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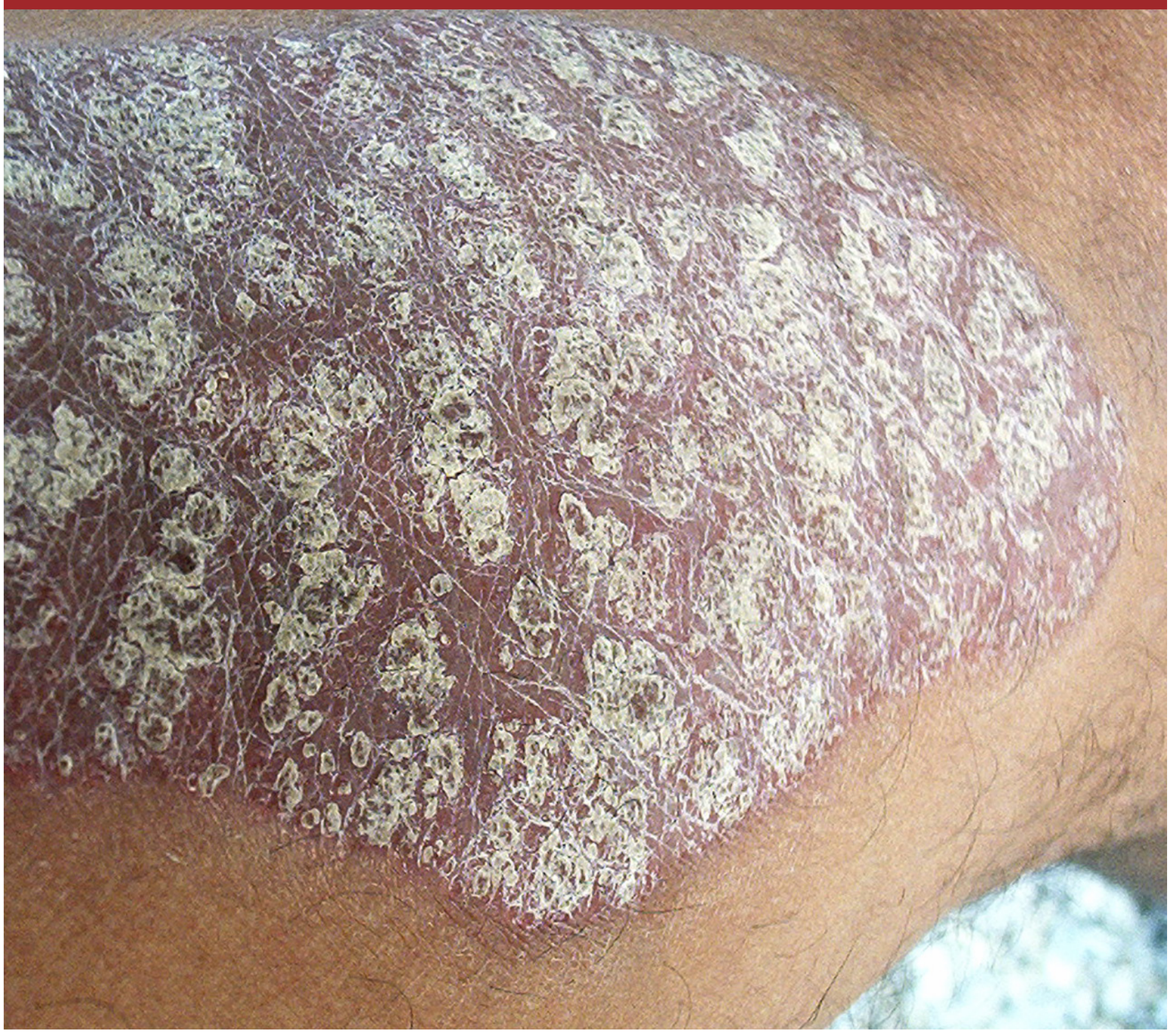

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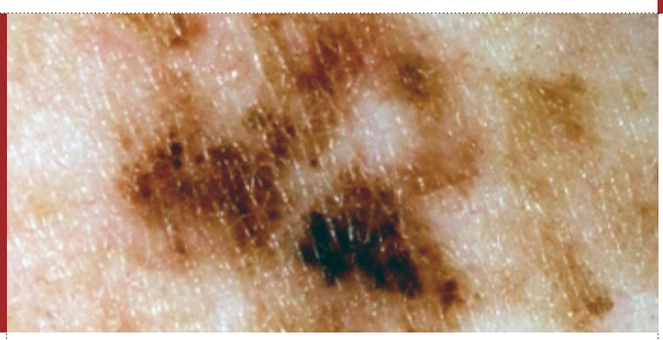
THE PIGMENTED SKIN LESION: A CASE BASED DISCUSSION OF THE ROLE OF BIOPSY IN DERMATOLOGY

J. I. O. Abiola, B. A. Esdaile and R. Ratnavel

The Pigmented Skin Lesion: A Case Based Discussion of the role of Biopsy in Dermatology. Patient Management.



Abstract

Diagnostic skin biopsies play an essential role in dermatology and provide information that can be correlated with the clinical impression to give a diagnosis. We discuss the presentation and management of two patients with pigmented skin lesions in order to highlight some important principles of skin biopsy. The biopsy strategies varied in each case due to the clinical impression, the size and site of the lesion. Excisional biopsy is the method of choice for clinically suspicious lesions. Other methods such as incisional biopsy, punch biopsy or curettage may be used for benign or pre-malignant lesions depending on lesion characteristics and patient preference.

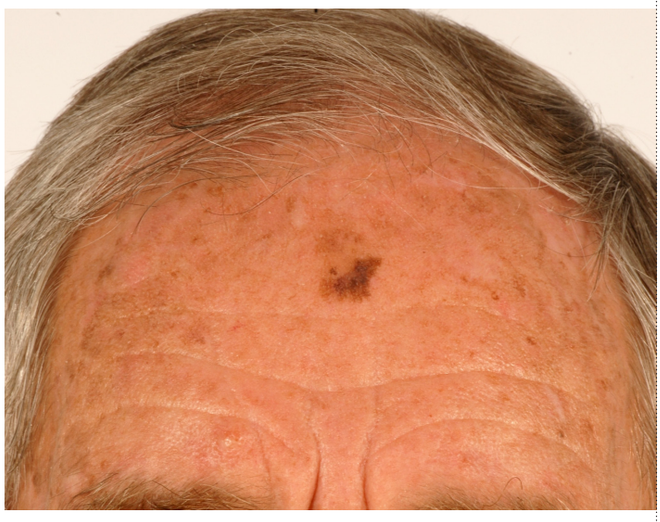
Aim

We present two patient's pigmented skin lesions. We have used these examples to highlight some important principles of the role of the biopsy in dermatology.

The Cases

Patient A

An 83-year-old gentleman presented with a pigmented lesion on his forehead which had been present for 6 years and was gradually increasing in size.



- **Which skin conditions would you want to exclude?**
- **What would you do next?**

Malignancy must be excluded in pigmented lesions that are symptomatic and/or changing. Details of the evolution of the lesion and patient risk factors must be gathered. A detailed history is required from the patient[1] (see Box 1). In practice however, experienced dermatologists would occasionally make a clinical diagnosis without the history!

History taking

Development of the lesion

- *Site of origin*
- *Rate of growth*
- *Pre-existing lesion*
- *Has the patient noticed changes in*
  - *Outline*
  - *Surface characteristics*
  - *Colour*
  - *Elevation*
  - *Surrounding tissues*
- *Is this a recurrent lesion?*
- *How were previous lesions treated and what was the response*

Symptoms

- *Itching/ tenderness*
- *Awareness of lesion*
- *Bleeding/ Serous discharge*

Risk factors

- *Previous skin cancers- Type of lesion and previous treatment*
- *Type of skin*
- *Sun exposure as child & sunburn*
- *Protective behaviour*
- *Countries lived in and time spent abroad*
- *Use of sun beds*
- *Occupation*
- *Previous transplant?*
- *Immunosuppressant treatment*
- *Leukaemia*
- *Exposure to carcinogens*
- *Family history of Skin Cancer*
- *Scottish/ Irish parents*
- *Any genetic predisposition to skin cancer*

The pigmentation pattern was unchanged and there was no pruritis or tenderness. He had no significant medical history or family history and was not on any regular medication. Having lived in Kenya for 30 years, he had significant sun exposure. His general health was good and his systems review was unremarkable.

- **What do you think this lesion is?**
- **What would you like to do next?**

The differential diagnosis for pigmented skin lesions is quite extensive (see Box 2) and examination findings offer valuable clues.

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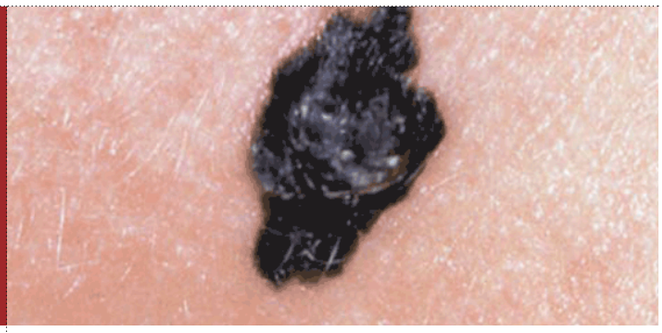


Examination

A formal examination of the lesion should be conducted to identify and document any features of malignancy. There should be particular focus on:

- **Site**
- **Colour**
- **Borders**
- **Size**
- **Shape**
- **Symmetry**
- **Induration**
- **Spread should be assessed clinically by examining regional lymph nodes.**

A general examination of the patient should be conducted to assess the overall health of the patient, local affects of the tumour or for evidence of metastatic spread.

On examination, there was a 25mm irregularly pigmented macule on his central forehead. The lesion was asymmetrical in shape and pigmentation. Complete examination of the skin revealed widespread areas of chronic sun damage.

The differential diagnoses included a solar lentigo, lentigo maligna (melanoma *in situ*) and an atypical naevus. Photographs were taken for medical records. Incisional biopsy of the most irregularly pigmented aspect of the lesion was done because there was a low clinical suspicion of malignant disease. The histology showed evidence of lentigo maligna, a pre-malignant condition, and his case was discussed at the skin cancer multidisciplinary team (MDT) meeting where a surgical excision was suggested.

The diagnosis was explained to the patient and he was warned of the risk of developing a melanoma in the lesion. However, he was still not keen on surgery and was then offered 5% Imiquimod cream to apply to the lesion. He will be closely followed-up as an outpatient. Imiquimod is a drug that up regulates the immune system and has both antiviral and anti-tumour properties. It is currently regarded as an experimental treatment for lentigo maligna and patients on imiquimod should be monitored closely[4].

Patient B

A 56-year-old woman was referred to the dermatology clinic by her GP with a mole on her abdomen, which had been present for many years, had changed shape and increased in size over three months. There had also been a change in colour but no itching, oozing or bleeding.

She was a retired business woman who smoked and had a moderate history of sun exposure with a tendency for her skin to burn in the sun. There was no family history of skin cancer. Her general health was good and the systems review was unremarkable.

On examination there was a 17mm by 9mm pigmented macule on the right lower abdominal wall, with an irregular border. There was a variation in pigmentation throughout the lesion. There was no scaling or erythema of the surrounding skin and no regional lymphadenopathy was detected clinically. A clinical diagnosis of a malignant melanoma was made and the patient was booked for an urgent excisional biopsy, which was performed by a member of the skin cancer multidisciplinary team in a secondary care setting. The histology confirmed a superficial spreading malignant melanoma with a Breslow thickness of 0.5mm that was excised with a 2mm margin. The case was again discussed at the skin cancer MDT meeting where it was decided that the patient should undergo a wider excision of the scar as per NICE guidelines[5]. The histology from this further excision showed scar tissue only with no evidence of residual melanoma. She will be followed-up in clinic for surveillance.

Biopsy Discussion

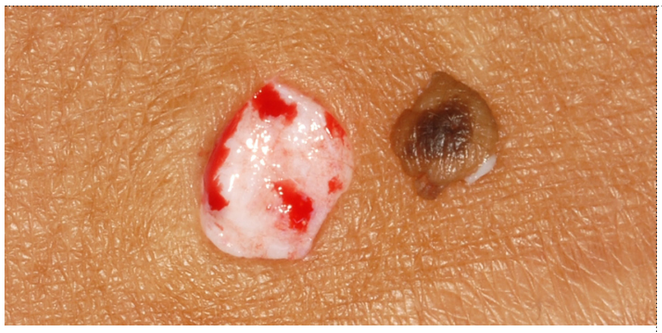
There are over 2000 dermatological diagnoses. Many of these require biopsy for clinical–pathological correlation. There are 6 biopsy modalities most commonly employed[6].

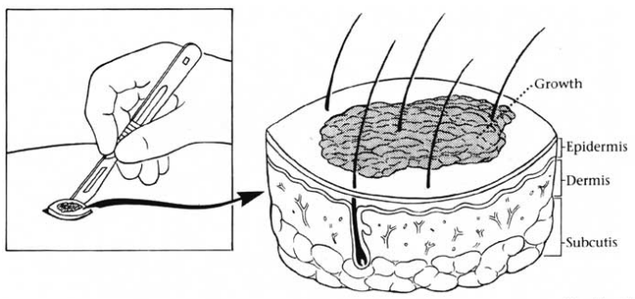
Excisional biopsy

In excisional biopsy, the entire lesion is excised allowing it to be analysed as well as potentially being the definitive treatment. This method of biopsy is employed for presumed malignant skin conditions and benign conditions that are particularly problematic. In general all suspicious pigmented skin lesions are removed with an excisional biopsy (Figure 2).

THE PIGMENTED SKIN LESION: A CASE BASED DISCUSSION OF THE ROLE OF BIOPSY IN DERMATOLOGY

J. I. O. Abiola, B. A. Esdaile and R. Ratnavel





Incisional biopsies

Incisional biopsy removes only a part of a lesion. The specimen should include macroscopically normal skin to allow for comparison and assessment of any early pathological changes. It is generally used for inflammatory conditions and only occasionally used in malignancy prior to definitive treatment. Sampling errors may lead to inaccurate diagnoses, as there may be histological variations within a lesion.

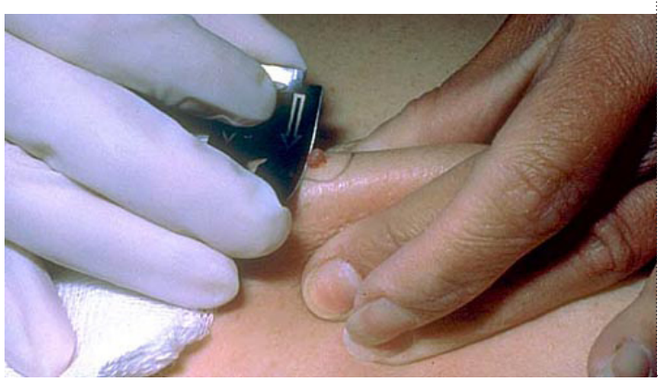
In general, pigmented skin lesions are usually excised with a 2mm margin. Incisional biopsies of pigmented skin lesions should only be performed in certain clinical settings by a specialist in that field, as taking small biopsies of a pigmented skin lesion can lead to false reassurance. The need for further excisions will be guided by the histology.

Punch biopsy

This is the biopsy technique of choice for the diagnosis of the dermatoses whereby small cylindrical sections of skin are obtained for histological analysis. The depth required to confirm the diagnosis must be born in mind during the procedure. Punch biopsies would remove part of a lesion and there is very little role for punch biopsy in the diagnosis of pigmented skin lesions.

Shave biopsy & Curettage

Benign papular or nodular skin lesions are often scraped or planed using the blade of a scalpel or a curette. In experienced hands this can also be used to treat certain forms of basal cell carcinomas and should be performed by experienced specialists as these methods provide only fragments for histological analysis. Shave biopsy and curettage are generally not used for excising malignant lesions with a margin but may be beneficial in other settings as they are less invasive and have a better cosmetic effect.



Scissor biopsy or Snip excisions

Pedunculated lesions can be removed with surgical scissors and the small defect is often left to heal by secondary intention causing minimal scarring.

Before biopsy, informed consent must be sought and potential hazards, such as bleeding, infection and scarring, discussed. The impact that lesion size and location may have on scarring risk may be of concern to some patients; appropriate counselling must take place.

Peripheral vascular disease, diabetes mellitus, long term steroid use and smoking impair healing and caution must be taken in those at risk of developing chronic ulcers. In some cases, the assessment of the potential benefit of histological diagnosis in the light of significant co-morbidity may lead to the decision not to biopsy.

Anti-coagulated patients tend to have a higher complication rate in dermatological surgery[7]. There is some controversy over routinely discontinuing anticoagulants for skin biopsy, but the risks and benefits of doing so should be weighed in every case. Local policy may vary but generally, warfarin is stopped 4-7 days before the biopsy and INR checked 2–3 days later. An INR of <2.5 is desired for biopsy to proceed. In some centres, anti-platelets are be stopped 7–14 days before biopsy. Anticoagulation can be resumed after the biopsy is performed and haemostasis achieved.

Clinical assessment is essential in the selection of biopsy strategy. As a general rule, excisional biopsy is the method of choice for all suspicious pigmented lesions. There was a strong clinical suspicion that Patient B had a malignant melanoma and was therefore offered excisional biopsy. Subsequent histology not only confirmed the clinical diagnosis but gave valuable prognostic information. Lesions that are likely to be malignant on clinical assessment undergo excisional biopsy, which both aids diagnosis and provides treatment. In Patient A, however, an incisional biopsy was an acceptable strategy as the lesion was not clinically malignant; it may have been a harmless lentigo. Histology confirmed the diagnosis of lentigo maligna, a pre-malignant condition; various therapeutic options were thus available. The patient was provided with all the clinical information and elected for non-surgical treatment.

THE PIGMENTED SKIN LESION: A CASE BASED DISCUSSION OF THE ROLE OF BIOPSY IN DERMATOLOGY

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Summary

Biopsy is required for histological confirmation of a diagnosis. Selection of an appropriate biopsy technique depends on clinical features and patient preference. Excisional biopsy is the definitive treatment in some cases and is generally the biopsy method of choice for malignant skin lesions. Incisional biopsies have a role in diagnosis before definitive treatment. The punch biopsy is the procedure of choice in the diagnosis of dermatoses. The method of biopsy used should be chosen by considering patient factors, lesion specific factors and choice of treatments available. A thorough clinical assessment is essential in selecting the appropriate biopsy technique.

Single Best Answer Self Assessment

Question 1.

A 45-year-old woman presented with a new mole on her thigh. She first noticed the lesion develop six months ago. Since then it has itched and bled on two occasions. The lesion measured 13mm in diameter with an irregular border and asymmetry of pigmentation. What choice of biopsy would you perform?

a) Incisional biopsy
b) Shave biopsy
c) Scissor biopsy
d) Punch biopsy
e) Excisional biopsy.

Question 2.

A patient visits his GP because his wife has noticed that a mole on his back has changed. Which of the following is not a warning sign of melanoma on examination?

a) Pink nodule
b) Regular pigmentation
c) Irregular pigmentation
d) Asymmetry of mole
e) Irregular border.

Question 3.

A 41-year-old female patient presents with a 2-month history of an itchy rash over her torso and arms. Clinically she had a widespread pink papular eruption over her body. How would it be best to biopsy the rash?

a) Curettage
b) Shave biopsy
c) Scissor biopsy
d) Punch biopsy
e) Excisional biopsy.

Answers and explanations

1. e)

Clinically this is consistent with a Malignant Melanoma. The lesion should be removed urgently with a 2mm margin by an excisional biopsy. There is no role for any other biopsy in this scenario.

2. b)

Regular pigmentation is not a classical sign of melanoma. There is usually asymmetry in shape as well as irregular pigmentation. Melanoma can present as a pink nodule – BEWARE the amelanotic malignant melanoma!

3. d)

Punch biopsy is the modality of choice for the diagnosis of dermatoses.

Acknowledgment

Many thanks to Dr Mohsin Ali for supplying Figure 2

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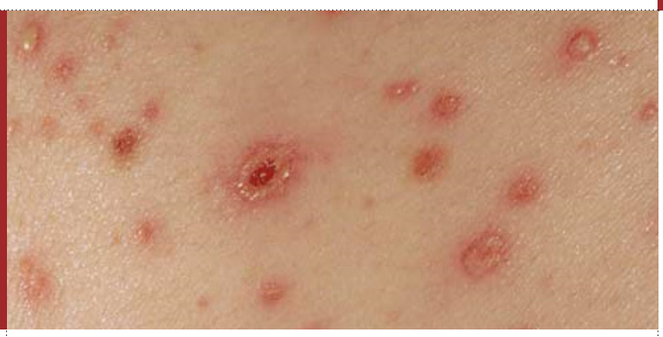
GENERALISED SKIN RASH

Vijay Joshi and Ashis Banerjee



Generalised skin rash.
Patient Management.

Abstract

A generalised skin rash progressing to full thickness skin necrosis is described in a 71-year-old male presenting with upper gastrointestinal bleeding in the presence of alcoholic liver disease. The clinical diagnosis, role of investigations and management are discussed. An infective aetiology is postulated for the rash.

Case report

A 71-year-old male, with a past history of alcoholic liver disease, was admitted as an emergency with melaena. He underwent emergency surgery for a bleeding duodenal ulcer.

He became acutely unwell 2 weeks post-operatively, with high grade pyrexia. A non-blanching, maculo-papular erythematous rash was initially noted on his trunk. Over the next 2 days, the rash progressed and became purpuric, involving the extremities and the entire torso. The rash subsequently became vesiculo-pustular, and multiple areas of full thickness skin necrosis were seen involving the lower limbs (see Figures 1 to 4).

Blood tests revealed normal full blood counts (WBC 8.35 X 10^9/L neutrophils 6.25; platelet count 205 x 10^9/L), renal impairment (creatinine 166µmol/L), raised C-reactive protein (103mg/L) and erythrocyte sedimentation rate 80m in the first hour. The international normalised ratio (INR) was 1.62. Hepatitis serology, vasculitis screen, including auto-immune profile, and complement (C3, C4) levels were within normal limits. The p-ANCA (anti-neutrophil cytoplasmic antibody) level was lower than normal. Syphilis serology was negative. A swab from a pressure sore on the left heel isolated methicillin-resistant *Staphylococcus aureus* (MRSA). Blood cultures grew Gram positive cocci, subsequently confirmed to be MRSA.

Questions

1. What is the likely cause of the skin rash?

The coexistence in varying combinations of purpura, both palpable and non-palpable, papules, urticaria/angioedema, erythema multiforme, vesicles, pustules, ulcers, and skin necrosis is suggestive of leukocytoclastic vasculitis. The lesions initially appear in dependent regions (lower limbs and buttocks) and occur in crops. Synonyms include hypersensitivity vasculitis, cutaneous small vessel vasculitis and cutaneous leukocytoclastic angiitis.

Leukocytoclastic vasculitis[1,2] is a presenting feature of a range of clinical disorders, including infection, neoplasm and connective tissue disease. It is the most common form of small vessel necrotizing vasculitis, being histologically characterised by fibrinoid necrosis of small dermal blood vessels, a polymorphonuclear neutrophil infiltrate, leucocytoclasis, endothelial cell swelling, and red blood cell extravasation.

Most often, the lesions are confined to the skin. Occasionally there may be involvement of joints, gastrointestinal tract and kidneys. Renal involvement, in particular, should be actively sought in all cases. The characteristic skin lesion is palpable purpura, which appears in recurrent crops, tends to coalesce and preferentially involves areas of stasis such as the lower legs. Nodules, urticarial lesions, haemorrhagic blisters and ulcers may be seen in the course of evolution. Lesions may heal spontaneously in 1 to 4 weeks, with residual scarring or pigmentation (Boxes 1 and 2).

American College of Rheumatology criteria (1990) for leukocytoclastic vasculitis[3]

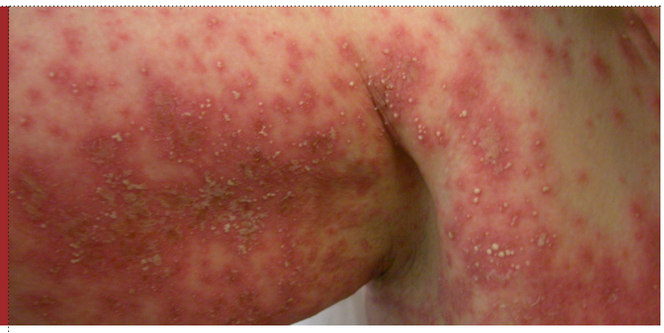
- Age at disease onset > 16 years
- Medication at disease onset
- Palpable purpura
- Maculo-papular rash
- Biopsy including arteriole and venule, showing granulomata in perivascular or extravascular location

Diagnosis needs at least 3 of 5 criteria
(sensitivity 71%; specificity 83.9%)

Box 1

GENERALISED SKIN RASH

Vijay Joshi and Ashis Banerjee



Generalised skin rash.
Patient Management.

Typical investigation results in leukocytoclastic vasculitis

- Normal full and differential blood count
- Normal electrolytes and liver function tests
- Normal urinalysis including microscopy
- ESR and CRP: mild to moderate elevation in <50% patients
- Negative ANA, RF, ANCA, anti-hepatitis B and C assays, cryoglobulins
- Normal C3, C4
- Normal chest x-ray

Note: In the presence of renal involvement abnormalities are to be expected on urine and blood testing

2. What further investigation might help in confirming the nature of the skin rash?

Biopsy of an acute skin lesion (less than 48 hours old) will reveal leukocytoclastic vasculitis of post-capillary venules. Direct immunofluorescence reveals variable and non-characteristic deposition of immunoglobulins and complement in capillaries, post-capillary venules and arterioles.

A report on a biopsy specimen from a purpuric skin lesion in our patient reads: The skin shows marked erythrocytic extravasation and perivascular and interstitial inflammation of the dermis. The infiltrate is composed of neutrophils predominantly with a minor lymphocytic component and occasional eosinophils. The findings can be related to late stage vasculitis or mild neutrophilic dermatosis.

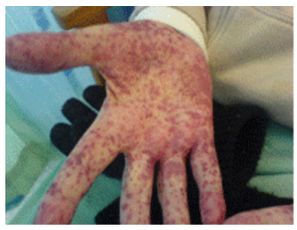
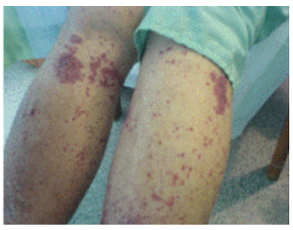
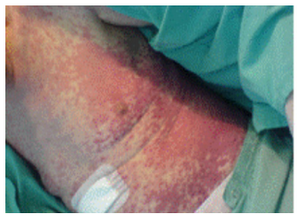
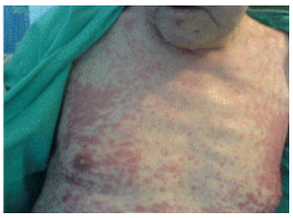
3. What treatment is indicated?

Treatment strategies are empirical[4] and depend on disease severity.

They can be listed as follows:

- Mild disease – removal of the offending agent; leg elevation; non-steroidal anti-inflammatory drugs (NSAIDs); H1 receptor blocking anti-histamines
- Persistent disease – colchicines; dapsone; hydroxychloroquine
- Refractory/severe disease – glucocorticoids; immunosuppressive agents: azathioprine

In our patient, a clinical diagnosis of leukocytoclastic vasculitis secondary to MRSA sepsis was made. He was treated w ith intravenous vancomycin for 2 weeks along with oral prednisolone for 7 days. While on the treatment, his rash gradually resolved with improvement in the inflammatory markers. At the final review 3 weeks after onset, the rash had completely resolved.

