisy go

In early January 2017 Daisy was admitted to hospital with an infection. She had celebrated her 12th birthday a few weeks previously.

As sepsis took hold, Daisy was taken to intensive care and intubated. I saw she was closing down. It was time to let her go.

The most important thing for me now was to give Daisy dignity in death. I had hoped that we could transfer her to home or hospice for a compassionate extubation but she was too unstable. The last thing I wanted was for her to die in an ambulance in the middle of London.

I was offered the chance to move her to a private room for her final moments, but I did not want her disturbed any more. We pulled the curtains around, had the lights dimmed and played music. Patients were moved temporarily so we had no strangers around us.

A team of familiar nurses and a doctor kept a respectful distance as they took out lines, muted alarms, and prepared to extubate Daisy. When the ventilator was switched off they retreated from the bed and waited behind the curtains. Daisy’s three siblings and I held her hand and sang to her as she took her last breaths.

Living with loss

That evening we brought Daisy home. Our palliative nurse liaised with the hospice and funeral directors to organise this, and the hospice at home nurse set up a special cold blanket on Daisy’s bed. We also spent time at the hospice where Daisy could be visited by friends and family. A little girl with her family again—not a patient.

A year on, I miss Daisy desperately. When she died I felt that, not only had I lost my child, I had lost my role, my purpose. I miss our medical teams: they were so much part of our life. Together, we gave Daisy 12 years of life, more than we had ever hoped for when she was born.

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Using the BMJ

0.5 HOURS

WHAT YOU NEED TO KNOW

• When children with complex needs have multidisciplinary teams looking after them someone needs to coordinate care.
• Start end of life planning conversations early so that the families have ownership of decisions when the time comes.
• Allowing families to have private time with their children at the moment of death is important.

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Cite this as: BMJ 2018;360:j5771
A 38 year old man with a known testicular germ cell tumour presented with acute right sided abdominal pain but no other symptoms. Clinical examination showed positive Murphy’s sign. Laboratory investigations showed leucocytosis of 10.6×10^9/L (reference range 4.0-9.0×10^9/L) and serum C reactive protein of 59 (0.2-9.1) mg/L. Serum liver enzymes were unremarkable. A computed tomography scan of his abdomen and pelvis was performed (fig 1). What abnormality does this scan show?

Submitted by Timothy Shao Em Tan and Foong Koon Cheah

Cite this as: BMJ 2017;359:j5182

ENDGAMES For long answers go to the Education channel on bmj.com

SPOT DIAGNOSIS

An uncommon cause of abdominal pain in a young man

A 38 year old man with a known testicular germ cell tumour presented with acute right sided abdominal pain but no other symptoms. Clinical examination showed positive Murphy’s sign. Laboratory investigations showed leucocytosis of 10.6×10^9/L (reference range 4.0-9.0×10^9/L) and serum C reactive protein of 59 (0.2-9.1) mg/L. Serum liver enzymes were unremarkable. A computed tomography scan of his abdomen and pelvis was performed (fig 1). What abnormality does this scan show?

Submitted by Timothy Shao Em Tan and Foong Koon Cheah

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CASE REVIEW

Blisters in disguise

A 77 year old man with a history of hypertension, angina pectoris, chronic obstructive pulmonary disease, and prostate hyperplasia presented to the dermatology department with a 6 month history of thick, oozing, foul smelling skin lesions in the groin and around the umbilicus (figure), and erosions on the lips.

His medication included metoprolol, isosorbide mononitrate, seretide, flixonase, tamsulosine, and desloratadine.

Physical examination revealed swollen, erosive lips with rhagades and crusts. He had thick oozing inguinal and periumbilical papillomatous plaques.

Laboratory studies showed erythrocyte sedimentation rate of 47 mm/h (normal range <20 mm/h) and mild eosinophilia (12.8% of leucocytes, normal range 1.4-6.2% of leucocytes) with a normal leucocyte count (normal range 3.5-10.0×10^9/L).

Histopathological examination of skin biopsy from the groin showed a broadened epidermis with elongation of the rete ridges with focal hyperkeratosis and abscesses in the hair follicles, and a dense plasma cell infiltrate. Immunofluorescence of perilesional skin showed intercellular depositions of IgG, IgA, and C3 complement, and enzyme linked immunosorbent assay showed IgG antibodies directed against desmoglein 3.