Figures 1-4

GENERALISED SKIN RASH

Vijay Joshi and Ashis Banerjee

While there is a well recognised association of leukocytoclastic vasculitis with streptococcal infection, we have been unable to discover any reports of an association with MRSA infection. In our patient, the temporal association with MRSA sepsis, and resolution with vancomycin, support this postulated association. The risk factors for MRSA sepsis in our patient included old age, recent surgery, prolonged hospitalisation and antimicrobial therapy. MRSA is a major source of hospital-associated infection, and this complication adds to the spectrum of disorders potentially associated with its presence.

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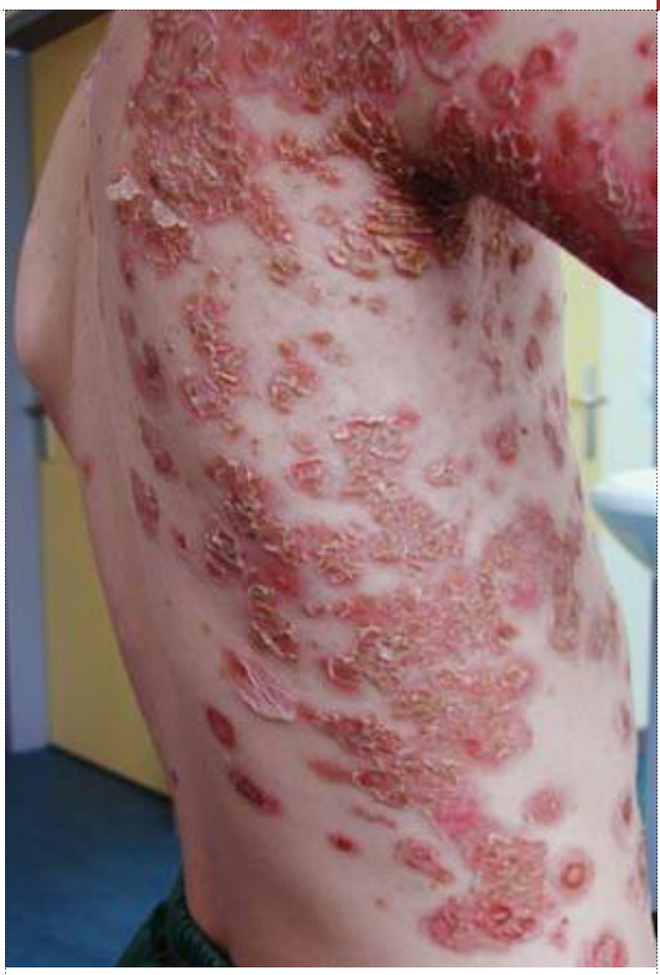

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REDUCING THE RISK OF SKIN CANCER

Dawn M. Caruana and Clare Patterson

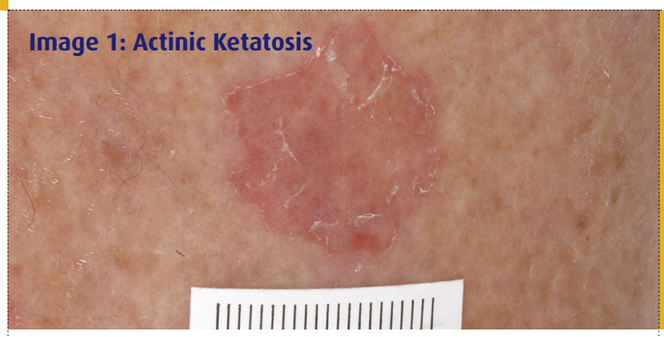


Image 1: Actinic Ketatosis

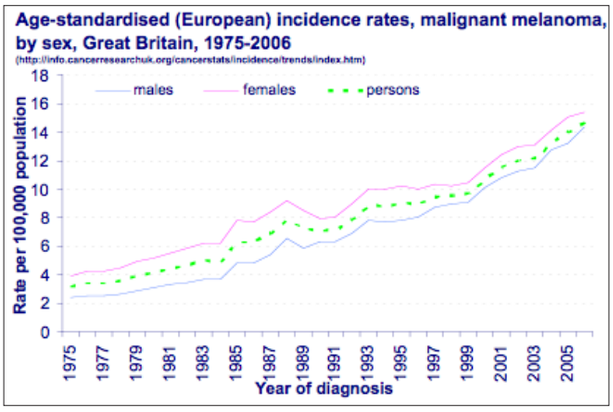
Reducing the Risk of Skin Cancer.
Good Clinical Care.

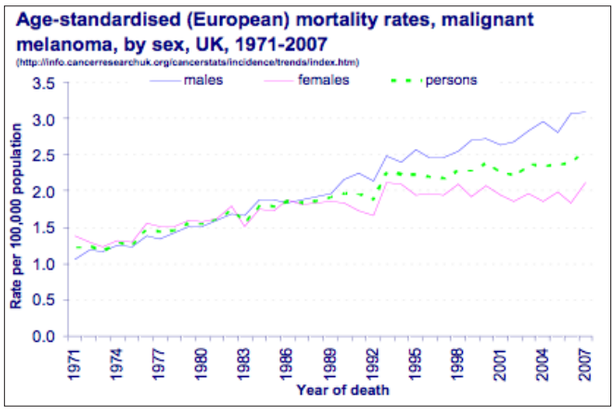
Prevention in skin cancer is paramount. Ultraviolet (UV) radiation is the major cause of skin malignancies and is therefore one of the most avoidable causes of cancer in humans. The light-hearted approach with which many in the general public look at skin cancer is an aspect which cancer prevention organisations and health care workers have to challenge. With a rising incidence of all kinds of skin cancer, protection from UV radiation and early recognition of pre-malignant and malignant skin lesions are essential to decrease morbidity and mortality associated with these neoplasms.

How big is the problem?

Melanomas

The incidence of melanoma is increasing at a faster rate than any other major cancer. Melanoma was found to be the 6th most commonly diagnosed cancer in 2006, as well as the 16th most common cause of cancer deaths in the UK, making this cancer an increasing public health concern. One third of patients are under the age of 50, and approximately 15 years of life are lost for each death, placing melanoma amongst the top five cancer causes of lost life years. The mortality rate has increased at a slower pace than incidence, possibly because a significant proportion of the melanomas are under 1mm in Breslow thickness, and therefore have a good prognosis.





Non-melanoma skin cancers

Basal cell carcinoma (BCC) incidence rates in Europe range from 50 to 130 per 100,000. Squamous cell carcinoma (SCC) incidence is highly dependent on geographical latitude, with values of 1,000 in 100,000 person-years in Australia as compared to 44.3 in 100,000 in Sweden.

What is the main reason for the problem?

UV radiation

In 2006, the World Health Organisation published a report which estimated that between 50% and 90% of the burden of disease from melanoma is due to ultraviolet radiation exposure.

Intensive UVR exposure in childhood and adolescence, especially in those with Type I and II skin (Table 1), is associated with the development of BCCs and SCCs. Nevertheless, sun exposure has benefits. Amongst these, the most recognised is UV radiation as the major source of Vitamin D.

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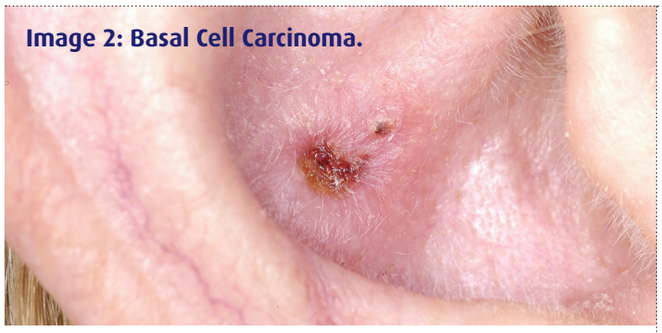

Image 2: Basal Cell Carcinoma.

Type	Skin characteristics	Effect of sun
I	Very pale skin, may have light coloured or red hair, freckles	Burn easily, never tan
II	Pale with fair complexion	Usually burn, may gradually tan
III	White to olive, may have dark eyes and darker hair	Sometimes burn, usually tan
IV	Brown with dark eyes and dark hair	Rarely burn and tan easily
V	Dark brown with dark eyes and hair	Very rarely burn, only with very prolonged exposure, darken easily
VI	Black skin with dark eyes and black hair	Almost never burn, darken very easily

Table 1: Skin types and the effects of UV radiation.

The incidence of melanomas amongst dark skinned ethnic groups is around 1 in 100,000 per year as compared to levels of more than 50 per 100,000 per year among light skinned people in those areas with the highest rates. Similarly SCCs and BCCs are more common in fairer skin types. Immunosuppressed patients are at a higher risk of developing all types of skin *cancer,* in particular SCCs. They should be encouraged to take all preventative measures to avoid UV radiation.

It is important to identify at risk groups in order to be able to target preventative measures. These include:

- Caucasians – especially fair skinned (Type I and II) with blonde or red hair
- Sun burns and cumulative sun exposure especially in early life
- Atypical mole syndrome and multiple atypical naevi
- Family history of melanoma e.g. CDKN2A mutation
- Living at low latitudes
- Radiotherapy
- Social attitudes and behaviour
- Actinic Keratosis and Bowen's disease
- Chronic skin inflammation or infection

What can we do?

Primary Prevention

1. Sun avoidance behaviour

• Avoid excess sun-exposure

The sun is at its strongest between 10am and 2pm, especially in the summer months and patients should be advised to avoid the sun during these hours. Good robust shade structures should be sought if this is not possible. The WHO recommends that when the UV Index predicts radiation levels of 3 or above, sun safety practices should be taken.

In those cases where sun exposure is unavoidable, especially for outdoor workers, employers should ideally encourage their employees to wear sun protection gear. Mandatory sun protective clothing in the work place reduces UV radiation-induced skin damage significantly, as opposed to those workers whose employers do not impose a sun-protective dress code.

• Protective clothing

Like sunscreen, clothing itself provides sun protection. This is measured in vitro as the ultraviolet protection factor (UPF). This measures protection against UVB as well as UVA. The degree of UPF offered by clothing varies according to the material, colour, dye type and concentration, thickness and tightness of the weave and tightness of the tailoring. For example, dry, baggy, dark denims would provide high UPF, whereas white, tight cotton would only provide a low UPF. Titanium is one of the substances being incorporated in fabrics to increase the UPF. Photoprotective laundry additives are also being developed. A hat with a wide brim offers good sun protection for the eyes, ears, face and the back of the neck.

• Sunscreen

Sunscreens should be photostable and broad spectrum to protect against both UVB and UVA, i.e. broad spectrum. The Sun Protection Factor (SPF) measures the erythema response of skin to UV light, and is a marker of UVB exposure. An SPF equal to or more than 30 should ideally be chosen for UVB protection. This means that untanned skin can withstand 30 times the amount of UVB before it develops erythema.

UVA skin damage is not reflected by the degree of erythema therefore SPF does not correlate well to UVA protection. This has led authorities such as the American Academy of Dermatology to set standards before a sunscreen can be considered as broad spectrum.

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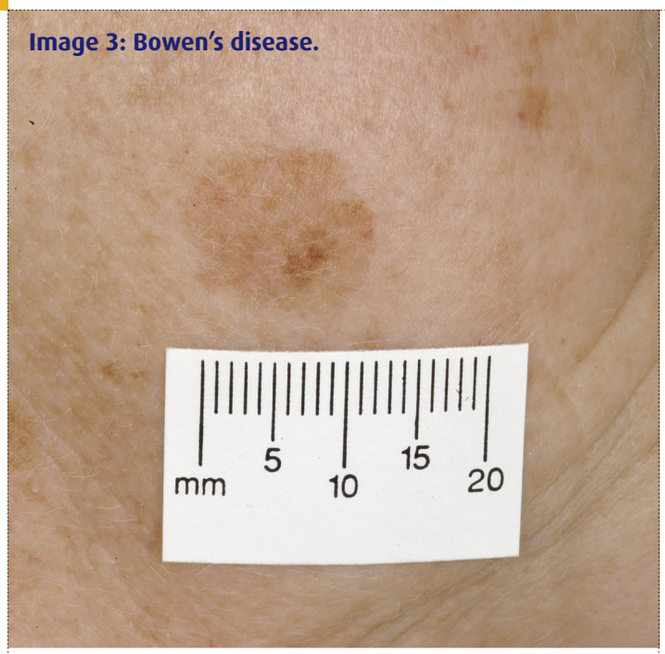

Image 3: Bowen's disease.

The amount of sun protection offered by a sunscreen depends on the way the cream is used, and in particular, the quantity applied not just the SPF. An easy way to achieve an adequate concentration of 2 mg/cm^2 is to use the teaspoon rule of application: greater than one-half teaspoon should be applied to each arm and also to the head and neck, and greater than one teaspoon should be applied to each leg, the chest and the back. Individuals should apply sunscreen approximately 30 minutes prior to sun exposure and then every 2 to 3 hours thereafter.

• Chemoprevention

There are many products with antioxidant properties under investigation including calcitriol, caffeic acid, Polypodium leucotomos, Cistus, butylated hydroxytoluene, isoflavones, flavenoids and lycopene. Two of the most commonly used are a combination of Vitamin C and E. T4 endonuclease V is a DNA repair which is currently being studied as an encapsulated liposomal form for topical application.

• Avoidance of artificial UV light including sun beds

A study carried out in Switzerland analysed the amount of UV burden generated by sun beds. Sun beds have UVB emission spectra similar to solar spectra, but with UVA range reaching 10 to 15 times as much as those generated by the sun. A review by the International Agency for Research on Cancer (IARC) Working Group found that first exposure to sun beds in people younger than 35 years increased the risk of malignant melanoma by 75 percent. The WHO now recommends that anyone under the age of 18 does not use them at all.

2. Organisations and Education

• Intersun

The Intersun Programme was set up in 1992 after the United Nations Conference on Environment and Development declared the need for more measures to control activities which lead to UV exposure. Intersun also provides information and scientific evidence on the effects of UV exposure. It advises countries regarding UV radiation prevention programmes and draws guidelines in order to reduce the global burden of disease caused by excessive UVR exposure. Other international organizations like the United Nations Environment Programme, World Meteorological Organisation, International Agency on Cancer Research and International Commission on Non-Ionising Radiation Protection, and several WHO collaborating centres are actively involved in Intersun.

• Education Programmes

General public education programmes, media awareness and specific programmes directed at children and teenagers in the UK have been associated with reduction in melanoma thickness and improved prognosis.

• Primary care services

Primary care plays an important role as a source of health information in the community. This could be in the form of simple visual aids in waiting rooms or advice given during a consultation. Primary care practitioners can recognise patients at high risk, and advise about sun protection and self-examination. Most importantly they can recognise skin cancers and refer patients to specialised centres for early treatment. Often the skin cancer may be an incidental finding in a patient who attended with a different matter.

Secondary Prevention

1. Skin self-examination (SSE)

Everyone, especially those at high risk of skin cancer should be encouraged to perform skin self-examination regularly. A recent report suggested that SSE may provide a useful and inexpensive screening method to reduce the incidence of melanoma as well as prevent the development of advanced disease. An educational campaign in western Scotland, promoting awareness of the signs of suspicious skin lesions and encouraging early self-referral, showed a decrease in mortality rates associated with the campaign.

This could be explained by the fact that, very often, melanomas exhibit a prolonged horizontal growth phase during which time the tumour expands centrifugally beneath the epidermis but does not invade the underlying dermis. This horizontal growth phase may provide lead time for early detection. The subsequent vertical growth phase carries increased risk of metastatic potential.

2. Identification of potentially malignant lesions

There are a number of pre-malignant lesions and again their presence is related to cumulative UV radiation exposure.

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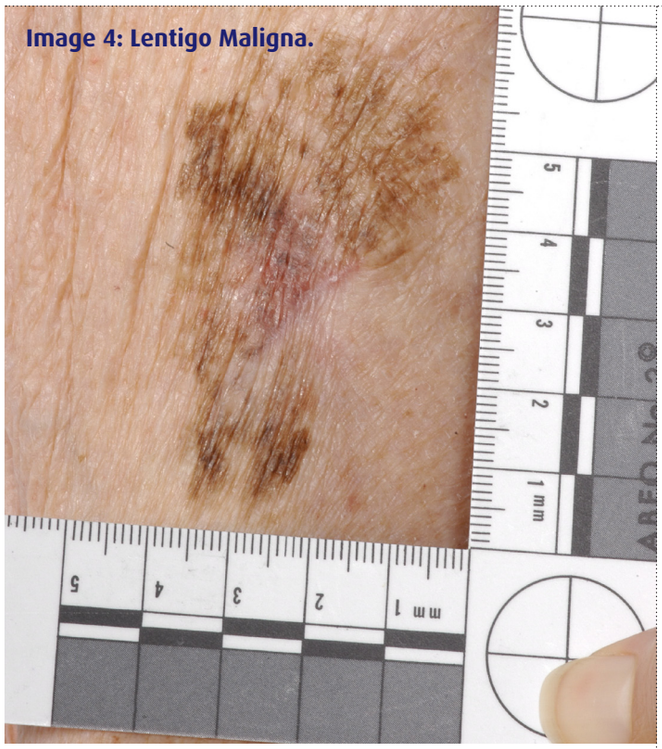

Image 4: Lentigo Maligna.

• Actinic Keratosis (AK)

In Ireland and the UK, an average of 22% of patients above the age of 60 and 3–6% of patients between the age of 40 and 49 were found to have AKs. For an individual with an average of 7 AKs, the probability of at least one transforming within a 10 year period is approximately 10%. AKs are usually diagnosed clinically. A skin biopsy is performed when there is doubt as to the presence of a neoplasm. For solitary or for limited numbers of lesions, lesion-directed therapy with liquid nitrogen or curettage and cautery is performed. In more widespread lesions, field-directed therapy with Diclofenac gel or 5-Fluorouracil cream is preferred.

• Lentigo maligna (LM)

LM appears clinically as an irregular area of pigmentation which grows slowly with time. In 5–15% of cases it develops into the invasive Lentigo maligna melanoma, which clinically appears more indurated and irregularly pigmented. This is treated with surgery or if the patient is not fit enough for this, radiotherapy is instituted. The topical immune modifier Imiquimod 5% has been recently found to clear these lesions and is used in selected patients in whom surgery is not an option.

• Bowens disease

Bowens disease typically presents as erythematous, scaly plaques on the lower limbs of a female patient. These are usually solitary and enlarge slowly with a potential to progress in 3% of patients to SCC. The anti-neoplastic, agents 5-Fluorouracil and Imiquimod 5%, have been shown to be effective topical treatments. Photodynamic therapy is also used with variable success. Surgical options include cryotherapy, curettage and cautery.

Summary

The incidence of skin cancer is on the increase. Some people are genetically and phenotypically more prone to develop this neoplasm, however ultraviolet radiation remains one of the most important modifiable risk factors. Various worldwide and national organisations aim to educate the public taking care with sun exposure and the importance of early detection of skin cancers. These remain the key messages in any campaign to reduce the incidence of skin cancer.

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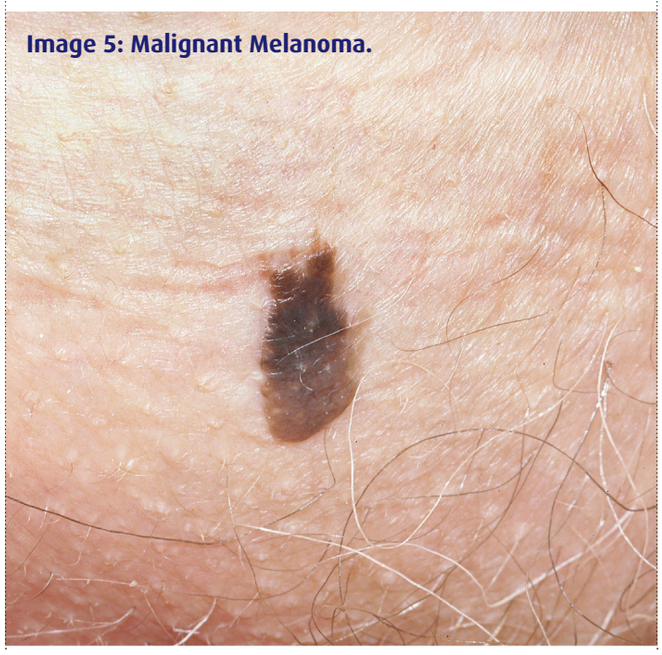

Image 5: Malignant Melanoma.

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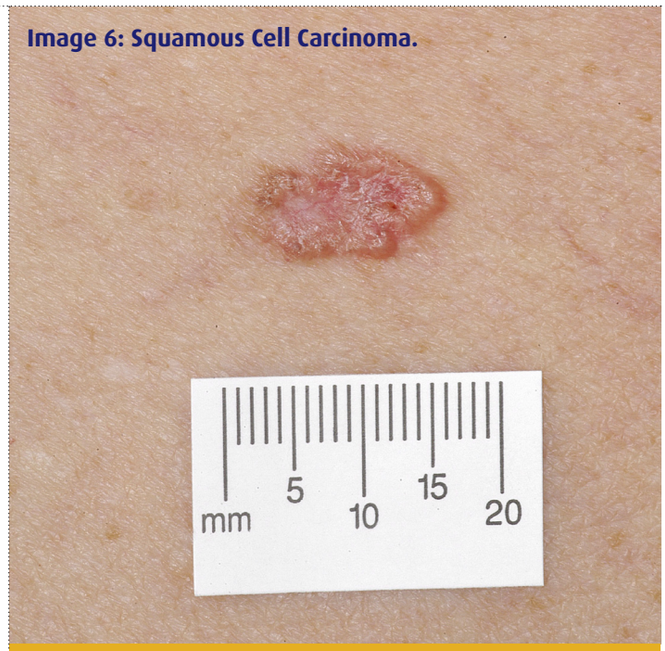
Image 6: Squamous Cell Carcinoma.



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Good Clinical Care.

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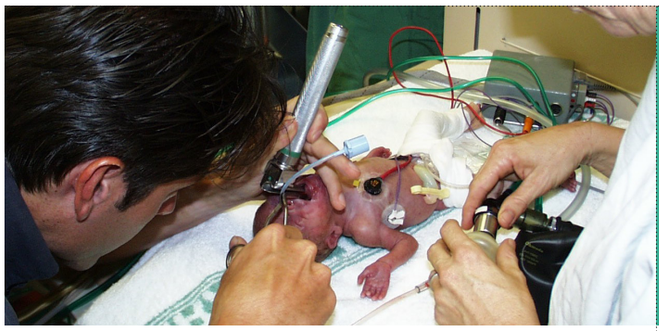
NEONATAL RESUSCITATION AND INTENSIVE CARE: A CASE BASED DISCUSSION

F Garrard, S Rathi and Z Elanjikal



Neonatal Resuscitation and Intensive Care: A Case Based Discussion. Teaching & Training.

Abstract

Neonatal resuscitation and intensive care is based on a systematic approach. In this article, an atypical case of neonatal respiratory distress highlights fundamental transferable lessons applicable to all foundation trainees. Although neonatology is a complex speciality, knowledge of the key differences between adults and neonates will help to reinforce resuscitation principals and the important points of clinical assessment. An increased focus on respiratory distress and causes of neonatal sepsis, will allow juniors to manage many problems effectively. Finally, in paediatrics it is of increased importance to consider and involve the family.

Case History

The paediatric team was crashed bleep to resuscitate a 2.6kg, term female, born by induced vaginal delivery for prolonged rupture of membranes, with sufficient antibiotic cover. There were no other septic risk factors or any significant antenatal history of note. The baby was born floppy, blue and bradycardic; and after prolonged stimulation, was making only occasional gasping respirations. Inflation breaths were delivered and on arrival of the paediatric team, the baby had started to make regular but grunting breaths and had a normal heart rate. The baby was wrapped and transferred to SCBU, with Apgar scores improving from 1 at 1 minute, to 7 at 5 minutes. Initial assessment revealed the baby was normothermic, with saturations of 96% on 35% oxygen. Although the baby's tone, colour and reactivity had improved, she was still grunting and had bilateral crepitations on auscultation. Initial venous blood sampling revealed a mild respiratory acidosis and hyperglycaemia. As the respiratory distress was presumed to be of septic cause; the plan included establishing IV access, getting further bloods and a chest X-ray, and starting IV antibiotics and fluids. Initial bloods revealed a leukocytosis of lymphocytic origin, with a normal CRP.

Fourty-five minutes after birth, the chest X-ray (Figure 1) revealed a left sided pneumothorax with significant mediastinal shift. Clinically, the baby had a consistent oxygen requirement but now had reduced air entry on the left side. The on call consultant was called and a chest drain inserted. Repeat chest X-ray at 3 hours of age (Figure 2) revealed effective drainage, with lung re-expansion and mediastinal relocation. The baby clinically improved with a reduced oxygen requirement and her pH normalised.

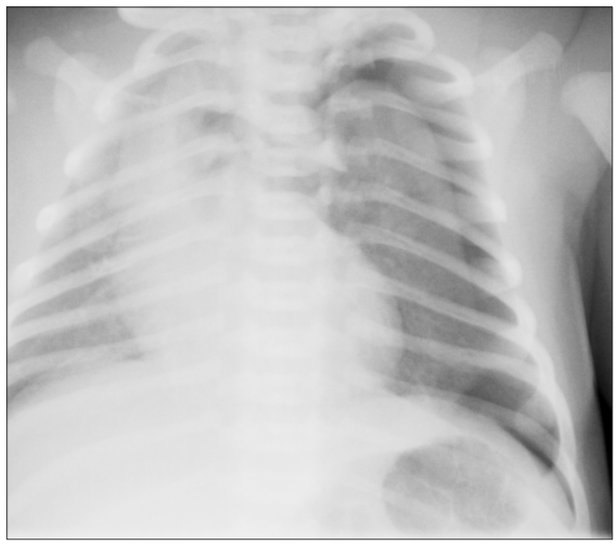


Figure 1

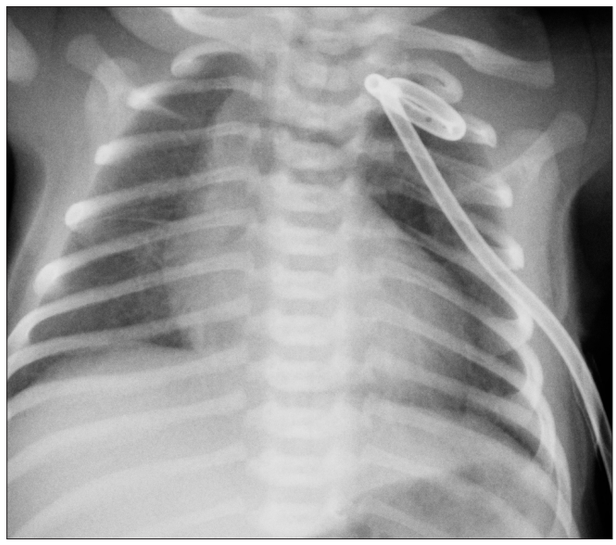


Figure 2

NEONATAL RESUSCITATION AND INTENSIVE CARE: A CASE BASED DISCUSSION

F Garrard, S Rathi and Z Elanjikal

The drain became static one day later, and so this was clamped and removed. Enteral feeds were commenced at 60ml/kg/day and this was tolerated well. The antibiotics were stopped on day 3, in view of the baby being clinically well with negative blood cultures and a normal CRP. Over the next 48 hours her demand breastfeeding improved and she was discharged on Day 6.

Discussion

Neonatal resuscitation varies greatly from adults and even children in its focus. All children, including neonates are much more likely to have a respiratory cause for asystole. This is why the outcome of resuscitation is much more dependent on early and effective respiratory assistance. Neonatal and paediatric resuscitation algorithms reflect this, in their focus on ''rescue breaths' ' before commencing cardiovascular assessment or support. The most important difference for neonates is that drying, stimulating and wrapping them is often enough to make them breath. Hypothermia is also a key cause of respiratory distress and secondary hypoglycaemia. The neonate breathing will improve all Apgar score criteria (Colour, Heart Rate, Reactions, and Tone), which is a useful assessment of progress, but should not delay resuscitation.

If this fails to work, then intervention is warranted. Unlike in adults, the airway should be supported in a neutral position. Since neonates have very compressible soft tissues, only bony structures should be held. Inflation breaths, ideally with positive end expiratory pressure, will increase the patency of distal airways. It is rare that further support is required, but if the heart rate is still below 60, then chest compressions should commence and airway adjuncts can be considered. If this is the case, then the neonate is likely to need a definitive airway and any oxygen requirement is a criterion for admission to SCBU.

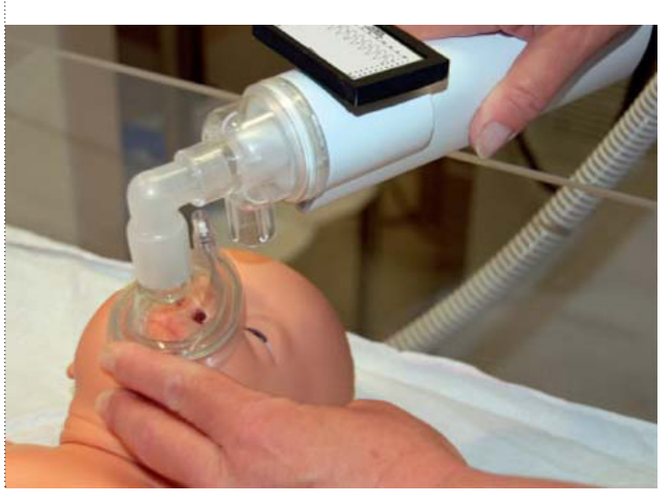
Despite the complexities of neonatal intensive care, some basics remain the same. All patients require effective venous access. In neonates this can be via a peripheral cannula, long line or umbilical venous catheter. Intraosseous access can also be used in the initial resuscitation period. Effective monitoring is required, and as preterm infants can suffer apnoeic episodes causing desaturations and bradycardias, this also includes an apnoea alarm. Daily review should include an assessment of the airway, breathing, circulation, feeds (and glucose), growth, neurological status (including head scans) and medication. In addition to special needs, it is important not to forget basic neonatal care that includes a newborn check, hearing and blood spot screening.

For foundation doctors being exposed to paediatrics, the most important lesson is that children compensate very well for illness. Although this is excellent for neonatal outcomes, it means it can be easy to miss severe illness. Always actively look for signs of respiratory distress, fully examine children and check observations closely with age adjusted normal values. A neonate with totally normal observations, who looks well, should reassure you. However, beware of those with slightly deranged observations, particularly if the parents are saying they aren't right. Continuous grunting should be taken seriously as it is an attempt to create positive end expiratory pressure and maintain airway patency.

Pneumothorax can be primary (spontaneous) or secondary. In children it has a bimodal presenting age distribution, presenting either as a neonate, or as a late adolescent[7]. A retrospective 10 year analysis of infants (28 days to 1 year old) admitted with suspected spontaneous pneumothorax, showed that all of the sample had underlying conditions predisposing to pneumothorax. However, this evidence is based on a small sample size and it is always important to look for potential reversible causes. It is also important to consider that newborns are much more likely to have a delivery acquired infection, birth trauma or be a first presentation of severe congenital abnormality.

Although the cause of this pneumothorax was never established, possible causes include:

- *Resuscitation* – CPR and artificial ventilation[5].
- *Sepsis* – Septic risk factors in neonates include maternal pyrexia, premature rupture of membranes, and a maternal history of group B streptococcus. It is important to ask about previous pregnancies, as GBS is not always screened for antenatally and a maternal history of a baby with GBS sepsis is often seen as a criterion for prophylactic antibiotics.
- *Aspiration* – Commonly meconium aspiration at birth.
- *Cystic Fibrosis*
- *Congenital Thoracic Malformation (CTM)* includes a range of abnormal lung morphology. Many of these are detected antenatally and shrink considerably in the third trimester. Untreated these can cause pneumothorax, but most do not need treatment[4].



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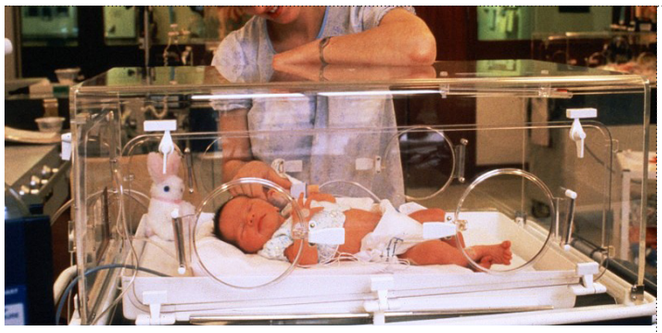

In neonatal intensive care, it is particularly important to consider the parents in your management plan. When neonate are taken to SCBU, the mother is often having medical attention herself and the anxiety caused by her child being unwell, being separated from her and a lack of up to date information should not be underestimated. It is important that paediatricians introduce themselves briefly to mum and birthing partners at delivery, encourage parents to visit their child on SCBU and be involved in its basic care. This will empower patients with the skills needed post discharge and encourages bonding. Measures such as graduated discharge to the postnatal ward or parents staying on the intensive
care unit to practice nocturnal care, are all measures that increase parental confidence and prevent unnecessary re-admission.

Questions

1. You are bleeped to the delivery of a term infant with meconium stained liquor. The midwife has dried and wrapped the baby but the baby is making occasional deep gasping respirations. Do you:-

a) Reassure the midwife and return the baby to Mum and Dad.
b) Assess the Agars, give inflation breaths and then oxygen.
c) Dry and stimulate the baby again, by rubbing him with a towel.
d) Intubate and ventilate the baby.

2. Your next patient is an 18-month-old child in resuscitation. He has subcostal recession, nasal flaring and occasional head bobbing, with oxygen saturations of 89%. While inspecting, you notice there is decreased chest movement on the left and the trachea is deviated to the right. Auscultation reveals absent breath sounds on the left side. The child is slowly becoming more breathless. You have never seen anything like this before. What should you do?

a) Get IV Access.
b) Get a Chest X-Ray.
c) Start oral prednisolone and nebulised salbutamol.
d) Start oral antibiotics.
e) Fast bleep the paediatric registrar and find a senior colleague in A&E to perform a needle thoracostomy.

Answers

Answer 1. b)
Gasping ventilations are not sufficient respiratory effort for life. The next important step would be to give inflation breaths and reassess response, and check colour/SpO2.

Answer 2. e)
In any patient with a tension pneumothorax, do not waste time doing anything but relieving that tension. As an F2 who has ''never seen anything like this,'' it may be beyond your level of experience to perform a needle decompression yourself. Since the patient is currently compensating and can wait for a few seconds, fast bleep your registrar and find an A&E senior to perform it or at least supervise you. Although the cause may be septic and the resuscitation may require IV access, you should manage breathing problems before moving onto circulatory or other problems. Severe asthma can present with a silent chest, however it is unlikely to be localising.

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UNDESCENDED TESTES

Aruna Abhyankar and Kalpana Patil

Undescended testes.
Good Clinical Care.

Abstract

Undescended testis is a common indication for referral to paediatric surgery. Its surgical management is guided by clinical examination findings. We present a case based discussion encompassing the aetiology, presentation, surgical management and outcome of an undescended testis.

A two-year-old boy is referred to the paediatric clinic by the general practitioner. His left testis is undescended and not present in the scrotum. His mother is very worried.

The boy has no significant medical history.

On local examination the right testis is descended and can be seen and palpated in the scrotum. He is not happy to be examined, but the left scrotum appears empty.

How will you proceed?

After a systematic history taking a careful examination should be carried out, if necessary with your consultant present. Examination of a two-year-old child can be quite tricky. However, most children respond favourably to a relaxed and warm environment. The examination findings then should be explained to the mother with a plan for further management.

An examination by your consultant confirms a palpable testis in the left inguinal region. It cannot be brought down to the scrotum. The right testis is mildly retractile and can be brought into the scrotum and easily remains there. The child is uncircumcised and has normal penile anatomy. There is no evidence of an inguinal hernia on either side.

What will you do next?

This boy's left testis will not descend spontaneously and thus he needs an open orchidopexy. The right retractile testis does not require surgery at present but merits observation. Thus the next step is to counsel the mother regarding the need for surgery and offer relevant details about the management of undescended testes.

Is it a common problem?

An undescended testis is a common medical condition and is present in about 3–4% of boys at birth. By three months of age 1.5% boys have an undescended testis, the left testis being more commonly affected than the right. Its incidence increases with prematurity and low birth weight. A study from Denmark showed an overall incidence of 3.2% with increased concordance in brothers (8.8%) and twins (24%).

What history will you seek?

The birth history, prematurity and any medical history should be noted.

• It is more prevalent in premature babies and associated with certain syndromes, such as Prader Willi syndrome and Noonan syndrome.

• Family history of undescended testis.

• Other genital abnormalities: Increased incidence of maldescent is seen with hypospadias. An undescended testis associated with contralateral impalpable testes may prompt investigations (karyotype and hormonal assays) to rule out disorders of sexual differentiation (intersex).

• History of operations in the inguinal region, such as previous inguinal herniotomy and orchidopexy on the affected side. A child may have undergone an emergency hernia repair or previous orchidopexy. Testicular atrophy or retraction of testes due to scar formation in the incision may occur, in which case, clinical examination may be more difficult or the orchidopexy more challenging.

• Inguinal hernia: Presence of a clinically apparent hernia with an undescended testis has a two-fold clinical significance. First, the hernia may become irreducible which can cause vascular compromise to the testes and second, it may be difficult to diagnose torsion of an undescended testis as the signs and symptoms could be very similar to those of an irreducible hernia.

Most of the undescended testes are known to be associated with a patent processus vaginalis (PPV), rather than a hernia. A hernia in infancy needs an early surgical repair (inguinal herniotomy). Simultaneous orchidopexy may or may not be performed depending on the clinical presentation and operative findings.

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One should also inquire if testis has ever been felt or seen in the scrotum. The child has a complete medical check after birth (by the neonatologist) and thereafter at 6–8 weeks by the general practitioner. Subsequent medical assessments occur at 2 years and preschool and are not mandatory hence are conducted at a variable age as guided by the primary health care policies and the population needs. The red book may be a useful source of information related to various health checks.

If the boy has a retractile testis the mother may recall that she could see the testis while bathing the child, or during his nappy change.

How will you examine the child?

Conducive environment:

Make sure that the room and your hands are warm. It may need some time and patience before the child is distracted and cooperates with the examination. Simple toys and pictures can prove a useful tool to keep the child engaged. While examining the child ask the mother to stand close to him near the couch, hold his hand to reassure him. A general examination should precede the local examination.

If you think you need help to perform the examination, it is appropriate to perform the examination along with your senior colleague so that the child does not have to undress twice and avoid distress for both the child and parent.

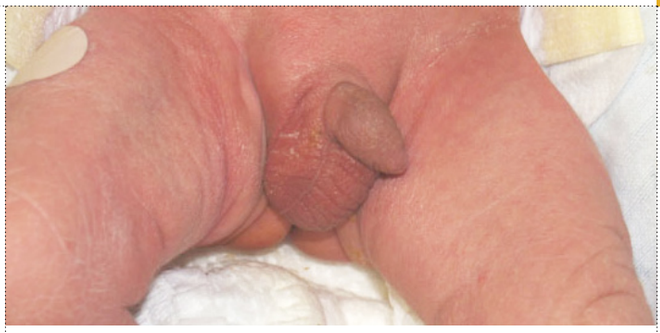
Inspection:

See if the testis is obviously retractile in which case the testis may be pulled towards the external ring or inguinal canal, as the nappy is undone. Look for the presence of a hernia which may be seen as a groin swelling when the child strains or cries. Note if there is associated hypospadias. Abnormal appearance of the foreskin will be a clue to this diagnosis. An intact foreskin is unlikely to be associated with significant hypospadias.

Palpation:

First assess the contra lateral testis for position and size. Then gently palpate for the testis in question. The left hand is glided firmly along the inguinal canal, starting from the left iliac fossa above the internal ring towards the scrotum while simultaneously feeling for the testis with the right hand. An emergent testis may be thus manoeuvred out of the deep ring. In the majority of cases the testis is palpable at the external ring.

If the testis appears to reach the scrotum, check if it sits in the scrotum with and without support from the hand.



What advise will you offer to the mother?

The indications for orchidopexy may be stated as follows:

At this age, the undescended tests will not achieve spontaneous descent. An undescended testis, if untreated, is associated with poor quality sperm count. A scrotal testis may be cosmetically more acceptable and allows ease of self examination and easier diagnosis and management of any future testicular pathology.

The operation is performed under a general anaesthetic and unless there are other medical indications necessitating an inpatient stay, it is performed as a day case procedure. General anaesthesia requires an appropriate period of fasting prior to the operation. After the operation the child would be observed for about four hours and is allowed home when he is comfortable, accepted oral feeds and passed urine.

After the operation the child is reviewed in the clinic 2–4 months later to ascertain the early outcome and complications if any.

While awaiting surgery, if the child experiences any episode of irreducible swelling or pain and discomfort associated with the testes, immediate medical attention must be sought via emergency GP or A&E services. Although rare, incarceration of hernia associated with an undescended testis or torsion of the testis may occur. These two conditions require urgent surgical intervention.

Mother is worried about the future effect on the child's fertility. What will you advise her?

The effects of the undescended testis could be addressed by analysing the effect on fertility, time taken to conception and reported incidence of paternity. The child would not be infertile by virtue of his unilateral undescended testis.

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A recent study has failed to show any significant effect on paternity in patients operated for unilateral undescended testis as compared to the general population or any association with preoperative testicular position. Whereas the researchers found significantly low paternity rates in men who had undergone bilateral orchidopexy (65% vs 95%) There is no significant difference between paternity of normal males and those with unilateral undescended testis.

In patients with undescended testis there may be some impairment of sperm function. A study by Coughlin and colleagues shows that the time to conception was delayed to 12 months and 33 months in patients with unilateral and bilateral undescended testis respectively as compared to 9 months in those with two fully descended testes.

Mum is hesitant as she hopes the testis may descend further. She is also concerned whether it is safe to have general anaesthesia at a young age?

The recommended age for surgery is ever decreasing. Until recently referral for surgery was only made if the testis had not descended by two years of age. It is now recognised that an undescended testis is unlikely to descend after six months of age. Some studies show that when operated in early childhood, the sperm count is better in patients who have undergone early orchidopexy.

In clinical practice patients are usually referred for operation around their first birthday. However trained paediatric surgeons would be able to competently perform the operation before the child's first birthday. Paediatric anaesthesia, by paediatric anaesthetists in a paediatric theatre and recovery set up, is safe. The management of a paediatric patient must be carried out in an environment and medical set up specifically built to address the needs of the child and must be able to cope with any emergency situations.

What is the risk of complications after an orchidopexy?

General complications

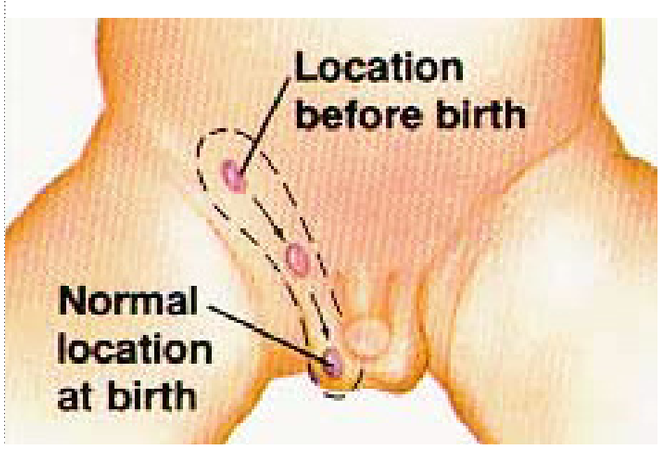
Infection and bleeding are complications which can occur after any operation with variable severity. However one does not expect these to be a major issue after an elective orchidopexy. Infection is rarely seen after elective clean cases. Thus the patient is not placed on antibiotics unless there are specific indications.

Complication specific to the orchidopexy are:

Testicular atrophy: 2%.
Injury to the vessels during separation of the patent processus vaginalis from the cord structures can lead to testicular atrophy which may be apparent at the follow-up assessment.

Damage to vas : <2%
Damage to the vas is a very rare occurrence and if recognised intraoperatively, re-anastomosis of vas with microvascular techniques could be performed.

Retraction of testis: 2-3%
Post-operatively the testis may retract away from its scrotal position. This may be due to persistent processus vaginalis or entrapment of testis within the scarred tissues. Need for repeat orchidopexy is reported to be 2–3%. When performed by an experienced paediatric surgeon or paediatric urologist re-exploration has a high success rate of 95%.



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Further discussion: What is the cause of testicular maldescent?

Testicular descent is a multistage process dependent on several anatomical and hormonal factors and their interplay.

The urogential ridge is morphologically identical up to 6–7 weeks of gestational life. SRY gene on the Y chromosome spurs the testicular development and Mullerian inhibiting substance (MIS) leads to regression of the Mullerian system. Briefly, the testicular descent is considered in two phases: abdominal and inguinal. The inguinal phase is dependent on androgens which act via the stimulation of calcitonin gene-related peptide (CGRP) a neuropeptide on the genitofemoral nerve.
However the aetiology of testicular descent is yet not completely elucidated.

What investigations are required in patients with undescended testes?

Radiological imaging is not indicated to ascertain the position of the testes as ultrasound scan, CT scan or MRI scan do not offer a superior sensitivity or specificity over a good clinical examination.

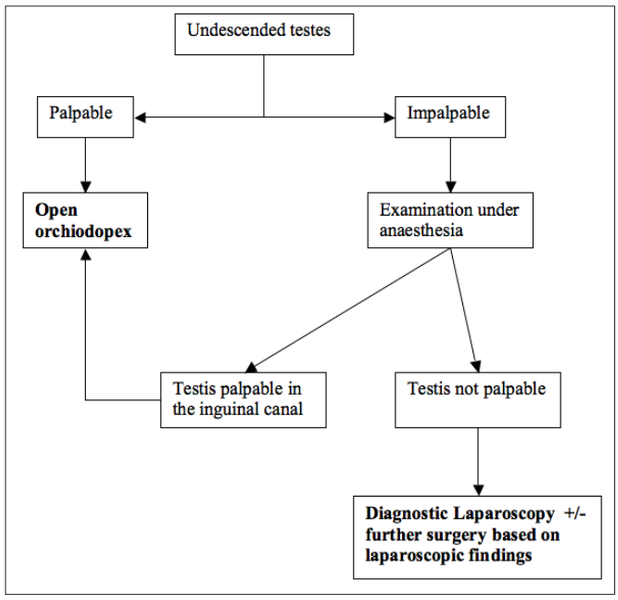
For management of an impalpable testis, examination under anaesthesia, +/- diagnostic laparoscopy is the gold standard. Further management depends on the findings at laparoscopy.

Patients who have hypospadias associated with unilateral or bilateral impalpable testis or bilateral impalpable testis without hypospadias should have karyotype assessment and urgent referral to a paediatric endocrinologist and urologist to rule out any disorders of sexual differentiation (DSD, previously referred to as intersex or ambiguous genitalia).

What is the overall surgical strategy for the management of a unilateral undescended testis?

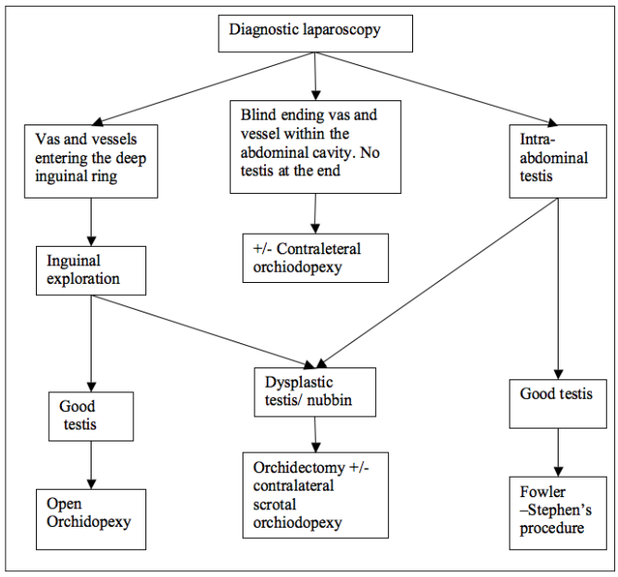
Consent:
A palpable testis is managed by open orchidopexy. When the testis is not palpable the child is placed for an examination under anaesthesia followed by either open orchidopexy or laparoscopy. There are several surgical options based on the finding at laparoscopy. All these are discussed and explained to parents while seeking their informed consent.

An undescended testis is not always cryptorchid. The undescended testis can be classified as palpable and impalpable. The management pathway differs in these two situations. The following algorithm defines the management strategy.



If the testis remains impalpable a laparoscopic examination is performed. Most commonly there are three possible findings:

The following algorithm demonstrates management of the testis based on the laparoscopic examination findings.



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Notes on surgical interventions:

· Some surgeons may not perform inguinal exploration when a careful palpation does not reveal a testis in the inguinal canal and laparoscopy rules out any intra-abdominal testis, as a viable testis is unlikely to be present. The authors follow the strategy of inguinal exploration if vas and vessels are seen entering the deep ring. In an overweight child, assessment of an inguinal testis on palpation may be suboptimal.

· Some paediatric surgeons may also prefer to perform a scrotal orchidopexy for the now solitary contralateral testis to minimise future risk of torsion.

· Fowler-Stephen's procedure: In a high undescended testis, the mobilisation of the cord structures is limited by the short testicular blood vessels. In this operation the testicular vessels are disconnected to achieve length and in the second stage the testis is mobilised to achieve a scrotal position.

· Rarely, there is a normal vas but no vessels or testis is found. A careful search must be performed along the normal line of descent up to the lower pole of the kidney before a diagnosis of "vanishing" testis is made, as the testis may lie in an ectopic position.

· When vessels are seen entering the deep inguinal ring and there is no vas, viable testis may still be located in the inguinal canal.

Why early orchidopexy is recommended?

1. Cosmesis:
· Orchidopexy offers cosmetic benefits.

2. Prevention of potential complications:
· Torsion of an undescended testis usually results in the loss of the testis. This may be prevented by an orchidopexy.
· Patent processus vaginalis may be associated with an inguinal hernia with its inherent complications. During standard inguinal orchidopexy the hernia is repaired too.
· It may help minimise impairment of germ cell function. A Danish study showed that testicular biopsies taken at the time of orchidopexy show the absence of germ cells from as early as 18 months of age, suggesting that persistent undescended position is harmful to the germ cells.

· Risk of malignancy: the statistics associated with risk of malignancy should be carefully interpreted to account for the types of undescended testes and age at orchidopexy. When orchidopexy is performed after 12 years of age, the relative risk of malignancy on the affected side is 2–6 times more than when the child undergoes surgery before 12 years of age. Relative risk of malignancy itself is between 2.5% and 8%.

3. Ease of self examination:
· It is easier to self examine scrotal testes. All young adult males are advised to self examine to increase the likelihood of early detection of testicular cancer.

Are there non-surgical methods to treat undescended testis?

Hormonal Treatment: Administration of hormones is a preferred mode of therapy in some European centres.

Luteinizing hormone releasing hormone (LHRH) or human chorionic gonadotropin (HCG) is sometimes therapeutically used preoperatively in impalpable testis for the presumed benefit that they may become palpable or for a palpable testis which may descend into the scrotum. The mechanism is based on the induction of the germ cells. Long-term benefits and the effects of early germ cell induction are unclear and not widely practised in the UK.

Note:
HCG stimulation test (to identify if testosterone secretion is increased) is utilised for assessment of patients with bilateral impalpable testes.

UNDESCENDED TESTES

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An 8-year-old boy is referred for the management of a unilateral undescended testis. But his parents recall, and medical records of routine preschool checks confirm, the presence of bilateral well descended testes.

Most paediatric surgeons now acknowledge the phenomenon of "ascended testis" where a previously descended testis is subsequently found to be "ascended" out of the scrotum. This testis is now in need of formal orchidopexy.

This phenomenon cannot be explained, only by difficulty in accurate assessment of its location in a young infant.
Medical records from various countries confirm that the rate of orchidopexy is about twice the incidence of undescended testes in infancy. This supports the clinical observation of "ascent" of testis.

How should one manage a retractile testis?

It is important to identify a retractile testis correctly. A retractile testis is one which descends into the scrotum when the child is warm and relaxed and moves cranially with an active cremasteric reflex. It may be seen when the child is being examined. A retractile testis can be brought down right to the floor of the scrotum without any tension in the spermatic cord.

Retractile testis is likely to settle down in the scrotum by 4–6 years of age, hence does not warrant orchidopexy.

However annual follow-up until puberty is advocated to ensure its descent. If ascended testis is diagnosed at any time during the follow-up, an open inguinal orchidopexy is advised.

Learning Points:

Assessment of an "undescended testis" requires careful examination to differentiate between a retractile, inguinal and impalpable testis.

In select cases karyotype assessment is necessary; however a simple undescended testis does not require any further investigations.

Orchidopexy offers ease of self examination, cosmetic benefits and possibly preserves the germ cells.

"Ascended testis" is a recognised cause of undescended testis in an older child.

Further Reading

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CHILDHOOD LIMP – A DELAYED PRESENTATION

Sandip Mandal, Ashis Banerjee, David Mbamalu and Jeroen G.V. Neyt

Childhood limp – a delayed presentation.
Patient Management.

Abstract

A case of delayed presentation of an important cause of painless limp in a 14-month-old child is described. The differential diagnosis is mentioned, and risk factors for the condition are discussed.

Case Report

A 14-month-old female child presented to the emergency department with a progressively increasing and painless left-sided limp since commencing walking in the preceding month. It was noted that she was walking with the left foot turned out. There was no history of injury and no systemic symptoms were present. The maternal pregnancy was uneventful and normal delivery had been achieved at full term. She was the second born child of her parents. There were no other symptoms at presentation. She had been seen for this limp by her general practitioner and was awaiting an ultrasound examination of the hip.

On examination, the left lower limb appeared shortened. The thigh was externally rotated, and left hip abduction noted to be limited.

What differential diagnosis would you consider?

The diagnostic possibilities for a painless limp in this age group are listed in Box 1.

Skeletal causes:
1. Developmental dysplasia of the hip
2. Clubfoot, or congenital talipes equinovarus (CTEV)
3. Congenital short limb

Neurological causes: :
1. Cerebral palsy
2. Spina bifida (Myelocele)
3. Poliomyelitis
4. Congenital hemiplegia
5. Muscular dystrophy
6. Peripheral neuropathy

Metabolic cause:
1. Rickets

Box 1: Differential diagnosis for painless limp in the one to two years age group.

What further investigations are needed?

As this is a painless limp, with no systemic symptoms and with specific findings related to the left hip, plain film radiology of the pelvis is indicated in the first instance.

What do the X-rays show?

An X-ray of the pelvis revealed dislocation of the left hip (Figures 1 and 2). The femoral head epiphysis was underdeveloped. The acetabulum was shallow and hypoplastic, and the left proximal femoral metaphysis was displaced superiorly.

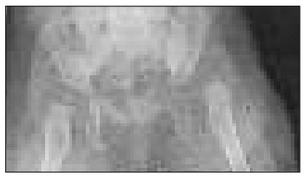

Figure 1

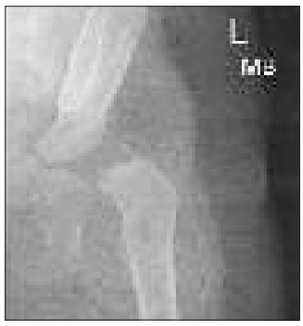

Figure 2

What management is indicated?