1 What is the most likely diagnosis and how is the condition diagnosed?
2 How is this condition treated?
3 What are the complications of this condition?

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Purtscher-like retinopathy suggesting systemic lupus erythematosus

A 23 year old man developed sudden painless visual loss in both eyes. There was no history of trauma. His best corrected visual acuity was 20/40 (right) and 20/667 (left). Funduscopy showed bilateral multiple white patches in the retinal posterior pole (right). There was no clinical response to supportive and trophic retinal treatment. Suspecting an underlying inflammatory disorder, immunosuppression with oral prednisone and methotrexate was commenced. One month after the initial onset of visual symptoms, the patient developed a malar rash. Rheumatological assessment and immunological markers supported a diagnosis of lupus erythematosus. Visual acuity improved gradually over four months.

These features are typical of Purtscher-like retinopathy. Purtscher retinopathy is caused by an occlusive microvasculopathy after severe indirect trauma, and is characterised by retinal whitening and haemorrhages. It is most commonly associated with autoimmune diseases, acute pancreatitis, and renal failure.

Time trends in dementia

As everyone knows, the number of people who have dementia is rising. The reasons, of course, are that people are living longer and that the likelihood of cognitive decline increases steeply with age. But looked at by cohort of birth, time trends in dementia might be going in the opposite direction. Analysis of incidence of dementia in the Einstein Ageing Study from New York finds that successive generations experience lower rates (JAMA Neurol doi:10.1001/jamaneurol.2017.1964). Whether this decrease in incidence will be large enough to compensate for increasing expectation of life is another matter.

Missing data

In the real world of clinical research, data collection is often incomplete. There are several ways of dealing with missing values, but the commonest method is simply to exclude participants with incomplete information. An analysis in the American Journal of Epidemiology shows that this might give seriously misleading answers (Am J Epidemiol doi:10.1093/aje/kwx348). In that dataset, excluding participants produced a result which showed that smoking had a protective effect on spontaneous abortion. Using more sophisticated methods of dealing with missing data, such as multiple imputation or inverse probability weighting, the results were very different.

Intestinal epithelial cells

The intestinal epithelium is the most diverse epithelium in the body, and a survey of the RNA profiles of individual cells reveals that it’s even more diverse than we thought. Not only did the investigators discover previously unrecognised types of enteroendocrine cells and tuft cells, but they also showed that the response of the epithelium varied depending on the micro-organisms to which it was exposed. Helminth infection led to accumulation of secretory cell types, whereas Salmonella infection induced proliferation of absorptive enterocytes and Paneth cells. The research was carried out on the small intestine of the mouse, but it seems unlikely that the human intestinal epithelium will prove any simpler (Nature doi:10.1038/nature24489).

Antibiotic resistance

Ampicillin, the first broad spectrum penicillin, became available in the UK in 1961. Only a couple of years later, ampicillin resistant strains of Salmonella emerged. A molecular analysis of historical samples of Salmonella typhimurium discovers that it’s far more likely that resistance was due to the widespread use of penicillins as a feed additive for farm animals than it was to over-prescribing for infections in humans (Lancet Infect Dis doi:10.1016/S1473-3099(17)30705-3). The European Union banned the non-medicinal use of antibiotics in livestock production in 2006 but in other parts of the world antibiotics are still used to prevent disease and to promote growth in animals.

Reflux induced cough

Although gastro-oesophageal reflux is sometimes a cause of chronic cough, several trials have shown that acid suppressive therapy is ineffective. Prolonged oesophageal monitoring in patients with reflux induced cough found that coughing was more closely related to the volume of reflux and to how far it extended proximally than to pH (Gut doi:10.1136/gutjnl-2017-313721). From a therapeutic point of view, it might be better to focus on interventions that decrease the amount of reflux instead of trying to reduce its acidity.

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CORRECTION

Minerva of 9 December issue featured a photograph of Hermann Joseph Oppenheim, a German banker. The picture should have shown Hermann Oppenheim, the neurologist.

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Patient consent obtained.