Early diagnosis is essential as most hips respond to simple abduction splintage. Late presentation always requires surgery, the increase in complexity and the potential for incomplete correction being proportional to the length of delay in diagnosis (see Box 2). Delayed diagnosis may, however, not indicate inadequate physical examination at the time of screening, as some cases may develop between 6 and 12 months of age[1].

Up to 6 months of age – abduction splint, with 5% requiring surgery

6-18 months of age – closed reduction under anaesthesia is the major mode of treatment

After 18 months – open surgical intervention is necessary

Box 2: Treatment options for developmental dysplasia of the hip.

CHILDHOOD LIMP – A DELAYED PRESENTATION

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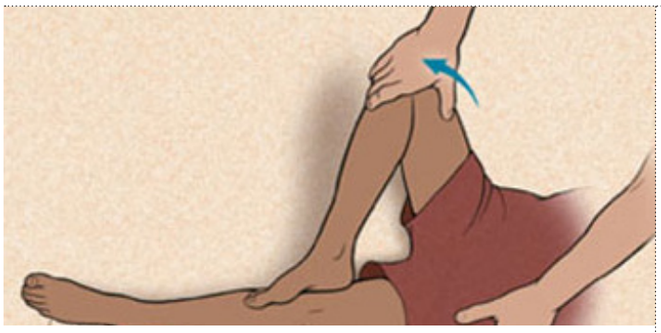

The child was thereafter referred to the orthopaedic team for further management, requiring closed reduction and adductor tenotomy, followed by immobilisation in a hip spica.

What is known about the early diagnosis of this condition?

Developmental dysplasia of the hip (DDH) is now recognised as part of an ongoing pathological developmental process, which is variable in manifestation and not always present at birth. It is defined by an abnormal relationship of the femoral head to the acetabulum. There is a spectrum of abnormality ranging from frank dislocation (luxation), partial dislocation (subluxation), instability and a range of radiological abnormalities of acetabular malformation. The term DDH replaced the term congenital dislocation of hip, recognising that the clinical findings may not be present at birth.

The incidence of DDH varies from 1–3 per 1000 live births. In 60% of cases, no risk factor is found. The left hip is more commonly affected, and in 15–20% of cases it is bilateral. About 80–85% cases are female, and 60% involve firstborn children. There is an association with breech presentation, maternal oligohydramnios, congenital neuromuscular anomalies (congenital torticollis, congenital talipes equinovarus, congenital vertical talus) and neurological disorders (cerebral palsy, meningomyelocoele, arthrogryposis multiplex congenita). A positive family history for DDH in first degree relatives is also a risk factor.

In the UK routine national screening for DDH commenced in 1966, with examinations at birth, at 6 weeks and at 6 months of age. Since the inception of screening, there has been no decline in late presenting cases. The national screening programme in the UK has not reduced the operation rate for late presenting cases[2,3]. The need for, and duration of, ongoing surveillance in high risk groups as identified above remains undefined. A useful algorithm for the evaluation of the hip in infancy has been provided in the American Academy of Paediatrics guidelines, which recommends hip examination at 2–4 days for newborns, by 1 month, 2 months, 4 months, 6 months, 9 months and 12 months of age[4]. This may, however, not be achievable in the UK currently.

After the age of 3 months, ligament laxity is reduced, and the neonatal test methods described by Barton and Ortolani can no longer be performed. At this stage, if the hip is subluxated or dislocated it is usually in a superolateral direction. The diagnosis at a later stage can be suspected on physical examination from the presence of asymmetrical thigh, gluteal and labial creases, external rotation of the lower limb and apparent shortening of the limb on the affected side. Tightening of adductor muscles leads to an adduction contracture of the hip, with restriction of abduction. Asymmetry of lower limbs is absent in bilateral cases, and thus a symmetrical appearance does not exclude the diagnosis.

Radiological evaluation is helpful only after 4 months of age, as before that the hip is mainly cartilaginous. Ultrasound scanning is helpful when there is clinical suspicion of DDH in the presence of risk factors, and the age of the child is less than 4 months.

Female sex, vertex presentation at delivery, normal delivery, rural birth and discharge from hospital less than 4 days after birth have been described in a South Australian screening programme as potential risk factors for late diagnosis of DDH[5].

Conclusions

Awareness of the possibility of delayed presentation of developmental dysplasia of the hip is essential. Early radiological evaluation of the limping child will facilitate detection of the late presentation of DDH.

Multiple choice questions

1. The following is not a risk factor for DDH

a) Sex of the child
b) Birth order
c) History of birth trauma
d) Positive family history of DDH
e) Breech position in utero

2. The preferred initial management of developmental dysplasia of the hip under 6 months of age is

a) Open reduction
b) Abduction splintage
c) Closed reduction
d) Surveillance and delayed correction
e) Osteotomy

3. In the UK national screening programme for developmental dysplasia of the hip, screening is recommended at:

a) Birth, 6 weeks and 6 months
b) Birth, 4 weeks, 6 months and one year
c) Birth, 6 weeks, 4 months and one year
d) Birth, 4 weeks, 4 months and one year
e) Birth, 3 months and 6 months

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4. The optimal method for confirming a diagnosis of developmental dysplasia of the hip during infancy is:

a) Clinical examination
b) Plain film radiography
c) Ultrasound scan
d) Arthrography
e) CT scan

Answers

1. c)
2. b)
3. a)
4. c)

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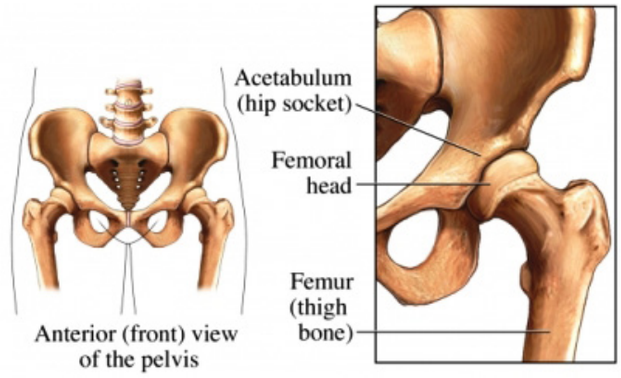

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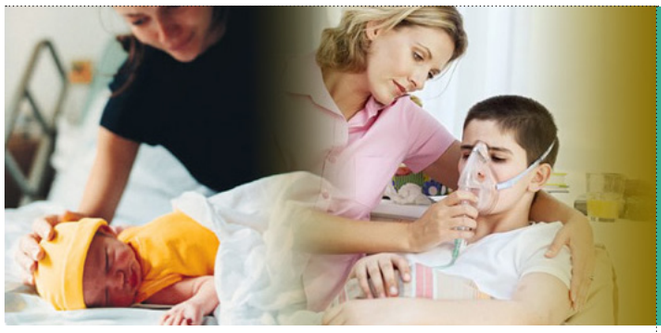
CAREERS IN PAEDIATRICS

S N Ahmed and N Ahmen



Careers in Paediatrics.
Teaching & Training.

Introduction

Paediatrics is a vast and varied speciality, which offers a wide variety of challenges and problems[1]. It is a specialty which contains many subspecialties, for example general, community paediatrics, neonatology and other subspecialties. There is also the added dimension of how the presentation of any diseases may change as the child grows and their development progresses[2].

Paediatricians look after children from the day they are born until they become adults, and this involves looking after the child's physical illnesses as well their emotional well-being, as children often need holistic care[3, 4]. Other important aspects of paediatrics include learning to deal with concerned parents, as well as preventative medicine[3].

What being a paediatrician is like

For a consultant paediatrician, the majority of their time is spent on clinical work, which can include seeing patients, administrative work relating to patient care or clinical meetings. The rest of the time is spent doing other tasks, such as teaching, administration, audits and research[5]. A number of paediatricians have said that there is lots of variety in what they do, and that every day is different[5, 6]. The European Working Time Directive states that the working week should only be 48 hours long[7], but most paediatricians that I know work a lot more than 48 hours per week.

Like all specialties, paediatrics has its benefits and its drawbacks. Benefits include a great deal of variety and a range of skills being required; opportunities for flexible training and training overseas; and being involved with a variety of multidisciplinary teams and other services involved in the child's care, such as families, education and social care. It has been said that working with children is one of the best parts of the job[6] (and I would certainly agree!). If you can make a difference to the life of a sick child, you also make a difference to their family.

Different subspecialties have different challenges and joys. For example, in Neonatology, you will see tiny newborns that can literally fit in your hand, and it is very satisfying to see these babies survive and grow. Such babies usually have many complications, and you must work with them for months before they are able to go home. After they are discharged, you will see them in your follow-up clinic. They may be growing and thriving, and this can be very rewarding. In General Paediatrics, every day on the wards you will see children getting better, interacting more, smiling and making progress. For example, a child might come in very ill with meningitis, and over the next few days, with treatment you will see them becoming more active, smiling and getting better. Even a field such as Child Protection, which most paediatricians shy away from, can be very fulfilling. You have the opportunity to work within a much larger multidisciplinary team, involving medical staff, social services and legal teams. You will play a part in removing a child from an abusive environment and you may also help put sex offenders behind bars. Work in neurodisability can also be extremely worthwhile, as you will see children for years and develop a good rapport and relationship with them. There are children that I have been seeing for 14 years, with cerebral palsy and severe disabilities, and each step of their progress makes me happy. Working with the families for such a long time, you develop a good working relationship with them as well as the children; they place a lot of trust in you to make the lives of these children as fulfilling as possible. The paediatrician's role is very central in the welfare of such children.

Drawbacks include heavy commitment, little scope for private practice[8] although private practice is possible[2], and courts can hire you as an Expert Witnesses in child protection cases; the work can be emotionally draining; and there is heavy demand for limited resources[8]. Dealing with the death of a child can also be very emotionally stressful, and telling parents that their child is dying can be extremely difficult and challenging. You tend to reflect on your clinical management and keep asking if there was anything more you could have done to treat the child. Dealing with abused children and child protection issues can also be very distressing. Parents may also feel betrayed when child protection issues have to be reported. However, you should be able to handle these issues with the parents sensitively. It is important to be honest with the parents, and if done properly they will understand and respect you. There may also be ethical issues involving consent and confidentiality, such as when parents do not want their child to find out about their illness or vice versa; or when parents and children want different treatments for a disease.

CAREERS IN PAEDIATRICS

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Careers in Paediatrics.
Teaching & Training.

Other opportunities as a consultant

In addition to standard full-time work, you may have the option to work part time. Such posts are also available for trainees[8, 9].

You can also apply to gain extra experience of paediatrics abroad[2, 8]. These opportunities may provide useful experiences which can widen your knowledge and skills. Such opportunities may be organised by the RCPCH, or by other agencies. They can also be taken by specialist registrars, as well as consultants.

It is also possible to pursue an academic career in paediatrics[2, 8]. Most people wishing to take an academic post may do a PhD or an MD during their specialist registrar years[8]. There are also Clinician Scientist posts, but the training pathways for these posts are slightly different[2].

There is also scope to develop your job by pursuing certain interests, and diversify your work. Paediatric consultants can, like any other consultants, take up additional roles in management alongside their clinical work, and become Clinical Directors or Medical Directors. Consultant community paediatricians can also take the designated role in certain specialties, such as child protection. Paediatricians can also become expert witnesses for courts. Some consultant paediatricians are also involved in the RCPCH examinations.

The training pathway in paediatrics

After completing your first and second Foundation Years, you will select a specialty. Specialist training in paediatrics can be up to 8 years and can consist of 3 levels[2, 10]. Currently, paediatrics is not an exceedingly competitive specialty – there are 4.1 applicants per place, and 2.1 first choice applicants per place. This is a little higher than the average of 2 applicants per place. However, the competition rates vary significantly between deaneries and also between paediatric subspecialties. The Kent, Surrey and Sussex deanery and the North-Western deanery have the highest competition rates for paediatrics, whereas the West Midlands deanery and the Wessex deanery were the least competitive[11, 12].

In Level 1 Paediatrics (which is done in the first 3 years of specialist training – ST1, ST2 and ST3 years or the SHO post), you learn the basic skills and competencies of paediatrics[10]. The first year of specialist training consists of broad training in paediatrics, and from the second year onwards you may be doing more specialised work[2]. During Level 1, you must complete the MRCPCH examination and assessments[2, 5, 10,] as well as Basic Specialist Training (BST) Competency assessments[2]. Level 2 consists of 2 years – ST4 and ST5 years, or a SpR post, and consists of 3 main areas – neonatology, community child health and acute paediatrics[5, 10]. Level 3 consists of up to 3 years, and may consist of more sub specialised paediatrics[2, 5, 10]. During Levels 2 and 3, you will undertake the Higher Specialist Training (HST) Competency assessments[2]. After Level 3, you will gain your CCT (Certified Completion of Training) and become a consultant paediatrician[2, 5, 10].

The MRCPCH examination consists of 3 parts (two written papers and a clinical examination) and can be quite difficult.

Approximately one-quarter of the paediatric workforce was sub specialised in 2007, and popular subspecialties included neonatology, paediatric intensive care and paediatric neurology. North-Central London had the highest number of sub specialised paediatricians (this region contains Great Ormond Street Hospital and University College Hospital)[13]. It is also possible for a general paediatrician to develop special interest in any sub speciality of paediatrics.

CAREERS IN PAEDIATRICS

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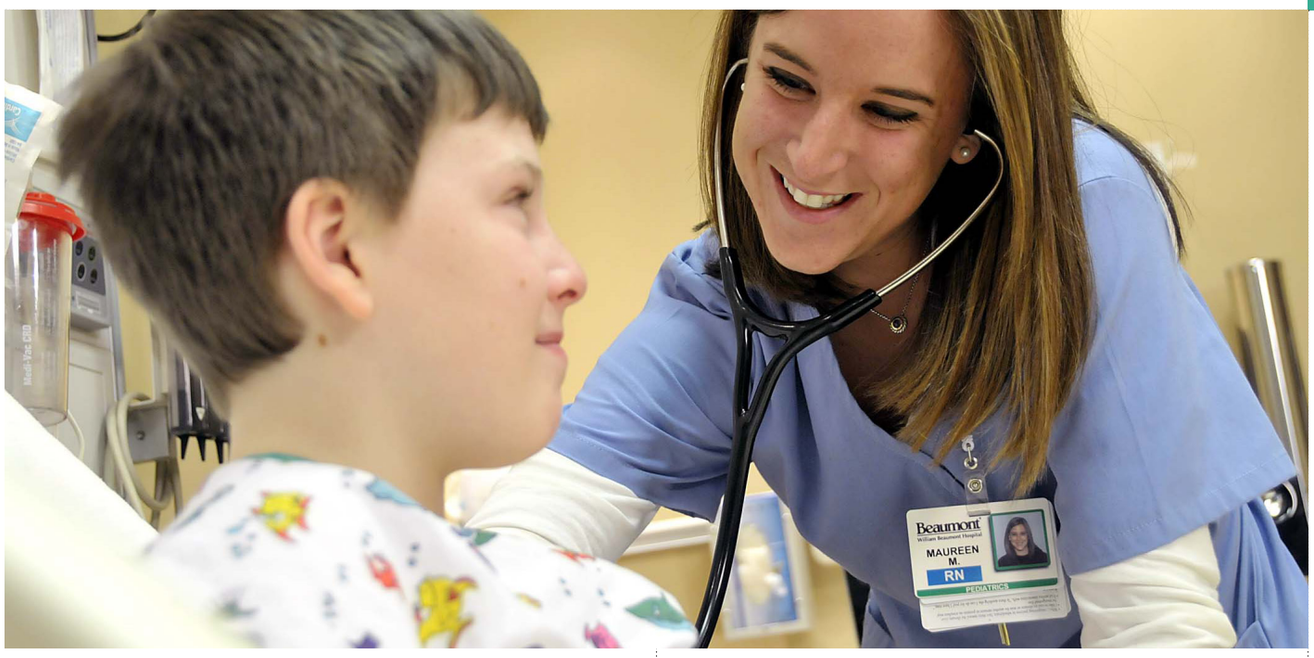

Conclusion

A career in paediatrics can be extremely rewarding. It has a lot of variety[2, 7, 8]. But involves hard work8 and can be emotionally difficult[7, 8]. There is also plenty of scope for progression once you have reached the level of a consultant. Everyday when I come back from work I feel satisfied and learn something new.

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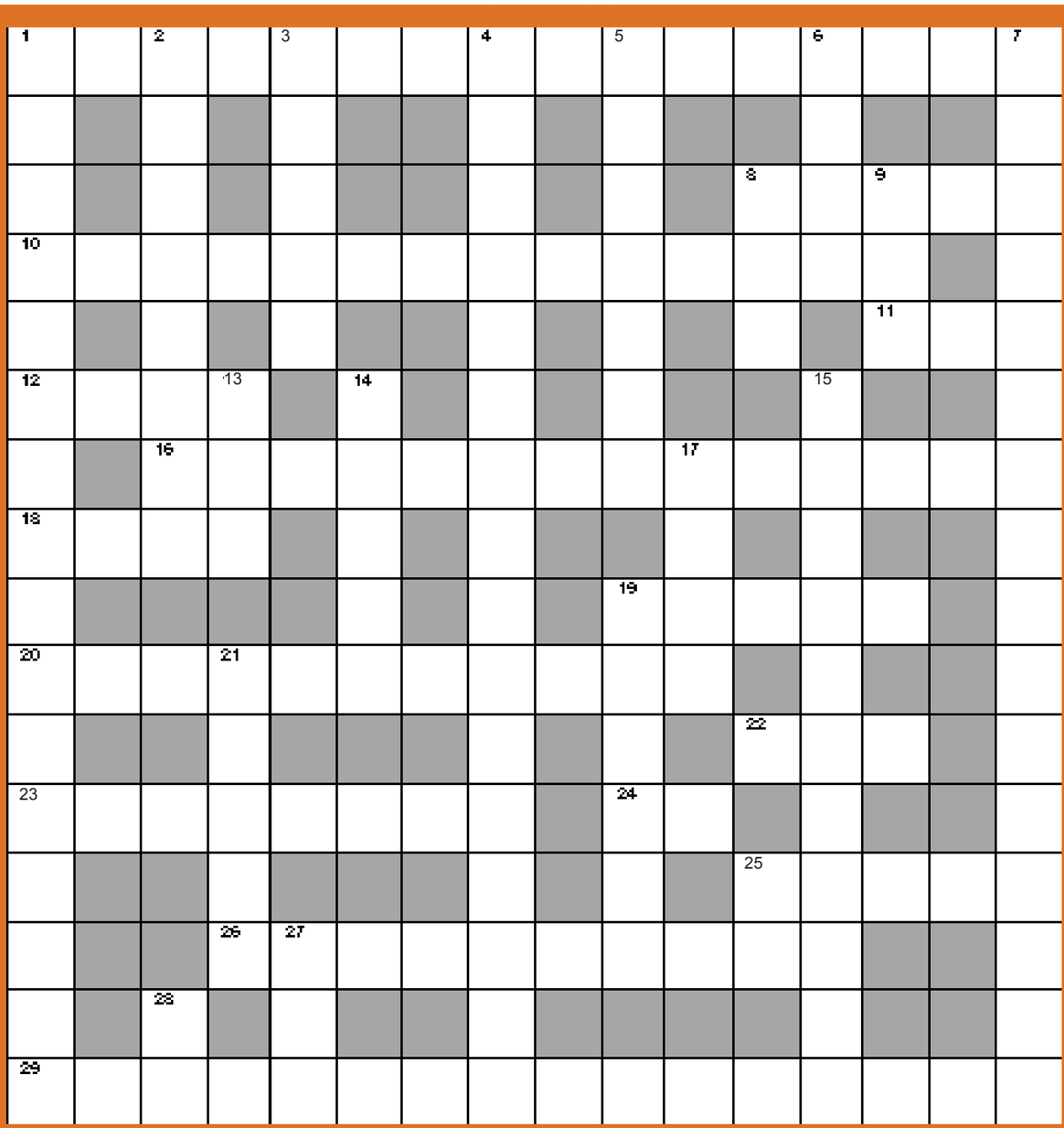
CHILD HEALTH CROSSWORD

Michael Brookman



Child Health Crossword.
Test Yourself.

CHILD HEALTH CROSSWORD

Michael Brookman

Child Health Crossword.
Test Yourself.

Questions (Please Cover Right-Hand Page With A Piece Of Paper Whilst You Test Yourself)

Across

1. Bruising and swelling of the crowning head during labour (5,11)
8. Calculus (5)
10. Can be caused by dehydration or diarrhoea (14)
11. Usual number of umbilical arteries (3)
12. Region between ribs and hip (4)
16. Marker for MI, MD and AKI (8,6)
18. Countryside walk to suddenly increase fitness (4)
19. Analgesic, antipyretic and anti-inflammatory (1,1,1,1,1)
20. Coxsackie is one; as is Polio. (11)
22. Shuffling this may delay walking (3)
23. Insult from placental abruption causes gasping (8)
24. Investigation (1,1)
25. Arteries supplying the umbilical arteries (5)
26. End result of potty training (10)
29. Deletion causes this or Prader-Willi (8,8)

Down

1. Lump when periosteum separates during delivery (16)
2. Needed for Guthrie (3,5)
3. Forcing eyelids apart may cause these (5)
4. A reason not to prescribe (16)
5. Complaint from otitis media (3, 4)
6. A group of antiviral drugs used against HIV (1,1,1,1)
7. Serious complication of spina bifida (16)
8. Poor in utero movements may warn of this floppiness (1,1,1)
9. This cereal grain contains small amounts of gluten (3)
13. Abbreviation for neonatal resuscitation equipment (1,1,1)
14. Protein:Creatinine is one. (5)
15. Juvenile idiopathic arthritis antibodies (11)
17. Do this and risk infectious mononucleosis (4)
19. A girl who has reached an age suitable for marriage (6)
21. The principle on which right/wrong behaviour is based (5)
27. Johnson's liquid fat for babies (3)
28. Type G crosses the placenta (1,1)

Answers

Across

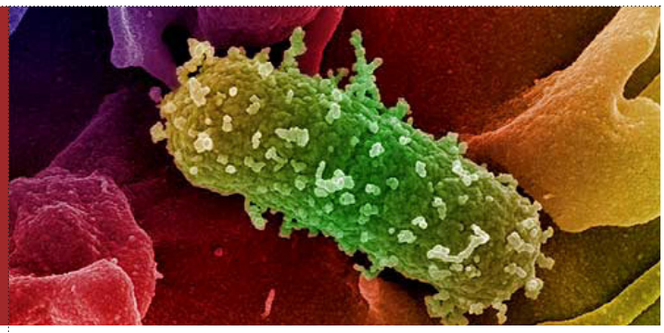
1. Caput succedaneum
8. Stone
10. Hypernatreamia
11. Two
12. Loin
16. Creatine kinase
18. Hike
19. NSAID
20. Enterovirus
22. Bum
23. Asphyxia
24. Ix
25. Iliac
26. Continence
29. Angelman syndrome

Down

1. Cephalohaematoma
2. Pin prick
3. Tears
4. Contraindication
5. Ear ache
6. NRTI
7. Myelomeningocele
8. SMA
9. Oat
13. NRE
14. Ratio
15. Antinuclear
17. Kiss
19. Nubile
21. Ethic
27. Oil
28. Ig

CASE-BASED DISCUSSION - HAEMOLYTIC URAEMIC SYNDROME (HUS) IN CHILDREN

Michael O Ogundele and Hani F Ayyash



Case-based Discussion - Hemolytic uremic syndrome (HUS) in children.
Patient Management.

Abstract

This case-based discussion is based on an 8-year-old girl who presented with haemolytic uraemic syndrome (HUS) characterised by the triad of thrombocytopenia, micro-angiopathic hemolytic anaemia and acute renal failure, following a diarrhoeal illness caused by *escherichia coli* O157:H7. The case will highlight relevant aspects of clinical history, physical examination, laboratory investigations, pathophysiology, complications, prognosis, disease notification, management and follow-up of children presenting with HUS.

The most common cause of HUS is systemic uptake of toxins in 5–10% of individuals infected by Shiga-like toxin-producing *E. coli* (STEC). Other infective agents such as pneumococci and HIV, complement genetic abnormalities, medications, transplantation, malignancy or autoimmune diseases are responsible for 10% of cases of HUS, referred to as atypical or D-HUS.

1 Case History:

An 8-year-old girl (RG) presented to the local hospital with a 3-day history of bloody diarrhoea associated with vomiting. She had also been complaining of abdominal pain, nausea and vomiting.

Question 1: What further history would you like to elicit?

- History of recent contacts with diarrhoeal illness or vomiting and foreign travels
- History of recent unfamiliar food or drinks or eating out
- A differential diagnosis for diarrhoea in infants include viral (most commonly rotavirus) gastroenteritis, parasitic infestations and other infective pathogens.

Further history: RG and her family (younger sibling and both parents) ate lasagne in a local restaurant a week prior to her illness. Other family members were asymptomatic at the time of her presentation.

Examination findings: RG was mildly dehydrated, not pale and had no abnormal rashes or bruising and afebrile (Temp 36.7). Her abdomen was soft and mildly tender with no organomegaly or palpable masses. She was admitted and offered intravenous fluids therapy.

Question 2: What would you do next?

The patient needs a management plan to be formulated after some basic investigations.

2 Simple Investigations

Full blood count (FBC), Electrolytes and Urea (E/U), C-reactive protein (CRP), clotting screen and stool microscopy/culture (MCS).

Outcome 1: RG had normal FBC, E/U and clotting profile. CRP was mildly elevated at 15mg/L. Stool was also requested from other family members for culture. *E. coli* 0157:H7 was isolated from her stool as well as from her sister and father.

Question 3. Since when has *E coli* 0157:H7 infection become a notifiable disease in the UK?

The Health Protection (Notification) Regulations 2010 for England[1] which is due to come into force on 6th April 2010, specifically identifies HUS as a notifiable disease and *E.coli* 0157:H7 as a notifiable causative agent (with effect from 1st Oct 2010). *E.coli* 0157:H7 infections could be notified under the Public Health (Infectious Diseases) Regulations 1988 as a cause of food poisoning.

Question 4: Are there any specific set of clinical and laboratory parameters that may predict the risk of developing HUS?

NO There are no universally agreed identifiable risk factors for predicting the development of HUS in susceptible individuals. A few studies have shown that fever, leukocytosis and elevated CRP levels may predict progression from Shiga-like toxin-producing *E. coli* (STEC) infection to HUS[2].

3 Clinical deterioration

RG continued to have bloody diarrhoea and she became oliguric. Her serum creatinine levels increased from 57 to over 200µmol/L within 24 hours and her urine output was less than 0.5ml/kg/hr. RG was referred to the paediatric nephrology team for further management on account of her deteriorating renal function and suspicion of HUS.

Further clinical examination showed that RG was very pale, puffy in the lower extremities up to both knees and around the eyes. She remained warm and well perfused peripherally. Her chest was clinically clear and there were no focal neurological deficits.

CASE-BASED DISCUSSION - HAEMOLYTIC URAEMIC SYNDROME (HUS) IN CHILDREN

Michael O Ogundele and Hani F Ayyash

Question 5: Do you suspect that RG has developed HUS now?

YES The acute diarrhoeal phase of STEC infection may be difficult to differentiate from other causes of gastroenteritis. Children usually present with diarrhoea 3–8 days after exposure to STEC and HUS often develops one week (1–10 days) after the start of diarrhoea.

Question 6: Is HUS caused by systemic infection with STEC 0157:H7?

NO Shiga-like toxins (Stx-1 and Stx-2) produced by STEC are responsible for the systemic complications of HUS. Shiga toxins bind to host cells which express the neutral glycolipid receptors bearing a terminal globotriaosylceramide (Gb3) moiety. HUS presents as a multi-organ system disease characterized by damage of endothelial cells via the inhibition of protein synthesis, cell activation to produce inflammatory mediators and amplification of the pro-thrombogenic state leading to tissue ischaemia and organ dysfunction[3].

Question 7: Is age a strong predisposing factor for developing HUS?

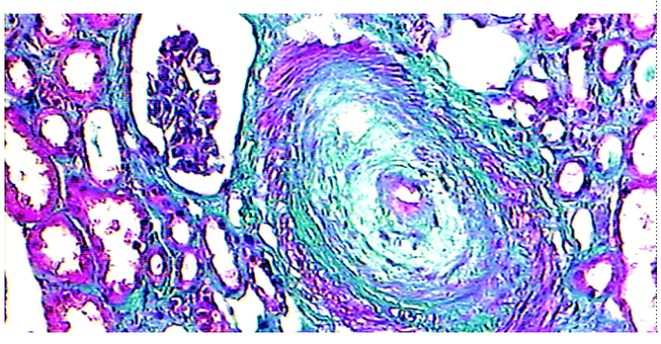
YES Young children, especially those aged 6 months to 4 years are most vulnerable to Stx-HUS because they express high levels of Gb3 receptors in their renal glomeruli. Older children and adults express lower levels of glomerular receptors but may become vulnerable through the up-regulation of the Stx receptors expression by the combined effects of lipopolysaccharides and cytokines[4].

4 Further Investigations:

Other lab tests done: FBC, E/U, CRP, clotting screen, complement factors screen, stool MCS, *E. coli* O157:H7 serology and urine sample for protein/creatinine ratio.

Outcome 3

On day 3 of admission, RG had a deranged FBC with leukocytosis, anaemia (Hb of 8.4g/dL), elevated urea (21.3mmol/L) and creatinine (431µmol/L), with CRP elevated at 107mg/L. The blood film showed micro-angiopathic haemolytic anaemia (Figure 1) and elevated reticulocyte count with the presence of schistocytes (fragmented, deformed, irregular or helmet-shaped red cells) and evidence of thrombocytopenia. Her amylase and lipase levels gradually increased to peak values of 450 and 4980U/L respectively. She had a normal clotting profile and complement factors. Her highest blood pressure was 140/90mmHg and she had antibodies against *E. coli* O157:H7 detected in her serum.



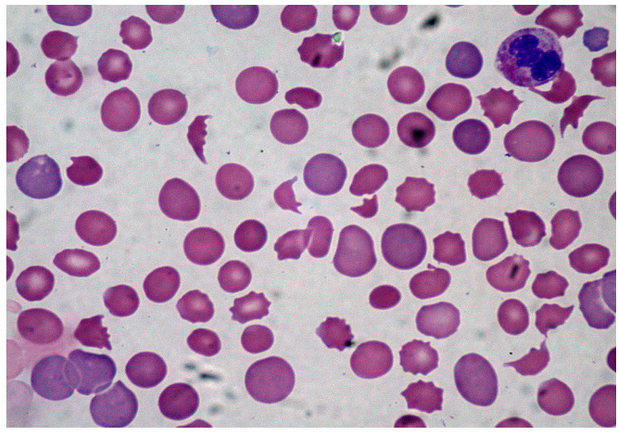


Figure 1: The typical blood picture of micro-angiopathic anaemia.

5 Further Management

RG was managed conservatively with total parenteral nutrition and nil by mouth, normal saline boluses to restore her intravascular fluid volume followed by restricted fluid regimen based on urine output. She was commenced on peritoneal dialysis for persistent anuria and deranged electrolytes. She required platelet transfusion before the insertion of a peritoneal dialysis catheter. She made a gradual recovery of her renal functions and urine output improved after 14 days.

She was gradually weaned to fluids and then solid food and was also treated with oral lansoprazole and ranitidine. She was discharged on day 15 to the referring hospital for convalescence with adequate urine output, stable levels of amylase and lipase, stable FBC (Hb 10.1g/dL, normal white cell count and platelets), high but falling levels of serum urea and creatinine.

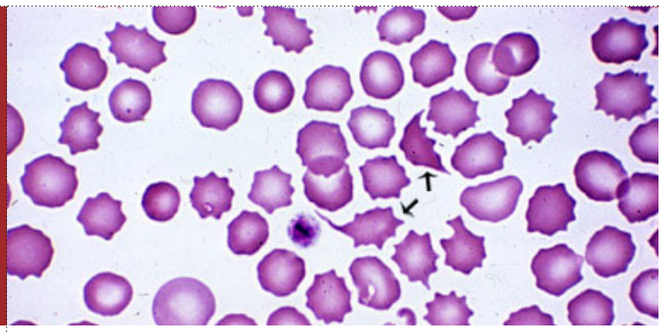
Question 8: Is there any role for antibiotics and anti-motility drugs in the management of acute phase of HUS?

NO Antimicrobials may have a potentially harmful role and may increase the risk of HUS in children with *E. coli* O157:H7 infection with high mortality and/or longer duration of diarrhoea, possibly by inducing intestinal production of Stx during the diarrhoeal phase of the illness[5]. However, a few studies have supported the hypothesis that some antibiotics, especially fosfomycin, may prevent the development of HUS[6]. Supportive care without the use of antibiotics is currently considered to be optimal treatment for all STEC infections unless HUS is associated with an entero-invasive species of *Shigella*[7].

CASE-BASED DISCUSSION - HAEMOLYTIC URAEMIC SYNDROME (HUS) IN CHILDREN

Michael O Ogundele and Hani F Ayyash

Case-based Discussion - Hemolytic uremic syndrome (HUS) in children.
Patient Management.



6 Complications

RG developed severe abdominal pains requiring moderate doses of intravenous morphine to control. She also had persistent vomiting and bilious nasogastric aspirate for one week, associated with rising levels of amylase and lipase. Her abdominal ultrasound scan was unremarkable.

7 Follow-up Care

RG was subsequently reviewed by her local paediatrician with repeat blood tests and measurement of her glomerular filtration rate (GFR) on alternate days in the first week, once weekly for 2 weeks and subsequently every four weeks until stablised. She was followed-up by the paediatric nephrologists for annual checks. At one year check, her blood pressure, serum electrolytes, urea, amylase, lipase and GFR were normal. Her urine dipstick showed a trace of protein only. At subsequent visit 6 months later her urine dipstick was completely normal.

Question 9: What is the role of close monitoring for sequelae and complications and long term follow-up in the management of STEC infection?

HUS has a case fatality rate of between 2% and 7% and a rate of long-term sequelae (such as renal impairment), neurological injury (such as seizures and encephalopathy) or hypertension in 12% to 30% of the cases[8]. Other complications of HUS in the acute phase can include intussusception, leukocytosis, hypertension and acute pancreatitis leading to transient hyperglycaemia.

8 Discussion

HUS is characterized by the triad of thrombocytopenia, micro-angiopathic haemolytic anaemia and acute renal failure. Children below the age of 5 years are the most susceptible hosts for the STEC-associated (D+) HUS and the main route of spread is by faecal–oral transmission. Other infective agents, such as pneumococci and HIV, complement genetic abnormalities, medications, transplantation, malignancy or autoimmune diseases are responsible for 10% of cases, referred to as atypical or D- HUS.

HUS is the most frequent intrinsic cause of acute renal failure in children, and a common cause of renal transplant. The main reservoir for STEC is cattle and other ruminants and many outbreaks have been associated with beef products and unpasteurised milk. Other food products that have been implicated include cheese, yoghurt, fermented sausage, apple juice and lettuce, contaminated water as well as direct or indirect contact with animals[9].

Atypical HUS can be either sporadic or familial. Up to 50% of cases of genetic HUS involve abnormalities of the complement regulatory genes including factor H (CFH), membrane cofactor protein (MCP; CD46) and factor I (IF)[10].

The clinical course and long-term progression for cases of classic D+ HUS is difficult to predict and its mainstay of management is supportive care. Recent research efforts are concentrated around development of oral and parenteral neutralising agents for shigatoxins and specific vaccines.

9 Self Assessment: Best of Five Questions

1. What is the mainstay of management of children with HUS?

a) Use of antibiotics in HUS not associated with an entero-invasive species of *Shigella*.
b) Appropriate fluid and electrolyte management may counteract the effect of thrombotic process and attenuate renal injury and dialysis for anuria greater than 24-48 hrs.
c) Platelet transfusion to maintain normal blood levels.
d) Blood transfused to raise haemoglobin up to normal.
e) Anti-motility agents, narcotics and non-steroidal anti-inflammatory drugs during the acute phase.

2. The following are potential complications of the acute phase of HUS except

a) Intussusception
b) Renal failure and hypertension
c) Encephalopathy and seizures
d) Pancreatitis
e) Non-autoimmune insulin-dependent diabetes mellitus.

CASE-BASED DISCUSSION - HAEMOLYTIC URAEMIC SYNDROME (HUS) IN CHILDREN

Michael O Ogundele and Hani F Ayyash

10 Answers

1. b) The mainstay of management for patients with HUS is appropriate fluid and electrolyte management, anti-hypertensive therapy if necessary. Parenteral volume expansion as soon as a patient is suspected to be infected with STEC 0157:H7 may counteract the effect of thrombotic process before development of HUS and attenuate renal injury[11].

Patients with anaemia need to be transfused to raise haemoglobin up to 70g/L (not to normal). Platelet transfusions may also be required for active bleeding or surgery, as well as dialysis for anuria greater than 24–48 hrs. Ongoing psychological and social support for the parents and relatives of patients with HUS is helpful during and after the disease acute phase, to help cope with the traumatic and disruptive events of the diseases[12].

2. e) Complications in the acute phase of HUS can include intussusception, acute renal failure, hypertension, encephalopathy, pancreatitis and seizures. Between 2.5–10% will either die during the acute illness or have permanent renal failure[13]. HUS may be complicated by transient hyperglycaemia in the acute phase and permanent insulin-dependent diabetes mellitus may present as a long term complication.

Patients with atypical HUS are more likely to develop complications with recurrent disease episodes, severe hypertension, chronic and end-stage renal failure with an alarmingly high risk of graft loss from disease recurrence or thrombosis.

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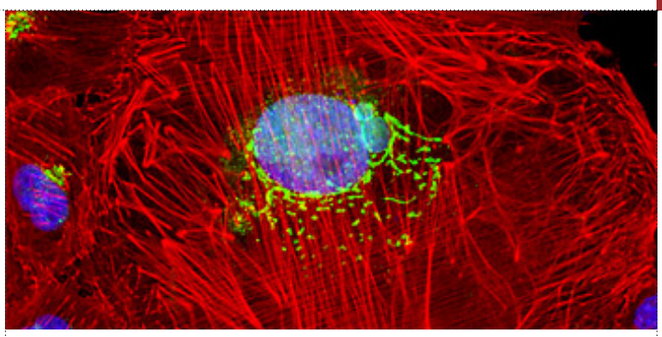

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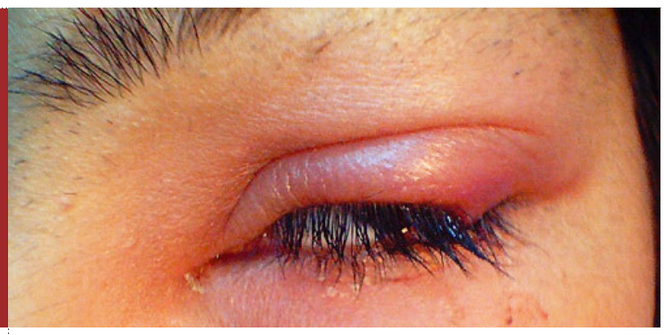
PICTURE QUIZ: A YOUNGSTER WITH A SWOLLEN EYE

Ian C Bickle



Picture Quiz: A youngster with a Swollen Eye. Patient Management.

This 6-year-old boy presented 24 hours earlier to A&E department complaining of a swelling of the right eye. He was assessed by a Casualty officer and given oral antibiotics for presumed peri-orbital cellulitis. His parents returned to A&E the following day as the swelling had progressed and he was unable to open his right eye. On examination there was no evidence of discharge or trauma. The boy's mum indicated that he had only a minimally ''runny'' nose. He had a mild pyrexia.

Following assessment by an ophthalmologist, a CT examination of the orbits and paranasal sinuses was requested. Selected images are shown.

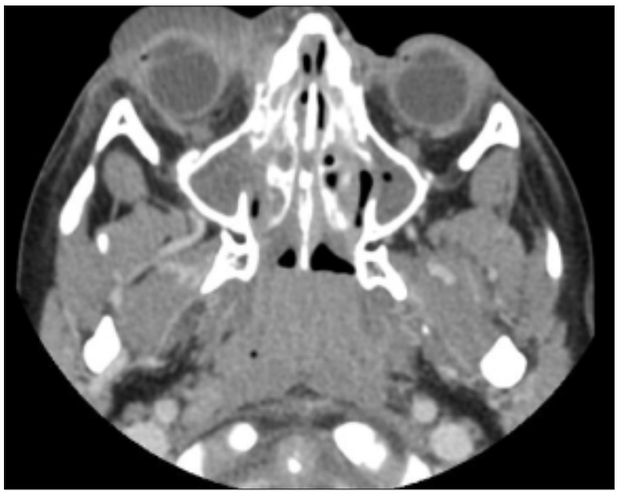


Figure 1: Axial CT of Orbits (post contrast) showing right pre-septal soft tissue swelling.

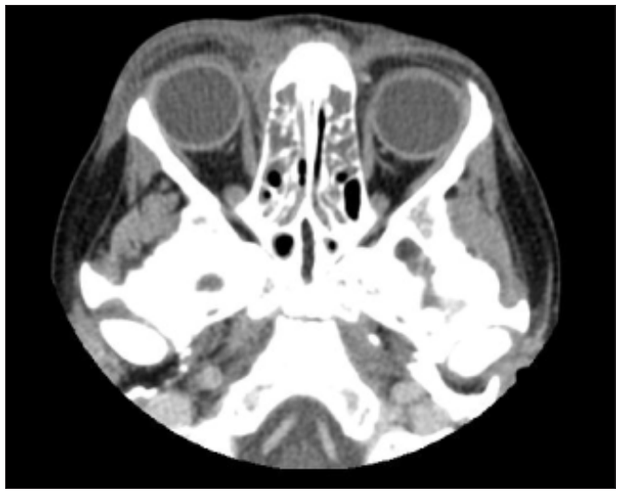


Figure 2: Axial CT of Orbits (post contrast) showing a small right sub-periosteal collection.

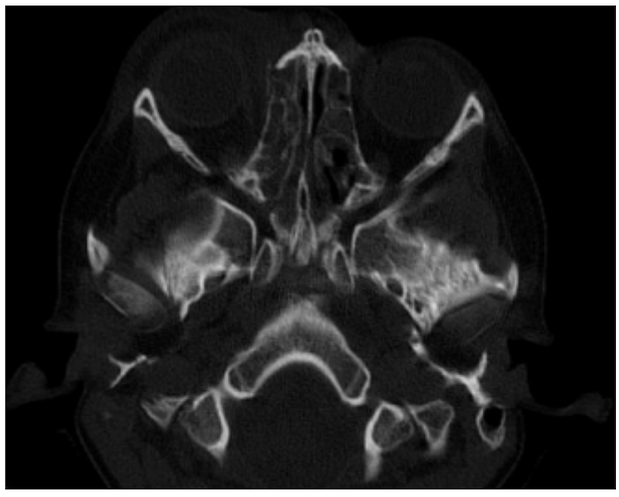


Figure 3: Axial CT of the Paranasal Sinuses (bone windows) showing the disruption of the right lamina papyracea.

PICTURE QUIZ: A YOUNGSTER WITH A SWOLLEN EYE

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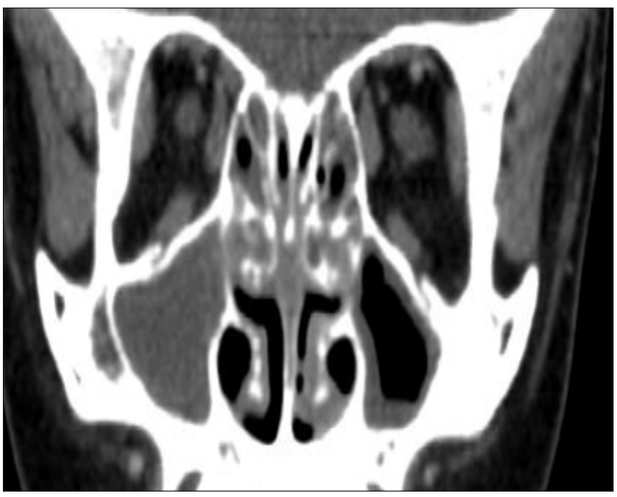

Figure 4: Coronal reformatted image CT of the Paranasal Sinuses (post contrast) showing extensive ethmoid and maxillary sinusitis.

Questions

1. **Why is orbital cellulitis an ophthalmic emergency?**
2. **What is the most common underlying cause of orbital cellulitis?**
3. **Why is the brain imaged with CT?**

Background

Orbital cellulitis with the development of a subperiosteal collection is a true paediatric surgical emergency. Prompt treatment prevents blindness and complications, such as intracranial extension.

Orbital cellulitis in children is common and is typically caused by bacteria. The vast majority of cases are associated with acute sinusitis, although there are other less common causes, such as trauma or pharyngeal infections. Ethmoidal sinusitis is the most common source of orbital infection, due to its anatomical proximity to the orbit. The medial wall of the orbit is formed by the lamina papyracea, which is thin and perforated by nerves and blood vessels.

Orbital cellulitis may be classified depending on severity (Figure 5).

Stage	Description
I	Pre septal cellulitis: inflammatory oedema of the eyelids
II	True orbital cellulitis: diffuse oedema of the orbital contents
III	Subperiosteal abscess: collection of the pus between the periorbital and the bony wall of the orbit
IV	Orbital abscess: abscess collection within the orbital tissues
V	Cavernous sinus thrombosis

Figure 5: Classification of Orbital Cellulitis.

Pathophysiology

Orbital cellulitis most commonly occurs due to:

1. Extension of infection from periorbital structures, most commonly from the paranasal sinuses.

2. Direct inoculation from trauma or surgery.

3. Haematogenous spread.

The medial wall of the orbit is formed by lamina papyracea, which is thin and perforated by nerves and blood vessels. This facilitates the communication of the organisms from the ethmoidal air cells into the subperiosteal space. For this reason the medial orbit is the most common site for an orbital abscess.

In orbital infections, the most common bacteria isolated are; *Haemophilus influenzae, S aureus, Streptococcus pyogenes, Staphylococcus epidermidis, Streptococcus pneumoniae* and group *A Streptococcus.* Venous drainage from the middle third of the face is through the orbital veins. Absence of valves in these veins facilitates the antegrade and retrograde spread of infections.

Presentation

Presenting complaints include fever, headache, malaise, pain on eye movement, or as is most commonly the case, swelling and redness of the eyelids with or without purulent discharge.

The above symptoms may be accompanied by one or more of the following signs on examination: dark red discoloration of the eyelids, chemosis, hyperaemia of the conjunctiva, proptosis, ophthalmoplegia, conjunctival chemosis or elevated intraocular pressure. Vision may be normal initially, but it may become difficult to evaluate in very ill children with marked oedema. Urgent surgical treatment is required to prevent blindness from the effects of raised intra-ocular pressure.

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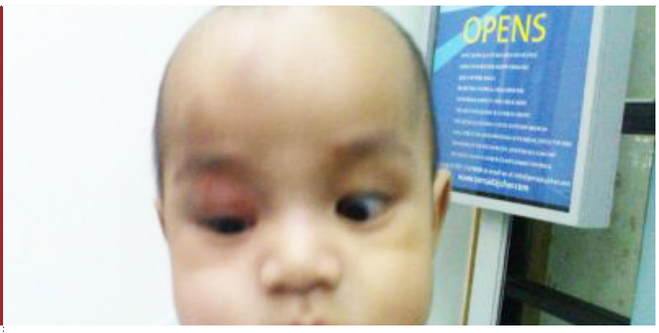

Picture Quiz: A youngster with a Swollen Eye. Patient Management.

Investigations

Urgent computed tomography (CT) of the orbits is indicated. The scanning range is typically extended to include the paranasal sinuses and the brain. The orbits are imaged both with and without contrast. The brain is imaged post contrast. This allows for the detection of complications, such as superior orbital vein and cavernous sinus thrombosis.

In the acute stage of orbital cellulitis, a CT scan may merely show peri-orbital oedema (Figure 1), but most importantly a subperiosteal abscess (Figure 2). The most common site of a subperiosteal abscess is adjacent to the lamina papyracea of the ethmoid sinuses, with the pus lifting up the periosteum (Figure 3), typically in an elliptical fashion. The collection lies in the extra-conal space. The paranasal sinuses frequently contain sinus disease (Figure 4).

Accurate CT staging, using thin slice thicknesses (1mm or less), is needed for appropriate treatment. Stage I and II are treated conservatively, surgery is preferred in stages III and IV.

Management

Management depends on various following factors:

1. The age of the patient.

2. The size of the sub-periosteal abscess.

3. Visual acuity.

4. Response to antibiotics.

Orbital cellulitis is usually treated conservatively initially. Intravenous (IV) antibiotics, decongestants and saline irrigation form the mainstay of the conservative treatment. If the clinical condition doesn't improve within the first 24 to 48 hours, patients are usually rescanned. Further management depends on the CT findings and the clinical situation. Usually patients with a radiographic abscess less than 10mm are treated conservatively, while surgical intervention is indicated in those with abscess greater than 10mm. Indications for prompt surgery are a large abscess, the deterioration of vision, worsening clinical picture or failure to improve, i.e. persistent fever, swelling or worsening ophthalmological findings, even after 24 to 48 hours of appropriate conservative treatment.

Surgical options include endoscopic, open or combined approaches based on the CT findings and the location of the abscess. There are no significant differences in outcome between surgical approaches. With a medial or medial-inferior sub-periosteal abscess, a trans-nasal approach is used, but with a superior orbital abscess an external incision is required.

Complications

Complications of the orbital cellulitis include:

1. Permanent loss of vision.

2. Intracranial complications like meningitis, intracranial abscess, cavernous sinus thrombosis.

3. Orbital pseudotumour.

Prognosis

Close monitoring of the patient with regular re-evaluation of the vision is advised. Once the patient is afebrile for 48hrs the IV antibiotics can be changed to oral administration. Patients need to be followed up in the out-patient environment, at least until it's safe to stop the medications. It may take up to 6 weeks for complete resolution.

PICTURE QUIZ: A YOUNGSTER WITH A SWOLLEN EYE

Ian C Bickle

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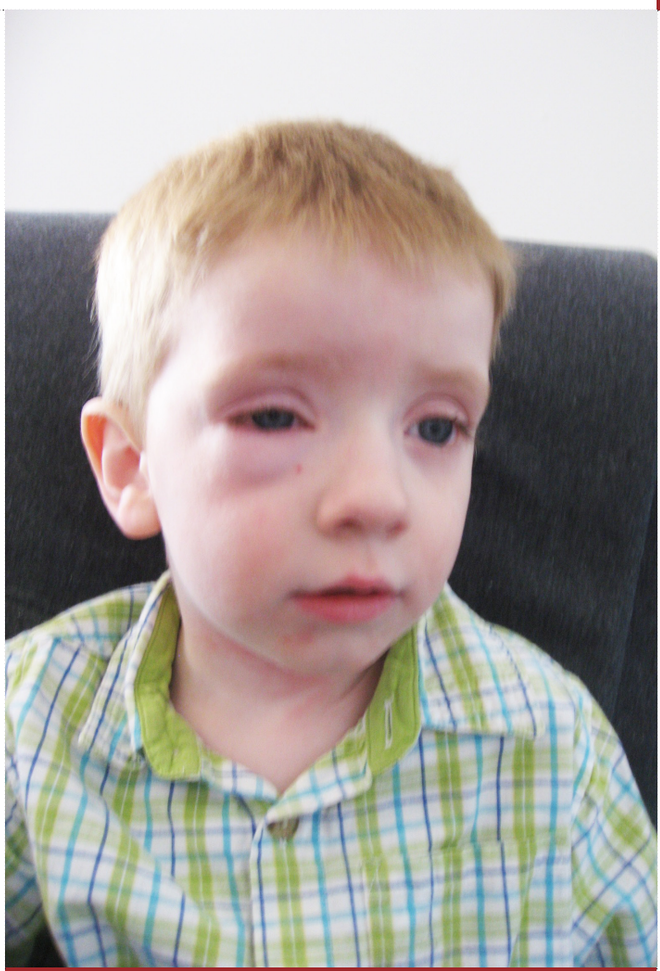
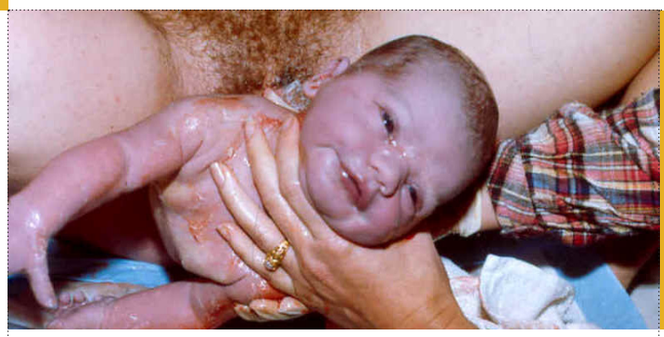


Picture Quiz: A youngster with a Swollen Eye.
Patient Management.

AN AUDIT OF TEMPERATURE CONTROL AT BIRTH IN PRETERM INFANTS

Mansoor Ahmed, Azhar Manzoor and Sobithadevi DN



An audit of temperature control at birth in preterm infants. Good Clinical Care.

Abstract

The newborn infant exhibits immature thermoregulation, when compared with older children or adults and therefore needs to be protected from extremes of temperatures. Neonatal hypothermia continues to be a significant concern, especially among extremely preterm infants. Hypothermia soon after birth may lead to potential complications.

Our initial audit looked at admission temperature of preterm newborns in the neonatal unit. Based on our audit results and best available evidence, we changed our guidelines on temperature control and delivery room care of preterm newborns, which included the use of plastic bags in preterm infants (born at < 32 weeks gestation and/or presumed birth weight of < 1.8kg) immediately after birth.

Results of re-audit demonstrated that the occurrence of hypothermia in preterm infants immediately after birth was significantly reduced by use of occlusive covering (e.g. plastic bag) which is a simple, non-invasive and inexpensive intervention.

Introduction

Temperature control is an important aspect of newborn resuscitation as hypothermia is a well recognized factor influencing newborn health[1,2,3]. Preterm infants are at higher risk of hypothermia at birth as they have an impaired ability to prevent heat loss[4] and decreased heat production capability[5]. Among other factors, excessive evaporative heat loss and the relatively cool ambient temperature may be important contributors. Potential causes of hypothermia in the newborn are summarized in Table 1.

Type of heat loss	Potential causes	Possible interventions
Evaporation	Wet skin or blankets; low humidity in ambient and/or inspired air	Rapid drying, plastic wrap or bag, increased humidity of ambient and inspired air
Radiation	Large areas of skin exposed to cooler surroundings	Covering skin, warming surrounding structures
Conduction	Contact with cooler bed materials	Pre-warming resuscitation surface and blankets
Convection	Flow of cooler air across baby's skin or mucous membranes	Increased temperature of delivery and resuscitation room, reduction of drafts due to inappropriately placed air vents, covering baby's skin with blanket or plastic wrap, transfer to pre-warmed incubator as soon as feasible, warm inspired air

Table 1: Potential causes of hypothermia in the newborn.

The risk of cold stress is greatest at birth during the transition from the warm, wet, well-insulated intrauterine environment to the cool, drafty delivery room. In preterm babies, hypothermia can develop soon after birth due to problems in delivery room resuscitation efforts, during transport of the preterm infant to the neonatal intensive care unit and during certain neonatal intensive care unit admitting procedures, such as weighing the baby.

Hypothermia in preterm infants can lead to adverse consequences including hypoxia, hypoglycaemia, metabolic acidosis and coagulation defects. Cold stress is thought to contribute to increased rates of morbidity and mortality in low birth weight infants[6]. Similarly, EPICure study showed that low admission temperature was an independent risk factor for neonatal death after adjustment for other known risks[7].

Initial audit: Historically, at Queen's Hospital Burton Upon Trent, we were using radiant warmer and fleece to maintain the temperature of premature babies during/after resuscitation of preterm newborns. A retrospective audit review of admission temperature of preterm newborns was carried out between 2003 and 2004. Table 2 illustrates the admission temperature. In 12/31 (39%) of preterm infants admitted to our neonatal unit (NNU), admission temperature was < 35.5°C. In view of the increased risk of morbidity and mortality in this vulnerable group of infants, the audit results led to a change in our practice at that time.

Gestational Age (Weeks)	Number of admissions to NNU	Admission Temp 35-35.5°C	Admission Temp < 35°C
23+0 to 23+6	1	0	0
24+0 to 24+6	3	0	2
25+0 to 25+6	2	1	0
26+0 to 26+6	5	1	0
27+0 to 27+6	7	3	1
28+0 to 28+6	13	2	2
TOTAL	31	7	5

Table 2: Initial audit admission temperature to NNU (2003-2004).

AN AUDIT OF TEMPERATURE CONTROL AT BIRTH IN PRETERM INFANTS

Mansoor Ahmed, Azhar Manzoor and Sobithadevi DN

First, we looked at the published evidence on the efficacy of plastic bags in preterm deliveries at birth. Vohra et al. conducted a randomised study on polyethylene wraps and found a statistically significant difference in maintaining temperature in babies of less than 28 weeks of gestation[8]. Leon et al. confirmed the usefulness of plastic bags in maintaining temperature of preterm infants of less than 29 weeks gestation[9]. To reduce the risk of hypothermia, both the Neonatal Resuscitation Program[10] as well as newborn life support guidelines from the resuscitation council United Kingdom (UK) have made the provision of warmth the first step in resuscitation of the newborn.

Our existing guidelines which were implemented soon after the initial audit are as follows.

All babies of less than 32 weeks and/or presumed birth weight of less than 1800 grams are placed directly into the plastic bags in the delivery room immediately after birth (without drying). The baby is covered up to the neck with a plastic bag and the head is covered by a hat as shown in Figure 1. The baby is weighed while it is still in the plastic bag. If resuscitation is required in the delivery room, it is conducted while the baby is still covered in the bag. The baby is transferred to the NNU and when the admission temperature is at or above 36.5^{0}C, the plastic bag is removed.

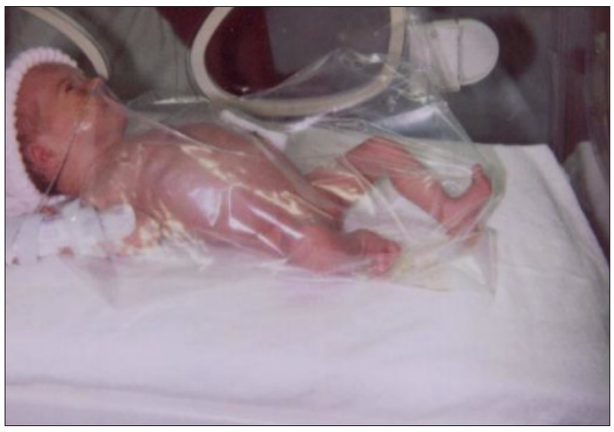


Figure 1 Use of plastic bag at birth.

Re-audit: We conducted a prospective audit to look at the effectiveness of plastic bags in maintaining the temperature of preterm infants on admission to the NNU. Sixteen babies were included over a 12 month period (2004–2005). On admission to the NNU, the initial temperature of these babies was compared with retrospectively collected data of 16 historical controls which were matched for gestational age and birth weight (babies born before this intervention). The average temperature in the study group was 37.1^{0}C and in the control group was 36.1^{0}C (Figure 2). The overall temperature difference between the two groups was statistically significant with a P value of less than 0.001 using the Mann-Whitney (Wilcoxon) test. Temperature > 37.5^{0}C was seen in only one patient in the intervention group and was not associated with any recognized adverse effects (Table 3).

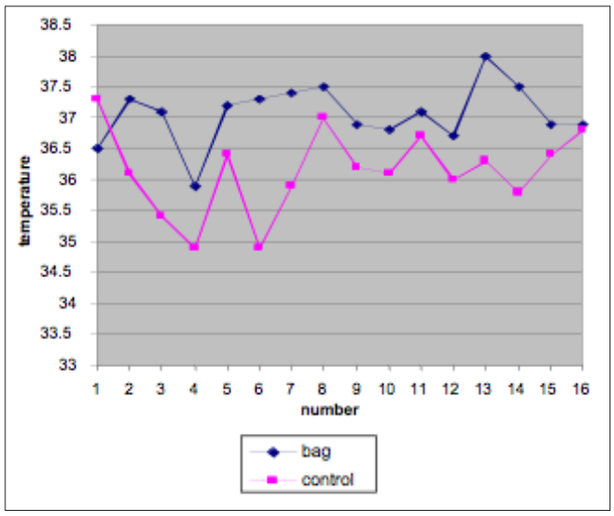


Figure 2: Re-audit (2004-200%)[5] admission temperature to NNU (cases and controls).

Discussion

Our re-audit confirmed that the occurrence of NNU admission hypothermia in preterm infants could be reduced by placing them in plastic bags immediately after birth. The significance of evaporative water losses in newborn infants has been recognized for decades, and preterm infants are known to have increased insensible water loss. Evaporative heat loss is greatest within the first few minutes after birth[12]. Hammarlund has shown that evaporative water loss is inversely related to gestational age[13].

Reduction of evaporative heat loss is probably the primary mechanism of action of the occlusive covering. It is, however, possible that there is also an effect on convective heat loss. Convection is affected by the amount of skin surface exposed to ambient air. Heat loss by convection is significantly reduced by covering the infant in a plastic bag. It is postulated that the thin layer of non-evaporated fluid on the infant's skin, after being entrapped by the occlusive barrier and warmed by the infant via conduction, may provide insulation analogous to that of a diver's wet suit[6].

Results of re-audit have demonstrated that the occurrence of hypothermia in preterm infants immediately after birth was significantly reduced by the use of an occlusive covering (e.g. plastic bag) which is a simple, non-invasive and inexpensive intervention. All vulnerable preterm infants should also be placed in occlusive covering to minimize the risk of hypothermia.

Competing Interests: None to declare

AN AUDIT OF TEMPERATURE CONTROL AT BIRTH IN PRETERM INFANTS

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An audit of temperature control at birth in preterm infants. Good Clinical Care.

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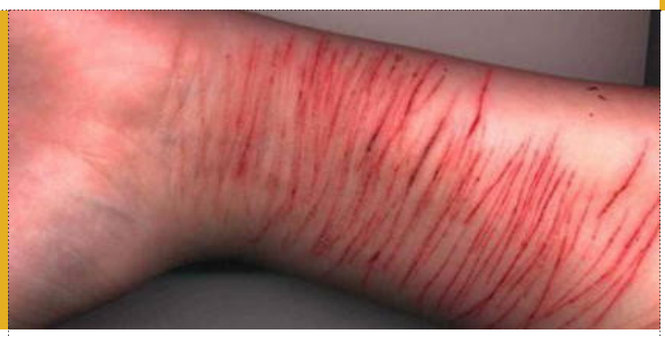
A CHALLENGING CASE OF DELIBERATE SELF HARM/SELF INJURY IN THE YOUNG ADOLESCENT

Richard Dickson-Lowe and Kamalakannan Veeramuthu

A challenging case of Deliberate Self Harm/Self Injury in the young adolescent. Good Clinical Care.



Abstract

This article gives a brief history of a deliberate self harm/self injury case in 2 young girls followed by a discussion about the management of the patients. Within the discussion a number of important factors will be briefly discussed including Gillick competence, capacity, confidentiality, child protection and the Acts that encompass all these issues (i.e. Mental Health Act, Mental Capacity Act and the Children Act). The reader is advised to refer to Trust and Local or National policies for further information.

Case History

Two girls, aged 16 and 14, had been brought into the Paediatric Emergency Department (ED) from a care home, after an episode of deliberate self harm (DSH)/self injury (SI). Both girls were "accommodated children" under Section 20 of the Children Act 1989. The term "accommodated child" refers to a child who is suffering or likely to suffer significant harm and alternative accommodation has been made for the child's safety.

The 14 year old had been in this care home for 3 months, with no previous history of DSH or parasuicide. The 16 year old girl had been at this particular care home for 2 years and had an extensive history of recurrent DSH and two parasuicide events. They both presented having consumed ten caffeine (ProPlus®) tablets, ten citalopram tablets (strength unknown), and an unknown quantity of smashed glass.

Hospital policy states that anyone over the age of 16 is seen in the adult ED department and anyone under the age of 16 is seen in the Paediatric ED department, however the girls made it very clear they didn't wish to part company. Given the circumstances and NICE guidelines which encourage departments to consider a patient's emotional distress in this situation, they were allowed to remain together in one cubicle in the Paediatric ED. Even though I was informed they did not wish to talk, on gentle persuasion from carer, nurses and myself, they told me exactly what they had taken, at what time (2 hours previously) and that they had taken it all at once. They stated that their intention was not to kill themselves but to take away their troubles. They did not have any systemic symptoms.

They refused any abdominal examination and any other form of investigation and claimed that they wished to go back to their care home. In conflict with this was the fact that on entry to the ED they had routine observations of blood pressure, pulse, respiratory rate, oxygen saturations and temperature, which in both girls were all within the normal ranges.

Discussion

Firstly it is important to realize that from the history and mental state examination (MSE) of an adolescent presenting with DSH, special attention should be given to the following:

- Confidentiality
- Young persons consent (Gillick competence)
- Parental consent
- Child protection
- Use of the Mental Health Act and Children's Act[1].

What would be the ideal plan from this point?

Take a few minutes to think about it and then read on.

TOXBASE, an online site which gives advice and specific overdoses of medications, was initially consulted. With the fact the girls were asymptomatic and they were refusing investigation, TOXBASE stating that the amounts of tablets ingested were not going to cause morbidity or mortality, was reassuring.

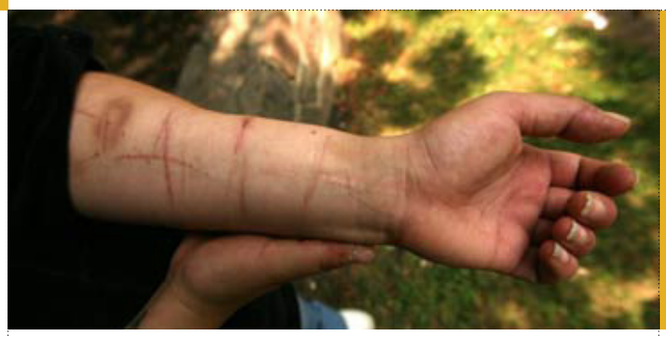
In the first instance, the girls had been assured that everything that was undertaken and talked about in hospital would be confidential.

What is Confidentiality?

Confidentiality is central to trust between patients and doctors. Without assurances about confidentiality, patients may be reluctant to seek medical attention or to give doctors the information they need in order to provide good care. Patients usually understand that information about them has to be shared within the healthcare team to provide their care. Confidentiality is an important duty but it is not absolute. You can disclose personal information if: it is required by law; the patient consents; it is justified in the public interest[2].

A CHALLENGING CASE OF DELIBERATE SELF HARM/SELF INJURY IN THE YOUNG ADOLESCENT

Richard Dickson-Lowe and Kamalakannan Veeramuthu



A challenging case of Deliberate Self Harm/Self Injury in the young adolescent. Good Clinical Care.

The situation was normalized for the girls and it was explained what the hospital did for anyone who presented in this way. This included blood tests to check Full Blood Count (FBC), Urine and Electrolytes (U+Es), Liver Function Tests (LFTs) and Clotting (International Normalised Ratio, INR in particular) in addition to Paracetamol and Salicylate levels at 4hrs. Also, due to the ingestion of smashed glass, chest and abdominal radiographs would be needed. It was explained that help and support would be offered to them for the future, in the form of a psychiatric referral. It was described that in order to carry out these tests and treatments, medical teams assess whether a person had capacity to make an informed decision about their treatment. In a person aged 16 or younger, this is referred to as Gillick competence.

What is Gillick competence?

Gillick competency is used to help assess whether a child has the maturity to make their own decisions and to understand the implications of those decisions. However, deeming a child 'Gillick competent' only allows the child to agree to treatment but does not give them the power to refuse treatment if this is deemed in the child's best interests[3,4].

What is Capacity?

In order to have capacity one must be able:

- to understand the information relevant to the decision
- to retain that information
- to use or weigh that information

as part of the process of making the decision

- to communicate his decision

(whether by talking, using sign language or any other means)[5].

What do you think my seniors advised me to do?

Take a few minutes to think about it and then read on.

The ED Specialist Registrar (SpR) agreed and decided that it was important to get them both into separate cubicles to evoke independent thoughts. It was essential to find out who has the legal rights to provide consent for the girls in the event of refusal of treatment, so a phone call was made to the manager of the care home. Both the care home manager and the parents had the power to provide consent to act as a legal guardian, with both girls best interests in mind.

What is Child Protection?

This is a term used for government-run services in place to protect children and young people and to encourage family stability. Included within this framework are foster care, adoption services, services to support at-risk families so they can remain intact, and investigation of child abuse. Most children who come to the attention of child welfare services for issues related to child protection do so because of child abuse which encompasses sexual, emotional, physical and psychological abuse as well as neglect[6].

What is Best Interests?

In order to be acting in a person/patient's best interests the following must be taken into account:

- the person's past and present wishes and feelings (and, in particular, any relevant written statement made by him when he had capacity),
- the beliefs and values that would be likely to influence his decision if he had capacity, and
- the other factors that he would be likely to consider if he were able to do so[7].

The Paediatric Specialist Registrar was also contacted, and advised approaching the girls again to request their compliance with investigations, preferable once separated for a short period of time. The serious consequences of their refusals and the proposed management plan with which they would hold a central role should be re-visited. In addition she advised me that both girls must be observed overnight, as stated in the NICE guidelines, but that they would only take the 14 year old girl to the hospital children's ward.

NICE Guidelines state that an emergency department and its staff should provide the following in a case of DSH:

- Consider a combined physical and mental health triage scale e.g. Australian Mental Health Triage Scale.
- Urgently establish physical risk and mental state in a respectful and understanding way.
- Establish mental capacity, willingness to remain for further assessment, distress levels and the presence of mental illness.
- Provide a safe and supportive environment for the patient[8].

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How do you think that second meeting with the girls went?

Would you have done anything differently up to this point?

We had managed to separate the girls into different cubicles in Paediatric ED. The 14-year-old girl became upset and distressed when we informed her of the serious implications to her health if she did not comply. She admitted that she had not taken any glass but had taken the tablets and agreed to the investigations we had proposed early on. Investigations usually relate to the type of DSH practiced. As already discussed, for any medications/substances taken, the TOXBASE website gives very useful guidance about how to act. This told me that the ProPlus® caffeine tablets normally come as in 50mg strengths, and are fatal at 5–10g. It suggested that peak plasma concentrations were between 5–90 minutes after ingestion and mean plasma elimination half-life was 4.9 hours in adults and 103 hours in neonates. These girls had taken 500mg, and were asymptomatic with a normal heart rate. They had also taken citalopram, a selective serotonin reuptake inhibitor (SSRI), which comes in 10mg, 20mg and 40mg strengths. The lowest recorded fatal amount is 2.8g with peak plasma levels occurring at 2–4 hours, with a half life of 36 hours. These girls had taken a maximum of 400mg and were asymptomatic. Learning these facts gave me reassurance that we were not dealing with worrying overdoses.

As advised by TOXBASE, we took blood in order to get a Full Blood Count, Urea + Electrolytes, Liver Function Tests, Clotting, Glucose and paracetamol and salicylate levels at 4 hours. Paracetamol and salicylate levels can be measured routinely in most EDs and is done in most cases of overdose to rule out the possibility of these substances having been taken in high quantities. All bloods came back normal and paracetamol and salicylate levels were below treatment levels. For self injury involving swallowing foreign objects radiographs (for glass and metal) or ultrasound scans (for wood and plastic) are needed. Abdominal and chest radiographs were done, which confirmed that she had not swallowed any glass after all.

At this point it was important to consider how were going to manage this 14-year-old girl who now had no medical reason for being admitted but had a significant reason for psychiatric follow-up with the Child and Adolescent Mental Health Services (CAMHS). Psychiatric conditions are usually managed by CAMHS using a biopsychosocial model incorporating short-term and long-term plans. Below is a brief summary of how to deal with DSH in an adolescent in the acute setting as set out in the NICE guidelines, which was used in this 14-year-old girl:

1. Treat as medically appropriate.

2. Full assessment of mental state is needed and risk assessment to answer the question: does this patient need admission using the Mental Health Act?

3. All adolescents should usually be admitted under the paediatric team overnight for observation.

4. Follow up by psychiatric team including discussions about needs for medication and therapy[8].

Adolescents aged 12 and older can usually be interviewed in much the same way as adults[1]. However, in all adolescents it is important to obtain a collateral history from a relative if available, and also possibly from school, or social services. In the case of this 14-year-old girl, the social services history and history from the care home manager was sought.

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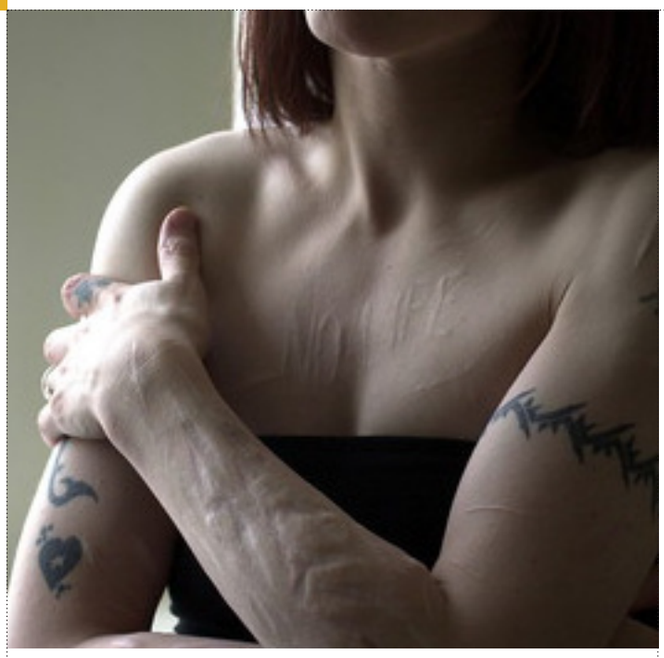

Risk assessment is very important in order to make an accurate assessment of the needs/management of a young adolescent who has self-harmed. It is important within the history and MSE to have answered these 4 questions:

1. What is the risk of suicide?

Detailed enquiry of the time leading up to current events must be carried out. Suicidal intent must be realized and the young person should be asked if they still wish to die. Careful enquiry into recent difficulties and whether they have resolved are important. With information obtained it will become apparent if there is a continuing risk of suicide. However, it must be realized that suicidal intent is not static and changes over time, thus will need to be regularly reassessed during follow-up.

2. What is the risk of further self harm?

Repetition of self harm is common, and evaluating the causes for self harm, e.g. life stresses, is important in order to be able to create a safe and definitive management plan.

3. What are the child and family's current problems and how have they led to DSH?

It is necessary to realize the current and ongoing child and family problems that have contributed to the DSH.

4. What resources do the child and family have?

It is necessary to realize the strengths within the child and family that may prevent further episodes of DSH[1].

The paediatric team observed the 14-year-old girl overnight and she was sent home the next morning with CAMHS follow-up in place for continuing assessment of risk and also her needs. The 16-year-old girl was worried about the police being involved should she leave the hospital without being fully investigated. Her blood results were also normal together with an unremarkable abdominal radiograph. She then agreed to remain with us until she had been seen by a psychiatrist and so waited in Paediatric ED until such time, and then she was discharged safely, having been risk assessed and with a comprehensive management plan in place.

Multiple Choice Questions

1. Which of the following is one of the true points required to assume a patient has capacity?

(a) a patient must be able to understand written information relevant to the decision.

(b) a patient must have had prior experience in dealing with the given situation.

(c) a patient must be able to retain that information for a period of 10 seconds.

(d) a patient must be able to use or weigh that information as part of the process of making the decision.

(e) a patient must be able to communicate his decision only by speech

2. Which one of the following is least important to you when assessing and managing a young adolescent who has presented to ED with DSH?

(a) Confidentiality.

(b) Young persons consent (Gillick competence) and parental consent.

(c) The percentage of adolescents who commit suicide within the year after a DSH attempt.

(d) Child protection.

(e) Use of the Mental Health Act and Children's Act.

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ANSWER: 1. (d).

In order to have capacity one must be able to understand the information relevant to the decision. This information does not necessarily have to be written, as stated in (a). One does not need prior experience in dealing with the given situation, as stated in (b). One must be able to retain that information, which does not have a defined time scale, as stated in (c). Then one must be able to use or weigh that information as part of the process of making the decision, which is the correct answer in (d). One then must be able to communicate that decision by talking, using sign language or any other means, contrary to the answer in (e) which states the decision must be communicated by speech.

ANSWER: 2. (c).

Answers (a), (b), (d) and (e) must be at the forefront of any health professional's mind when dealing with a young adolescent with DSH. These 4 points are stated in the NICE guidelines for managing patients with DSH in the Emergency Department. It is important that healthcare professionals with experience and knowledge in these areas are assessing these patients and deciding upon their management. Answer (c) is a useful fact but the least important of the 5 answers above.

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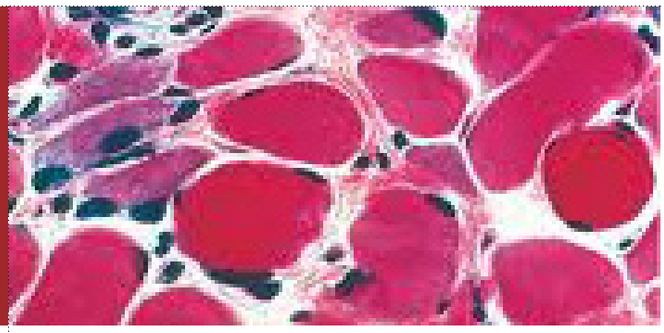
CASE-BASED DISCUSSION (MANIFESTING CARRIER FOR BECKER MUSCLE DYSTROPHY)

Michael O Ogundele, Stefan Spinty and Hani F Ayyash

Case-Based Discussion (Manifesting carrier for Becker Muscle dystrophy). Patient Management.



Abstract

This is a case summary based on an adolescent presenting at the age of 10 years with an inherited neuromuscular disease manifesting as scoliosis. The report highlights her clinical history, examination, investigations, complications and multidisciplinary management. It emphasises a holistic family-centred approach to care of chronic paediatric disabilities.

1. Case History

TF was diagnosed with moderate learning difficulties at the age of 6 years after a multi-agency assessment involving the educational psychologists, speech and language therapists and paediatricians. She was placed in a special school with a high adult to pupil ratio (6:1). During a routine annual medical review, the school doctor noticed a right-sided scoliosis and referred her to an orthopaedic surgeon.

Question1: What other details would you like to obtain?

Answer: A detailed paediatric history including pregnancy, delivery, development, past illnesses, family and social history.

(a). Pregnancy and delivery

TF was born at 40 weeks. Her mother was on treatment for epilepsy during the pregnancy. Foetal movements and liquor volume were normal. She had no significant neonatal problems though she was slow to feed and had a mild gastro-oesophageal reflux.

(b). Development history

She sat at 12 months, stood and walked at 18 months and 2 years respectively. She was clumsy eating with the cutlery and had messy handwriting. She could not tie shoe laces and was slow with buttons at the age of 10 years.

(c). Past medical history

She had recurrent ear infections and bilateral grommet insertion at 3 years. Her immunisation was complete.

(d). Family and social history

TF is the only child of her 45-year-old mother. Her father was 40 years of age and was affected by progressive limb girdle weakness from age 8 years. He was now having frequent falls and difficulty getting up from sitting.

She has a maternal aunt and two uncles with severe learning difficulties who were in residential care.

Question 2: What differential diagnosis would you consider?

Answer: The most likely diagnosis is a muscular dystrophy, the most common being X-linked Duchenne or Becker type. Other differential diagnosis to consider and exclude, include other neurological disorders such as Cerebral palsy, Hereditary sensory and motor neurone disease, Spinal cord compression syndrome and Syndromic learning disability e.g Fragile X.

2. Examination and further Investigations

A detailed examination was performed and a referral was made to the neurologist for investigations of TF and her father for possible hereditary neuromuscular disorder.

Clinical examination:

TF presented as a cheerful and cooperative girl with no dysmorphic features. Her weight and height were both on the 50th centile. Her head circumference was on 0.4th centile. Examination of the cardiovascular, respiratory and abdominal systems was normal.

Her gait was hesitant but not ataxic. Power was reduced to approximately 4/5 in the lower limbs, worse in proximal than distal muscles. Her joints were hyper-extensible with no contractures.

She could get up from lying unaided with modified Gowers manoeuvre (3 seconds) and stood on one leg. She had some wasting of her thighs. She had a large de-compensated right thoracolumbar scoliosis which was well corrected when lying prone. Upper limb and abdominal reflexes appeared normal.

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Investigations

X-ray of the spine showed a 67 degree curve between TlO and L3 with the apex on the right of T12.

Further investigations performed: plasma CK; nerve-conduction studies; EMG and muscle biopsy; western blot; DNA analysis and X chromosome inactivation studies; and brain and spine MRI scans.

Her CK was significantly elevated at 1124 to 2663. Other blood biochemistry tests were normal. MRI scan of her brain and spinal cord was normal. DNA analysis showed deletion of exons 45-48 in the dystrophin gene. Her X-inactivation studies suggested a skewed pattern.

The muscle histology showed a normal prevalence and distribution of fibre types with no evidence of fibre-type grouping.

Immunohistochemistry of her muscles showed abnormal dystrophin glycoprotein complex. Labelling for beta-dystroglycan, the N-terminus and the C-terminus of dystrophin was weak and variable. Approximately 10% of fibres labelled with neonatal myosin heavy chain-marker of regeneration or arrested development.

Immunoblotting showed reduced labelling for C-terminus dystrophin and for dystrophin rod.

Her father had CK of 252 to 443. He had a deletion of exons 45-48 of the dystrophin gene, confirming the diagnosis of Becker Muscular Dystrophy.

Question 3: What is the diagnosis and mode of inheritance?

Answer: TF had X-linked dystrophin deficiency of Becker type, consistent with manifesting carrier status.

Her microcephaly and significant learning disabilities remained unexplained after extensive investigations.

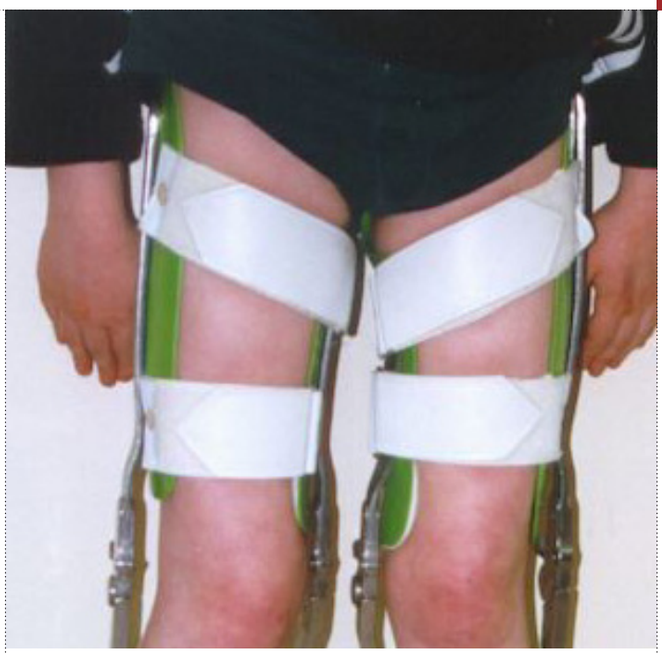
Question 4: Who will you refer the family to next?

Answer: Refer to the Geneticist.

Question 5: How would you manage her scoliosis?

Answer: Assessment of her suitability for spinal corrective surgery by the Orthopaedic surgeon.

She had staged combined anterior and posterior spine surgery two weeks apart for her scoliosis with spinal instrumentation and fusion. She made a good recovery from the surgery and had an excellent spinal correction with hardly any residual curve.



3. Further management

Regular multidisciplinary management and follow-up.

- TF was referred to the ophthalmologist and cardiologist who reviewed her annually. She had bilateral slight ptosis and a slightly hypermetric saccades in horizontal plane. She had infantile esotropia associated with nystagmus and previous squint surgeries at ages of six months and three years respectively.
- Referred to the social services for DLA support and home adaptations.
- Referred to the paediatric dentist for crowded teeth and poor oral hygiene.
- She was regularly reviewed by the physiotherapists and occupational therapists.
- The family received support from the local "Muscular Dystrophy Campaign" parent group and the neuromuscular care advisers.
- She had regular clinical psychological interventions.
- TF had a statemented special education needs which was reviewed annually.

Question 6: What possible complications do you anticipate and how do you manage them?

Answer: Regular monitor her general health, pain control, special vaccines, bladder and bowel function, mental health, nutrition and growth, mobility and functional ability, bone health, pulmonary function, orthosis and ophthalmology.

Social circumstances and welfare was also monitored by regular enquiries about housing adaptations, disability allowances, transport, family members and social network, respite care, education and review of end of life plan (Table 1).

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System	Complications	Management / Prevention
CVS	Congestive heart failure dilated cardiomyopathy	Regular Monitor of ECG, ECHO? Prophylactic ACE inhibitors, propranolol
Renal	Rhabdomyolysis and acute renal failure	Regular urinalysis, clinical surveillance and blood tests
Ophthalmology	Slight ptosis, Squint	Regular monitoring
Anaesthesia	Tachyphylaxis to depolarising neuromuscular blocking drugs and volatile agents including hyperkalaemic cardiac arrest[4]	Avoid these agents Use regional anaesthesia if possible
Respiratory	Recurrent chest infection Respiratory insufficiency nocturnal hypoventilation desaturation during REM sleep	Early antibiotic therapy/prophylaxis Monitor FVC and regular sleep oxygen saturation studies Cough assist devices
Spine	Kyphoscoliosis	Regular orthopaedic review and surgery
Education	Learning disabilities	Individual Education Plan
Nutrition	Malnutrition	Monitor bulbar functions, PEG/NGT feed
Neuromuscular	Contractures	Physiotherapy, Passive stretching of joints and splinting
Mental Health	Depression, anxiety disorders	psychosocial and spiritual support
Palliative care	Terminal illness	Review regularly active end of life care plan

Table 1: Possible complications of Duchenne/Becker Muscular dystrophy.

- Her pulmonary function was regularly monitored with FVC standing and lying. The family was advised to commence oral antibiotics early for a suspected chest infection and seek medical attention if there was no improvement within 48 hours.
- Her nutritional status gradually deteriorated and she suffered from episodes of dehydration from poor fluid intake, despite no problems with swallowing or chewing. Her weight and height had drifted to 2nd to 9th centile within five years. She had slightly delayed puberty development and attained menarche at the age of 15 years.
- Her vitamin D and bone profile was regularly reviewed from adolescence.
- Regularly urinalysis was done for screening renal impairment.
- TF suffered from regular sleep disturbances and unprovoked outbursts of aggressive behaviour.
- Her functional abilities deteriorated slowly over time. Her walking distance reduced from 500m in 15 minutes at diagnosis to 100m over five years. She was requiring progressively more time of rest after walking a short distance. She used both rails going up the stairs.
- TF was offered 2 respite nights every 4 weeks at a local centre.
- She had a phased transitional to adult neurology and cardiology services arranged.

4. Discussion:

Alterations in dystrophin gene carried on the X chromosome can cause 2 different types of muscular dystrophy affecting boys but can be passed on by girls who are carriers: Duchenne and Becker muscular dystrophy. Duchenne is a more severe condition. Some female carriers may have symptoms from Duchenne muscular dystrophy but it is rarer for carriers having symptoms from Becker dystrophy.

Dystrophin is a 427 kDa protein, which forms part of the cytoskeleton of the muscle cell plasma membrane (Figure 1). It consists of an N-terminal domain and a central rod domain - which binds actin with the greatest affinity, a cysteine rich domain, and a C-terminal globular domain, which binds to the trans-membrane dystroglycan complex. Patients with genetic mutations in these regions have more severe phenotypes. The clinical phenotype depends on the amount of functional dystrophin[2]. The clinical phenotype of dystrophinopathy is very wide and includes asymptomatic cases with elevated creatine kinase (CK) only, cramps and myalgia and cases with dilated cardiomyopathy with no skeletal muscle involvement.

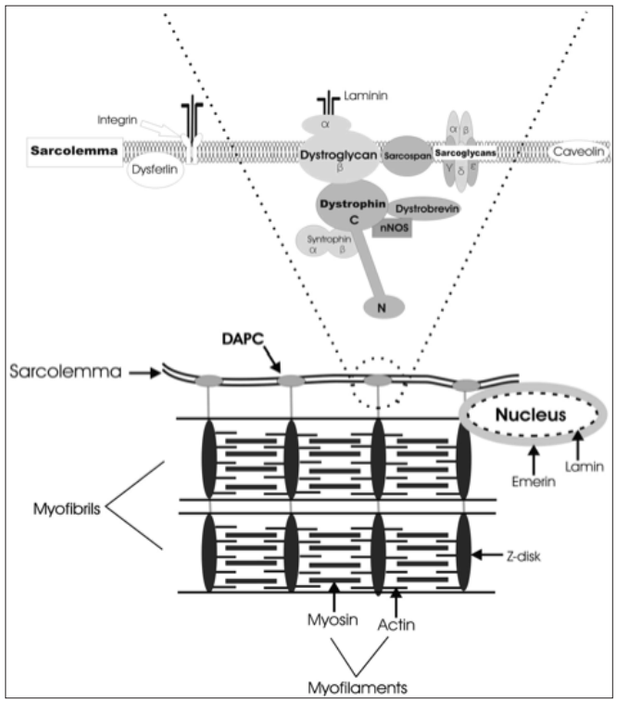

Figure 1: Schematic model showing the molecular linkages of the sarcolemma via the dystrophin-associated protein complex (DAPC) to the underlying contractile apparatus. Cytoskeletal components that are affected in the more common muscular dystrophies are indicated. Source: RM Lovering et al. (2005) Muscular Dystrophies: From Genes to Therapies. *Physical Therapy.* 85 (12):1372–1388.

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Diagnosis is based on several methods including the quantification of dystrophin protein levels in muscle biopsies with immunohistochemistry and Western blotting. DNA analysis may demonstrate a deletion (65%), duplication (5%) or point mutations in the dystrophin gene[1].

Muscle biopsy analysis may include fibre-typing, immunohistochemistry, oxidative enzyme-staining, immunoblotting, enzyme-analysis or electron-microscopy. EMG may show a clear myopathic or denervating pattern, however the picture is often mixed.

Muscle ultrasound can demonstrate increased echogenicity of the involved muscles. MRI can identify the pattern of muscle groups involved.

The study of X-chromosome inactivation pattern is used to identify the protective effect of the normal X chromosome in modifying the symptoms of the disease. Some studies suggest that it does not predict the severity of the disease[5]. About 17% of female carriers have some demonstrable muscle weakness and some of them may have cardiac involvement without muscle weakness.

Recent prospects of genetic therapy using utrophin (an alternative dystrophin-like protein) has been hampered by various challenges about delivery systems and the suggestions that it may not prevent dilated cardiomyopathy in treated patients[4].

Most patients with Duchenne disease become immobile before the age of 13 years and usually die before 25 years mainly due to respiratory infections/insufficiency and cardiac failure. Most patients with Becker type have a milder disease and remain ambulant into their 40s or beyond.

Self Assessment: Best of Five Questions

1. The following symptoms and signs in the neonatal period or infancy may be characteristic of children with a neuromuscular disease except:

a) arthrogryposis,
b) hypotonia,
c) feeding difficulties,
d) unexplained respiratory problems,
e) toe walking.

2. Which of the following is not a goal for management of inherited neuromuscular diseases?

a) family support and education,
b) prevention and management of complications,
c) genetic therapy,
d) enhancing functional skills,
e) palliation of symptoms,

Answers

1. e)

The Duchenne and Becker muscular dystrophies are the most common paediatric muscular dystrophies and have X-linked recessive inheritance. A neuromuscular disease could be suspected in a pregnancy complicated by polyhydramnios and reduced foetal movement. Neonates or infants may present with arthrogryposis, hypotonia, early feeding difficulties, respiratory problems or a need for respiratory support in the absence of any significant pulmonary pathology. Toe-walking or global developmental delay may manifest later in childhood.

2. c)

To date, there is no specific treatment for inherited neuromuscular conditions. The prospect of genetic therapy has been very disappointing, hampered by various challenges of finding effective delivery systems and poor clinical responses.

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Case-Based Discussion (Manifesting carrier for Becker Muscle dystrophy).
Patient Management.

Other Multiple Choice Questions (True or False)

1. Pregnancy with a foetus with a neuromuscular condition may be complicated by polyhydramnios and reduced foetal movement.
2. Early neonatal period or infancy may be characterised by arthrogryposis, hypotonia, early feeding difficulties, respiratory problems or a need for respiratory support in the absence of any significant pulmonary pathology.
3. Later in childhood they may present with toe walking or global developmental delay.
4. DNA analysis in Duchenne or Becker muscular dystrophy demonstrates a deletion or duplication in the dystrophin gene.
5. Analysis of muscle biopsy may include: Haematoxylin and eosin; fibre typing; immunohistochemistry; oxidative enzyme staining; immunoblotting; enzyme analysis; mitochondrial DNA analysis; and electron-microscopy.
6. EMG may show a clear myopathic or denervating pattern, however the picture is often mixed.
7. Muscle ultrasound can be valuable in detecting myopathies and muscular dystrophies, both of which are associated with increased echogenicity of involved muscles.
8. MRI cannot identify the pattern of muscle groups involved.
9. To date, there is no specific treatment for inherited neuromuscular conditions. The aims of management are:
   i. family support and education
   ii. prevention and management of complications
   iii. enhancing function abilities and
   iv. palliation of symptoms.
10. The dystrophinopathies (Duchenne and Becker muscular dystrophies) are the least common form of muscular dystrophy seen in paediatric practice.
11. The dystrophinopathies have X-linked recessive inheritance.
12. They are characterized by the finding of dystrophic changes on muscle biopsy: variation in fibre size; fibre splitting; necrotic fibres; and excess of fatty and fibrous tissue.
13. Classification can be defined at the level of the specific protein deficiency by immunohistochemistry and immunoblotting and at DNA level by mutation analysis.
14. Around 65% of males with dystrophinopathy have a deletion mutation of one or more exons of the gene, 5% have a duplication, the remainder have point mutations.
15. Approximately two-thirds of the mutations are new mutations.
16. The clinical phenotype depends on the amount of functional dystrophin.
17. Boys with the more severe Duchenne phenotype have an absence of dystrophin, males with the milder Becker phenotype have partial dystrophin deficiency.
18. The clinical phenotype of dystrophinopathy is very wide and includes asymptomatic cases with elevated creatine kinase (CK) only, cases with cramps and myalgia, cases with dilated cardiomyopathy and no skeletal muscle involvement.
19. About 17% of female carriers have some demonstrable muscle weakness.
20. Female carriers without muscle weakness may have cardiac involvement, with approximately 8% showing evidence of dilated cardiomyopathy.

Other MCQs Answers

1. True
2. True
3. True
4. True
5. True
6. True
7. True
8. False
9. (i) True (ii) True (iii) True (iv) True
10. False
11. True
12. True
13. True
14. True
15. False
16. True
17. True
18. True
19. True
20. True

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HISTORICAL OVERVIEW OF THE DEVELOPMENT OF BIOETHICS GUIDELINES THAT GOVERN MEDICAL RESEARCH INVOLVING CHILDREN

E Karsten and EJ Estlin

Historical overview of the development of bioethics guidelines that govern medical research involving children.
Teaching & Training.

Abstract

For hundreds of years, children have been the subjects of medical research. Society can benefit greatly from performing research on children but it is crucial that children are protected as far as possible from harm when they are subjects of medical experimentation. From Jenner's 1-year-old son acting as the first person ever to receive an experimental smallpox vaccination, to the horrors of Nazi Germany and transparent coercion in a Hepatitis-affected school for disabled children and ending with the historic Ramsay vs McCormick debate, this review follows the key ethical developments that have occurred throughout history; their involvement with children, the events that led up to them and the laws that enforced them.

Introduction

All children can benefit from medical research involving children[1], as research can lead to innovations in health care that can improve their health and quality of life. Due to variations in diseases processes and physiology it is not always sufficient, scientific or ethical to carry out research with adults and apply the findings to children, although whenever it is possible, an adult is used as a research subject instead of a child. Many important ethical issues are raised when considering carrying out research studies that involve this population.

We have both a responsibility to protect children and an ethical obligation to ensure they receive the best treatment. Over time, the way children are regarded has changed. Initially children were seen as a vulnerable group that should be protected from the potential harm of research. The Declaration of Helsinki[2] then recognised the need of a sacrifice of the individual for the greater good. The historic Ramsey versus McCormick debates outlined the ethical arguments involved in research with child subjects. More recently the Council for International Organisations of Medical Sciences[3] has emphasised the importance of listening to children's views and respecting their autonomy. Laws have developed alongside these changes, and have both influenced and been affected by them. Thus, these reviews will explore the two intertwined features of law and ethics, and look at how they have progressed through time in relation to clinical trials. This first review will focus on the key developments that have underpinned contemporary thinking and guidelines for research ethics and children, and will begin with a brief discussion of those terms will arise in relation to any discussion that involves ethics.

Assent

This describes a child's affirmative agreement to participate in a study[4]. Failure to object should not be construed as assent.

Beneficence

This term requires that the well-being of research participants should be optimised by minimising the possibility of harm and maximising the possibility of benefit[5].

Child

In the UK, a person under the age of 18 is considered a child[6].

Clinical trial

Clinical trial[7] means any investigation in human subjects other than a non-interventional trial whose purpose is:

(a) To discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;
(b) To identify any adverse reactions to one or more such products;
(c) To study absorption, distribution, metabolism and excretion of one or more such products.

Competence

The ability of a person to understand the nature and consequences of the proposed procedure or treatment, and to use that information to weigh up options and ultimately make a valid choice in accordance with their own fundamental values[8].

Justice

Rawls[9] thought of society as a system of cooperation to mutually benefit all involved. Essentially, we can achieve a much higher quality of life if we work together than if we try and do everything on our own. Justice is the principle that tries to make it possible for everyone to receive a fair share of the benefits and burdens of research, as inevitably an individual would prefer to receive more rather than fewer benefits[10].

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Morality

Ideally morality would be the same for all human beings, but experience shows us that there is significant variation in the opinions of individuals when it comes to what they consider appropriate behaviour. The most obvious aim of morality is to prevent harm to others by doing what is considered "right" and therefore enable peace and unity.

The descriptive definition considers morality a code of conduct put forward by a society[11]. When it comes to describing morals, people often use the society that they are from as a reference. For instance, ''Nazi morality'' allowed research on Jews that a ''Catholic morality'' would consider unacceptable. Today we might say that the Nazis lacked morals of any kind, but an anthropologist could argue that, like law, morality can only apply with reference to a certain society. However even within a homogenous society there are differences in morals, so morality cannot be considered solely responsible for codes of conduct in society. For example, laws and etiquette generate codes of conduct in societies. Furthermore, an ethicist might say that some societies lack so many of the essential features of morality in the normative sense that they cannot be considered to have morality at all in a descriptive sense.

Respect for Persons

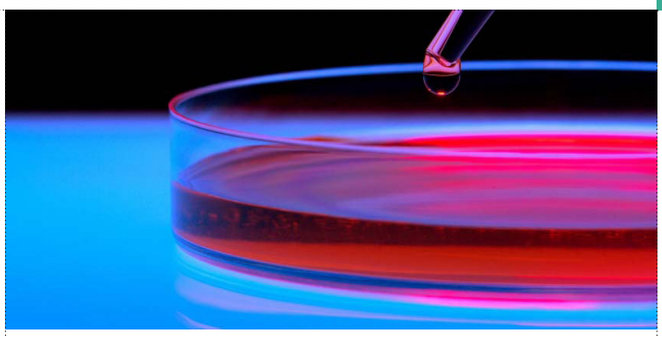
This requires that persons should have their opinions and choices respected, and that they enter research voluntarily and with adequate information[12].

Respect for Autonomy

Respect for autonomy demands for individual persons to be treated as autonomous agents that are capable of making an informed rational decision and taking moral responsibility for it. Children have diminished autonomy; this therefore entitles them to protection.

The Ramsey Versus Mccormick Debate

Having defined the ethical and legal key phrases, we now turn to factors and events that have influenced modern guidelines and practices. The National Commission for the Protection of Human Subjects[13] (NCPHS) was a landmark development in the progression of ethical research and laid the foundation of the guidelines in practice today. The committee, which contained an impressive range of eminent ethicists, clinicians and legal experts, obtained information by asking opinions from a wide range of people from federal agencies to ethicists to the general public. The only people they did not ask were children themselves.



In the 1970s a series of debates between two eminent ethicists, Paul Ramsey and Fr Richard McCormick, took place. It had a significant impact in informing the NCPHS of the ethical issues involved in using children as research subjects. Ramsey took a very careful approach, stating that: "Children, who cannot consent and thus cannot enter into covenants of loyalty, can never be used as research subjects"[14]. The only exclusion to this would be when the child was a direct beneficiary of the research. McCormick, on the other hand, presented an alternative view. Normally when a person gives proxy consent, they consider that the consent is based on what the person would wish for themselves if they could. McCormick considered that parents did have the moral authority to provide consent on behalf of their children because they would base their decision on what they as a human "ought" to do, rather than what they would do. He argued that, given the chance, an adult would choose to benefit others at little or no cost to themselves and that an infant should not forego that opportunity only because they cannot consent for themselves.

Ramsey disagreed with McCormick's idea of an obligation to consent and referenced Hans Jonas, who said that participating in research was not an obligation, but actually goes beyond the bounds of what was expected of an individual[15]. McCormick asserted that there was an obligation to help others that arose from the ethical concept of justice.

Ramsey's approach may not have been beneficial to society as a whole but it did protect children fully. McCormick accepted that if children were allowed to participate in non-therapeutic trials then they could be exposed to harm. He was quick to point out that it is acceptable to parents and society that children are exposed to risks in activities such as competitive sports because it is felt it helps their development and therefore provides a direct benefit to their growth. He argued that having a child involved in a research study may even help their moral development; this implies that they stand to gain simply by participating in research.

McCormick and Ramsey did agree that it was only morally acceptable to use a child for medical research if it was a willing participant.

After many months of debate considering the benefits and disadvantages of both sides of the argument, the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research produced the Belmont Report, which granted parents or guardians the right to give proxy consent for children to participate in non-therapeutic research. McCormick's theologian principles had defeated Ramsey's rhetoric.

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Developments Prior To The Mccormick Vs. Ramsey Debate

Hippocrates

Historically, the Hippocratic Oath shapes a doctor's moral compass to guide them through their career. In its original form 2,500 years ago it contained the key phrase "never do harm", often misquoted as "first, do not harm". According to the "Father of Medicine", the aim of being a doctor is to provide a net medical benefit to patients. This can be difficult in research, where taking a blood sample can be considered harmful and the benefits are not always reaped by the subject.

Recently, the Hippocratic Oath has come under heavy criticism, with claims that it is simply "routine" and "outdated"; there is definitely some strength in those arguments. Currently there are many variations on the original, with Lasagna's Charter on Medical Professionalism[16] probably the most likely to serve as a replacement. Changes to the original may have diluted the words of Hippocrates, but it is important not to underestimate the power of the oath. Interestingly it has become more popular in recent times: 24% of US Medical Schools took the oath in 1928 whereas closer to 100% do so today[17]. Every doctor is aware of the Hippocratic Oath to some degree and it is undeniable that it was a seminal document that shaped todays ethical conduct in medicine. The Hippocratic Oath is a basis for ethical conduct; there are more recent, although perhaps no more relevant, ethical guidelines.

In the 19th Century a French physiologist, Claude Bernard, applied Hippocrates' ideal of "never do harm" to research when he stated that one should not injure a person regardless of the benefits that might come to others[18]. This could be seen as a step backwards in ethical history, as it is reasonable to say that significant harm could be caused by using treatments that have not been researched using human subjects. Bernard opened up the longstanding ethical debate of the suffering of the individual against the benefit to society as a whole.

Edward Jenner

The first experimental vaccination occurred in 1796 when Jenner observed that exposure to cowpox seemed to reduce the risk of developing smallpox. He decided to expose his son to a small amount of fluid from a cowpox vesicle to see if it conferred immunity. He carried out his next vaccination on an 8 year old called James Phipps, the son of a labourer that sometimes worked for the Jenner family. A recent book[19] on Smallpox has dedicated a significant amount of time to the eight year old boy from the poor family. Phipps' parents would probably have been impressed by the wealthy and educated Jenner, who at the time had no requirement to ask for any kind of informed consent before he exposed their son to smallpox and observed the result. People have since pointed out that under current legislation the unproven vaccination would not have been allowed to occur, especially on a child. However Jenner did believe that his vaccine had the prospect of directly benefiting his patients, and the discovery of the vaccination remains one of the greatest medical achievements of all time.

The Reich Health Council

In 1931 the Reich Health Council of Weimar Germany created the "Rundschreiben"[20], which governed the Third Reich during the period of the Second World War. It is worth highlighting that these guidelines remained binding law throughout Nazi Germany, and existed to control experimentation on humans and try to create a morally aware health care system. Many people believe erroneously that the Nuremberg Code, which was implemented following the war, was the first example of modern ethical guidelines for research. However, not only do the "Runschreiben" predate the Nuremberg Code but, according to Hans-Martin Sass, the regulations did "seem to be stricter than those of the Nuremberg Code"[21]. The report created special guidelines for new therapies and human experimentation, although it did not specifically mention children. The guidelines recognise the link between the technical calculations of the design of the experiment and the moral calculations of the patient and physician[22]. This could definitely be considered to be a precursor to the risk to benefit ratio calculations that exist today.

Nuremberg

The Nuremberg Medical trial was an epochal step in the evolution of medical ethics[23]. It followed the unequivocal abuse of vulnerable prisoners for the benefit of research. The Nuremberg code was a landmark achievement that addressed the issues that arose from the Nuremberg trials and also incorporated the most recent developments in medical ethics across the world at the time.

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The key development of the Nuremberg code was that it became a legal requirement for informed consent to be obtained from the research subject[24]. Children are not specifically referred to in the document but we can assume that, as children are not considered capable of giving informed consent, they would have been excluded from research altogether.

Sadly, given the amount of suffering that took place ostensibly to benefit science, not a great amount of information was gained from the research carried out by the Nazis. This is partly due to the fact that Nazi Germany cut itself off from research taking place in the rest of the world and held many of their educated scientists captive or worse. This implies that conducting research without ethical guidelines produces no better results than carrying out research which takes the individual rights of the participant into account.

The Declaration of Geneva

As a direct response to the inhumane actions of certain Nazi doctors, the Declaration of Geneva[25] was written in 1948 to educate and remind doctors worldwide of their responsibilities. Described as a "contemporary companion to the 2,500 year-old Hippocratic Oath"[26], the Declaration strongly echoes that of Hippocrates with key phrases such as "the health of my patient will be my first consideration" and "I will not use my medical knowledge contrary to the laws of humanity". The declaration of Geneva does not make any specific reference to children.

The Declaration of Helsinki

In 1964, the World Medical Association met in Finland to discuss the ethical principles involved in human research. This resulted in the Declaration of Helsinki and since then the group have met regularly in various locations across the world to review and update their guidelines. Aimed at doctors but designed to be accessible to anyone performing medical research involving human subjects, the declaration highlighted the rights of the individual, stating that "concern for the interests of the subject must always prevail over the interest of science and society"[27]. Paul Ramsey held a similar point of view in America a decade later and this fairly rigid approach is meant to guarantee full protection of the subject, but at a potential cost to research.

Moreover, the Declaration of Helsinki developed the concept of therapeutic versus non-therapeutic research. The distinction between therapeutic and non-therapeutic research is now considered unhelpful and potentially misleading; it is no longer used. Essentially, therapeutic research was considered research that would directly help the subject and non-therapeutic research was not allowed to occur.

The Declaration of Helsinki is a particularly significant moment in the development of ethical guidelines for children as it was the first time that children were specifically considered. Minors were seen as a vulnerable group of the population that were incapable of informed consent. They were allowed to be involved in research only if "permission from the responsible relative replaces that of the subject". This superseded the total ban on research involving children that had existed since the creation of the Nuremberg Code. . However, this had little influence on research which was being carried out on children at the time; for instance, there were researchers in the United States already openly flouting the Nuremberg code as in the example of Willowbrook School as discussed below. Some felt it was not relevant to their situation and had even been performing research with a high potential risk to children.

Willowbrook School

Between 1963 and 1966, mentally disabled children at a state-funded school in New York were used as test subjects for research that aimed to produce a vaccine for Hepatitis A. The researchers exposed the children to the virus in order to cause Hepatitis and monitored their response to treatment with gamma globulins. Coercion clearly occurred when a special unit with better conditions was created at Willowbrook and any parent who allowed their child to participate in the studies was given expedited entry[28]. The research, which offered no prospect of therapeutic benefit to the children, sparked an intense media furore, despite doctors pointing out that outbreaks of hepatitis in the school were so frequent because of insanitary conditions that over 90% of the children contracted it within 6 months of arrival. The researchers argued that they believed infection with an attenuated form of the virus would protect children from the more severe complications of hepatitis and that after infection they would be immune to further attacks. Thus, the events at Willowbrook remain ethically disturbing to this day.

This was not the first time that researchers had used institutionalised children as convenient research subjects and it had been the focus of considerable criticism for years. For instance, Prussia had laws prohibiting non-therapeutic research on vulnerable populations from 1900[29]. In 1921 Konrad Bercovici wrote "No devotion to science, no thought of the greater good to the greater number, can for an instant, justify the experimenting on helpless infants, children pathetically abandoned by fate and entrusted to the community for their safeguarding"[30]. However despite intense criticism of the ethics of the practice, unscrupulous research involving vulnerable groups continued in United States until the 1970s.

This and other similar cases led to a need to clarify the ethics of research on children and try and find the thin line which validates scientific progress and safeguards against abuse of vulnerable patients.

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The National Commission for the Protection of Human Subjects

The NCPHS led to the abandonment of the concept of therapeutic versus non-therapeutic research in favour of risk versus benefit to the subject in 1974[31]. This is in line with current views that research without the prospect of direct benefit to individual participants is ethically justifiable in certain circumstances. Moving away from therapeutic and non-therapeutic to the more fluid concept of risk makes more research possible. The concept of risk is detailed further in the companion review of law, risk and legislation in relation to clinical trials involving children.

The National Commission did specifically refer to children and tried to reach a balance between protecting a vulnerable group of the population and not excluding them from the future benefits of research. They decided that as long as the research would benefit children as a class and did not pose an excessive risk, it could be acceptable.

The working of the National Commission has a profound influence on the working of Institutional Review Boards (IRBs) in North America (equivalent to Research Ethics Committees (REC) in the UK) and this has been a significant step in the progress of safer research involving patients. The role of the IRB/REC is to decide whether the research is ethically acceptable and to ensure that the child is as safe as possible. The Committees are required to make sure that the risks are minimised and justified by anticipated benefits and that the subjects are selected and treated fairly after adequate informed consent is obtained.

However, IRB/RECs do not always have to make an in-depth analysis of each case. It is only when the project entails a "greater than minimal risk" that they have to consider other factors, such as the child's assent to research.

Conclusions & Where Are We Today?

Until relatively recently, the welfare and well-being of children in relation to medical research has not been the focus of discussion or legislation, and there has been a paucity of studies that have determined the views of the children themselves in this field of ethics. However, currently, according to the 2004 European Union (EU) Directive[32], the protection of the clinical trial subject is safeguarded through risk assessment from pre-trial experiments, ethics committees, authorities of the Member States of the EU and rules on the protection of personal data. In the next review we will explore current ethical and legislative guidelines, discussing the role of the review boards, information and consent, assent and risk to benefit ratios and if the views of children themselves have informed these laws and guidelines.

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LAW, LEGISLATION AND ETHICS IN RELATION TO CLINICAL TRIAL RESEARCH INVOLVING CHILDREN

E Karsten and EJ Estlin

Law, legislation and ethics in relation to clinical trial research involving children.
Teaching & Training.

Abstract

Fundamental ethical principles are defined and their origins are explored: namely justice; morality; respect for persons; autonomy; and beneficence versus risk. The application of law in the UK is considered and the details of assent, consent and dissent in a child are described. The guidelines we have today have had input from a wide variety of people; from the general public to ethicists, social workers and judges. However, very little of our understanding of the ethics of children in research reflects the involvement of the children themselves.

Introduction

In the previous review, we explored the fundamental ethical principles such as justice and morality, and how these philosophies have impacted upon research ethics guidance for children since the time of Hippocrates. In this essay, we will explore further the ethical issues of assent, consent and risk/benefit as these apply to the area of clinical trial research involving children, and the application of law in the UK in relation to children and medical research is described.

Consent

Consent is defined as the voluntary agreement of a competent person, based on adequate knowledge and understanding of relevant information, to participate in research[1]. It is only legally valid and professionally acceptable where the participants (or their parental guardian) have the capacity to decide whether to take part in the research, have been properly informed, and have agreed without pressure or coercion[2]. In the case of proxy consent, the process of obtaining permission should be identical to that of obtaining informed consent[3]. The aim of consent is to protect the subject by only asking them to be involved in research that they feel comfortable with.

However, the law is fairly complex. Since May 2004, two legal systems have run in parallel, depending on whether the research involves the Clinical Trials Regulations[4]. Appendix 1 defines the differences between the types of trials. Any research not considered a clinical trial is regulated by common law.

The 2001 EU Directive recognised that anyone unable to give legal consent to a clinical trial was vulnerable and stated that they should be given "special protection". The concept of protecting vulnerable people, which is part of the ethical principle of Respect for Persons, had been described in the 1940s in the aftermath of Nazi Germany. However it was not until 2001 that a solid legal framework was developed that considered the autonomy and rights of children in research.

From an ethical point of view, protection of children would come under the basic principle known as Respect for Persons. Interestingly, despite being considered a fundamental ethical principle of modern medicine and one of the four principles detailed in Beauchamp's *Principles of Biomedical Ethics*[5], the concept was only developed in the 1940s, in the aftermath of the horrors that came out of the Nuremberg trials. Children were only given a "special protection" as research subjects in the 2001 European Directive.

The EU Directive left most of the exact rules determining how a child could be protected to the Member States. This means that there are discrepancies in the interpretation of "special protection" across the European Union. It is difficult to think how this could be avoided, because there will always be some variation in what is considered morally acceptable between different societies.

The Clinical Trials Regulations emerged in 2004 and added to the 2001 European Union Directive. The introduction of this Directive did not challenge previous ethical standards previously formed by articles such as the Declaration of Helsinki[6]. However, further regulations on consent for vulnerable people such as children were added, to protect them further, stating that "such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent". These rules are useful as they guarantee that children will not be used as research subjects if any viable alternatives are available[7]. It is significant whether or not the Clinical Trial Regulations apply, as even the definition of a minor varies. The Clinical Trial Regulations consider a child to be anyone under the age of 16, while common law in the UK states the age is 18.

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However, the law surrounding clinical guidelines is constantly evolving. In 1983 Victoria Gillick challenged her 16-year-old daughter's right to receive confidential contraceptive advice without her parental knowledge. This was swiftly followed by a High Court judgement laying down criteria to establish whether a child, irrespective of age, had the capacity to provide valid consent to treatment in specified circumstances. Their parents still retained the right to override their children's consent. Two years later, these criteria were approved in the House of Lords and under the guidelines suggested by Lord Fraser the "Gillick test" of competency was born. This then meant that any young person in England, Wales and Northern Ireland was entitled further rights in an amount proportional to their competence. Unfortunately this judgement does not include any caveats dealing specifically with research and in fact no such case law exists.

Currently the Gillick principles are generally considered acceptable to apply to research that is not covered by the Clinical Trial Regulations but ambiguity does remain and recent publications have called out for clarity. It is possible that this confusion could pose a threat to a vulnerable group of the population, so there is an urgent need for further clarification.

The law governing children is complicated further by an incongruity between Scotland and the rest of the United Kingdom. Gillick principles do not apply there, but there is some legal provision for young people aged 16 and 17. Consent is presumed until proven otherwise and young people have the right to both consent to and decline from procedures if they are capable. A Scottish young person could "consent on his own behalf to any surgical, medical or dental procedure where in the opinion of the qualified medical practitioner attending him, he is capable of understanding the nature and possible consequence of the procedure of treatment"[8]. Although this is clearer than law in the rest of the UK, the right for children to consent to medical research is not explicitly described. Instead, there is a tacit understanding that the principles of the statute can be applied to research.

Assent

There is uncertainty about the age at which a child may permit research on themselves and for those that do not have the legal right to consent, their agreement to a procedure is known as "assent".

There is considerable variation in the age at which researchers request a child's assent and fairly sparse evidence to support it. America led the way in this area with the National Commission for the Protection of Human Subjects[9], which grew out of the Ramsey versus McCormick debates. They considered, among other things, what conditions would be required for the child subject to authorise research. It is perhaps an oversight that although the committee considered an enormous amount of opinions on what would constitute ethical research that they did not ask the children themselves. This meant that they endeavoured to work out the circumstances under which children could assent without asking them what would motivate them to assent.

In 1981 an American study by Janosky et al.[10] assessed risk to children from participation in research and included some new data on assent. This study revealed that in 73% of research groups the investigator or a member of the research group was left to decide whether to seek assent from the child based solely on their clinical judgement. There are almost no guidelines on the topic other than a statement from the Medical Research Council in 1963[11] which suggests that "English courts would not consider a child of less than 12 years as capable of giving such assent, and that Scottish courts would take 14 years as the minimum".

It might seem surprising that there are calls for standardised ages for children to assent as all children develop at different rates, but most seem to develop capacities for moral judgement in roughly the same way. Through the conclusions of a small number of studies on the abilities of children to assent, two significant ages can be determined. At around 7 years of age it is possible to communicate with children about health and illness and generally they have begun to develop moral judgement[12]. Historically, the Roman Catholic Church has believed that from the age of 7 an individual is morally responsible for their actions.

The second key age is around 14 years of age[13], when the child's ability to make a judgement is the same as that of an adult's, although of course a 14 year old has less experience in making decisions. Legislature in the United Kingdom does not support these findings, but South African law[14] has given children over the age of 14 the right to consent independently of their parents since 1970. Currently in the UK, if a child does not consent to research and the parents wish them to undergo research because the child needs treatment not available outside of the context of research and the investigations shows promise of therapeutic benefit then a Research Ethics Committee must give its approval before the research can be initiated. This essay suggests that if the evidence from the recent research studies on children is to be supported by law in the UK, then from the age of 14 upwards the patient's refusal to consent to research should be legally binding. Also, perhaps the parents should only be able to refuse consent for their children to undergo non-therapeutic research. Currently they can refuse consent in any case except if emergency treatment is required and that which is only available as part of a research programme.

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Age, however, is only one way of looking at when to grant children's right to assent. Victoria Miller has suggested a developmental approach is more practical, because it enables each child to be assessed as an individual by considering their "biological, cognitive, psychosocial and contextual features"[15]. The thought of using individualised developmental graphs to plot a child's capability of giving assent is still in the future, as a great deal more data and understanding is required. However if it does become possible to allow "children to choose the extent that they are able", children could take a more active role in the decision making process.

The other difficulty which researchers must overcome is deciding how much information to give the child is appropriate. A 2007 study[16], exploring children's ability to assent, looked at children involved in a diphtheria vaccine research study. They gave the children enough information to allow them to assent properly and then checked their understanding. The study showed there was a huge difference in the level of understanding between different children of the same age. They concluded that, while it was important to try and involve the child in the decision making process to give them autonomy, it was not appropriate to provide all children with all the information. Interestingly, they also suggested that asking children to try and make a decision on something they do not truly understand would be unhelpful in the teaching of decision making skills. Therefore it seems that when it comes to children a very good understanding of the individual child's comprehension is required. The researcher must try and give the child enough information to enable their autonomy as far as possible, while not overloading and confusing them.

Dissent

There is a lack of clarity as to what specifies dissent by a child when it comes to a procedure. Currently, a child might show signs of reluctance, for example, verbally or by crying, but the parents may not withdraw their consent if they do not consider the distress to be too high. There are no clear guidelines as to when a researcher should override parental consent and withdraw a child from their study. A 2007 study on children undergoing venupuncture states that "only in relatively extreme circumstances [should] the researcher override the consent of the parent"[17]. It also stresses the importance of the role of the parent in deciding whether their child's reluctance to do a procedure is similar to that of a child not wanting to do a routine task such as homework, or if the dissent is actually more significant than that. It even goes as far as to say that if a parent is allowed to override a child's dissent for many daily activities because they consider it to be in the child's best interest, then it should be no different if they override their child's desire to be involved in research with minimum harm and maximum potential for benefit.

Beneficence versus Risk

Risk is an ambiguous word that can refer both to the probability that harm will occur and the severity of the possible harm. Both need to be considered when they are contrasted with the benefit, which refers to something of positive value related to health. It is accepted that generally it is difficult to measure risk and benefit in a quantitative way, especially as the available information on the potential risk factors is severely limited. For example, most people would consider a research project that involved filling in a questionnaire to be harmless and therefore of minimal risk, but if it generated anxiety, guilt or encouraged risky behaviours then it could be seen as exceeding minimal risk[18].

When it comes to risk versus benefit it is important to consider significant possible benefits to society as a whole, such as developing effective ways of treating childhood diseases, as acceptable to justify using children as research subjects. However when the risk to the child is more than minimal, and the child will not benefit directly from the research we are divided. One group consider undergoing research in those conditions unacceptable but others would argue that this would prohibit research promising great benefit to other children. Overall, the aim is to undergo studies where the benefits and risks are "in a favourable ratio"[19]. Where the line is drawn is now decided on a case-by-case basis by ethical committees, who are urged to ensure that the most systemic and logical analysis possible is performed. The US Department of Health and Human Services produced a table in 1991 that helps to tie together the concepts of consent, assent, risk and benefit.

Level of risk	Prospect of direct benefit?	Parental permission	Assent from child*
No greater than minimal	Not necessary	One parent	Yes
Justified by anticipated benefit Or at least as favourable as any available alternatives	Necessary	One parent	Yes
Minor increase over minimal	Not necessary	Two parents	Yes
Not defined	Not necessary	Two parents	Yes

Table 1: Reproduced from part of the Code of Federal Regulations, governing research involving human subjects, Subpart D "Additional Protections for Children Involved as Subjects in Research".

*An IRB may waive assent for certain ages of children if it determines the capability of the child is so limited that he or she cannot reasonably be consulted or that intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of research.

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The table emphasises the fact that when research exceeds minimum risk, there are only two scenarios where involving children in research can be considered acceptable. First, when research offers the prospect of direct benefit to the participant and is fully justified by a risk to benefit ratio that is as good as alternative non-research approaches to treatment. Second, when it is likely to produce information about their condition that will be crucial to the understanding or treatment of the disease or condition and the risk is no more than a minor increase over minimal risk[20].

The law does not specifically define what cases would be acceptable and what would be unethical, but that is because it is not possible to cater for every eventuality. This enables a more fluid approach that ensures as much research as possible is performed, while ensuring that the child is protected. A more draconian approach that, for example, detailed exact levels of risk and probabilities would not allow for as much freedom as currently exists. Therefore basic regulations ensure the protection of children and serve as a guide to researchers, while IRBs have the role of further considering each individual case.

What Motivates A Child To Be Involved In Research?

So far, studies looking at what would influence a child to become involved in research have involved speaking to the parents or the healthcare professional in charge of their care.

In 2000, a survey[21] of paediatric oncologists in the UK and USA were asked what they thought would motivate parents to enter their child into a phase I clinical trial. They suggested parents and children were motivated by a possible cure, possible palliation, pressure from medical staff and family members, altruism and to maintain the child's or parents hope. It would be interesting to compare these results with studies of the perceptions of children themselves, but at the moment there is very limited evidence to show what the children themselves think about concepts such as altruism and justice.

How Much Can Children Influence A Decision?

The United Nation's convention of Human Rights[22] considers the right to be informed, express a view and to influence a decision to be among the fundamental rights of a child. The *0-18 years: guidance for all doctors*[23] echoes this as it emphasises the importance of listening to children. It states that a doctor "should listen to and respect their views about health". It explains that one of the ways it uses "should" is for principles that will not apply in all situations. This could be considered a realistic approach to listening to children and responding to their desires. However, if there is no absolute incentive to try and obtain informed consent then there is a danger that doctors will not make much effort in communicating with children about their views on health. Rather than empowering children to make a voluntary decision, their views may be disregarded and their rights restricted. Priscilla Alderson, a senior researcher at the University of London, recommended that children can and should play a greater role in decisions about health care. They have called for a new Code of Practice that would make certain that every child who can express a view is given information and listened to[24].

Conclusion

There is a long and dark history of children who were sacrificed for "the greater good" in the name of experimental research and we must continue to remember their abuse and make sure that it is not repeated. There will always be conflict between the need to keep children out of harm's way and the more utilitarian need to benefit society. Nowadays, robust guidelines exist to protect children because of their vulnerable status and ethical review boards are in place in order to ensure that the standards are upheld.

However the guidelines do not necessarily reflect the involvement and thoughts of the children themselves or their ethical beliefs, for instance, their sense of altruism and justice. This could be further explored to enable children to gain greater autonomy and help them to be as engaged as possible with clinical research.

Appendix 1

Key terms as defined by the 2001 European Directive[4].

Clinical Trial: any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.

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Non-interventional trial: a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

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USING SAIL TO ASSESS CLINIC LETTERS

Emma Ginn, Ben Rodrigues And Mansoor Ahmed

Using SAIL to Assess Clinic Letters.
Good Clinical Care.

Abstract

Written correspondence is one of the most important forms of communication between health care providers. The Department of Health (United Kingdom) recommends that all letters that help to improve a patient's understanding of their health and the care they are receiving should be copied to them as of right. The Sheffield Assessment Instrument for Letters (SAIL) is a tool developed to assess good practice in written communication.

An audit of randomly selected outpatient clinic letters was conducted using SAIL assessment instrument. The audit results highlighted deficiencies in clear documentation of investigations, medication/doses and information shared with patient/family. Following the audit, regular teaching sessions were held to raise awareness and to train on various aspects of the SAIL tool. Re-audit confirmed improvement in the quality of clinic letters to General Practitioners.

We recommend that similar audits should be conducted on a regular basis in all clinical settings to establish ongoing trends that will help to target areas that need more attention.

Using SAIL to Assess Clinic Letters

Background

Good medical care depends upon efficient communication between patients and providers. Effective communication at all levels is a basic clinical skill that demands just as much teaching and attention as any physical examination. Not only is it important between doctors and patients but also among other health care professionals in different settings. Breakdown in communication leads to confusion, misunderstanding, unclear directions, errors and ultimately underperformance[1-2].

Communication at a basic level can be broken down into verbal and non-verbal. In a health care setting, this may include direct contact with patients, telephonic conversation, note keeping, referral letters, dictations/clinic letters, discharge letters and prescriptions. High-quality communication is imperative in continuity of care, helping to liaise and share with other professionals and agencies. Furthermore, information needs to reach the patient in an organised, concise and understandable format. Good quality information for patients can help to prevent disease progression/complications, promote self-care, support treatment choices and improve effectiveness of clinical care[3]. Unfortunately, information sharing is not always efficient in these areas.

Written letters are often used in secondary care to communicate clinic findings, proposed treatment plans and future management with patients and other health care providers. They also provide a good summary of the patient's past medical history. It requires synthesis of clinical data, but also reflects distribution of responsibility between providers, professional courtesy, legal requirements and the writer's ability to educate regarding a specific case. The efficacy of written letters depends largely on how clearly the letter is formatted and whether it includes relevant bits of information. A poorly written letter is likely to reduce effectiveness of subsequent care and bad communication is often one of the common causes of complaints and claims[4].

There is a long tradition of evaluating the readability and comprehensibility of health education materials using specially devised formulae[5]. However, there are fewer tools analysing correspondence letters to see how well information is being communicated. Research has shown that junior members of staff have an appreciation of what is relevant in good letter writing but do not receive instructions regarding how to construct rhetorically relevant letters[6]. Furthermore, there has been a lack of feedback to assess how well doctors are performing with regards to written communication[7].

The Sheffield Assessment Instrument for Letters (SAIL) is an assessment instrument developed from a consensus framework for good practice in written communication. It uses a checklist to assess a clinic letter, with a global rating at the end[8]. It was developed to assess and improve junior doctors' letters to General Practitioners (GPs). When developing SAIL, the researchers had to decide what made a "perfect" letter. They decided to use this description *"this letter clearly conveys the information I would like to have about the patient if I were the next doctor to see him/her"* – which was deemed as the gold-standard. They adjusted SAIL to make it a reproducible and discriminating assessment of the doctor's performance, but also allowed some scope for further discussion around the topic. They felt that a clinical/educational supervisor could use this as a way of providing systematic feedback to a junior to improve their referral letters.

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SAIL audit

At Queen's Hospital, Burton-Upon-Trent, the SAIL tool was used in two audits to study the quality of written communication between the hospital doctors and GPs between August 2008 and November 2008 and subsequently from December 2009 to February 2010. The aim of these audits was to assess the quality of the outpatient clinic letters with a view to establishing a good standard in written communication between hospital clinicians and GPs. The original audit (2008) analysed 200 randomly selected letters using SAIL. Various aspects of written communication are outlined in Box 1. Documentation regarding investigations, medication doses and information sharing with patient/family scored 50% or less.

Aspects done well:
- Medical problems list (85%)
- History (96%)
- Examination (81%)
- Follow-up plans (99%) and purpose (99%)

Aspects that could be improved:
- Plan to investigate (or not) (50%)
- Medication doses (34%)
- Information shared with patient/family (44%)

Box 1: Initial Audit: Summary of SAIL assessment.

The audit concluded that SAIL can be used as a means of establishing good practice via assessing effective written communication and feedback to individuals. The audit also pinpointed that we are required to further improve clear documentation of investigations, medication/doses and information shared with patient/family.

Following the audit, regular teaching sessions were held involving junior and senior medical professionals and anonymous outpatient clinic letters were discussed using the SAIL tool. Particular consideration was given to various aspects of the SAIL tool including the ones with less satisfactory outcome in the initial audit.

The audit cycle was completed in 2009–2010 without forewarning the medical staff by repeat outpatient clinic letter assessment using the SAIL tool to see if there had been any improvements since the previous audit. Box 2 outlines various aspects of written communication during the re-audit.

Aspects done well:
- Medical problems list (75%)
- History (100%)
- Examination (91%)
- Follow-up plans (98%) and purpose (100%)
- Plan to investigate (or not) (69%)
- Medication doses (69%)
- Information shared with patient/family (78%)

Box 2: Re-audit: Summary of SAIL assessment.

The re-audit showed that education/feedback to the consultants/ middle grade doctors about what is expected in clinic letters resulted in an improvement in the quality of clinic letters ~1 year after the original audit results were published. History and examination showed significant improvement along with substantial enhancement in documenting plans to investigate, medication doses and information shared with patient/family.

Discussion

Effective communication is a fundamental aspect of medical training and is applicable during day to day medical practice. It is important that information is expressed effectively in a variety of formats so that the right message is conveyed and errors are reduced. Referral and reply letters are common means by which doctors exchange information pertinent to patient care. Ensuring that letters meet the needs of letter recipients saves time for clinicians and patients, reduces unnecessary repetition of diagnostic investigations and helps to avoid patient dissatisfaction and loss of confidence in medical practitioners.

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Research has indicated that reflection and feedback regarding written letters is valuable in helping to improve the standards. Keely et al.[9] conducted a study to determine the feasibility and satisfaction of a peer assessment program on consultation letters. The researchers concluded that the peer assessment of letters was feasible and beneficial. Some of the participants felt that the feedback they received resulted in immediate changes to their letters. In their study using the SAIL assessment tool, Fox et al.[10] demonstrated that it provides a feasible and reliable method of assessing the quality and content of outpatient clinic letters. Their study also established that SAIL could be used to provide feedback with a powerful educational impact.

Documenting medication doses was noted as an area of improvement when re-auditing. Medication communication is a Quality Use of Medicines barrier. In his study on medication information in General Practice referral letters to a physician, Carney[11] established that accurate records of medications taken and drug dose on GP referral letters was 63% and 84%, respectively. In the same study, complementary/over-the-counter medication documentation occurred in 26% of the letters only. Documenting current medications provides a medication history that can easily be accessed in patient notes, helping other users to understand when medications have been introduced, changed or stopped.

Tattersall[12] compared letters from 31 oncologists before and after attending a training program, which included: feedback on their own letters; specific recommendations for content and style of letters; and a prompt card to help with further dictation. Following the training program, improvements were seen in the use of problem lists and use of headings.

Good practice guidelines implemented in April 2004 give patients the right to receive copies of all correspondence from health professionals which concerns them, if they wish. The general principle is that all letters that help to improve a patient's understanding of their health and the care they are receiving should be copied to them as of right (Department of Health, United Kingdom, 2003)[13]. It is evident from the published data that most parents and young people want correspondence following outpatient appointments[14]. The audit conducted at Queens Hospital, Burton showed significant progress in communicating information to parents/guardian about their children seen in outpatient clinics.

Continual improvement in letter writing can only be achieved by regular assessment, helping to highlight areas of achievement and aspects that could be improved. An effective way of doing this is by conducting an audit, especially when the subject can be re-audited. By doing audit cycles, members of staff can be made aware of particular areas that require more attention. With relevance to the SAIL audit conducted in Burton, substantial improvement was shown after 1 year of the original audit. This illustrates that the original audit successfully drew attention to areas of poor performance and subsequently encouraged staff to improve. Not only was the message conveyed to permanent members of staff but was also effectively communicated to staff doing rotational placements.

We recommend that similar audits should be conducted on a regular basis in all clinical settings to establish ongoing trends that will help to target areas that need more attention. Furthermore it will encourage doctors to continue practising what is already being done well while emphasising continuing problems in written letters. SAIL assessment has the potential of becoming an essential component of appraisal and revalidation process, providing an effective means for the quality improvement required by clinical governance.

The RCPCH assessment startergy has a guided to the **minimum number** of **satisfactory** assessments that must be completed in **Speciality** training (i.e new ST grades).

	Level 1 *			Level 2			Level 3	
Assessment	**ST1**	**ST2**	**ST3**	**ST4**	**ST5**	**ST6**	**ST7**	**ST8**
MRCPCH part 1	desireable	essential	-			n/a		
MRCPCH	-	desireable	essential					
PaedMini CeX	6	6	6	4	4	4	4	4
Paed eCbD	4	4	4	8	8	6	6	6
MSF (eSPRAT)	1	1	1	1-2**	1-2**	1	1	1
DOPS	1 satisfactory assessment for each procedure			1 satisfactory assessment for each procedure		1 satisfactory assessment for each procedure		
SAIL (Sheffield assessment instrument for letters)	none			5 letters		-	5 letters	-
ePaed CCF (formally SHEFFPAT)	none			none		1 assessment		
Portfolio review	1	1	(1)	1	(1)	1	1	(1)
Trainers report	1	1	(1)	1	(1)	1	1	(1)

* trainees must also complete accredited neonatal and paediatric life support training during Level 1 Training

Figure 1

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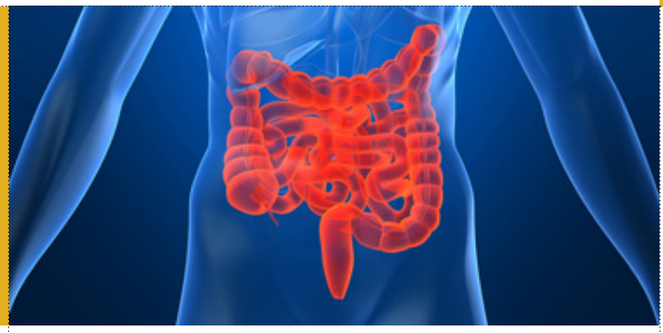
ANTIMETABOLITE THERAPIES IN PAEDIATRICS – DO THE LESSONS LEARNED FROM THE CLINICAL PHARMACOLOGY OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA APPLY TO THE TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS AND PAEDIATRIC CROHN'S DISEASE?

Thomas Hogan & Edward J Estlin

Antimetabolite therapies in paediatrics – do the lessons learned from the clinical pharmacology of childhood acute lymphoblastic leukaemia apply to the treatment of juvenile idiopathic arthritis and paediatric Crohn's disease?
Good Clinical Care.



Abstract

The antimetabolites methotrexate and 6-mercpatupurine form the mainstay of the maintenance therapy for childhood ALL, and are also employed in the treatment of childhood diseases such as juvenile idiopathic arthritis and Crohn's disease. For childhood ALL, the role of antimetabolite therapy has been defined to a significant extent by advances in the knowledge of the clinical and cellular pharmacology of these agents. This is not so true for other childhood illnesses, and the recognition of similar effector pathway of disease activity at the level of angiogenesis and diseases-modulating cytokines for ALL and illnesses such as Crohn's disease and juvenile idiopathic arthritis may support a "leukaemia treatment" approach for these diseases. This review highlights the clinical and cellular pharmacology of 6-mercapotpurine and methotrexate, and compares the clinical application of this knowledge for the treatments of childhood ALL, Crohn's disease and juvenile idiopathic arthritis.

Introduction

Despite having different aetiologies, childhood acute lymphoblastic leukaemia (ALL), Crohn's disease (CD) and juvenile idiopathic arthritis (JIA) have similar pathogenesis with features of angiogenesis and dysregulated cytokine expression [1-3] and the treatments for all are similar, being largely antimetabolite-based. Over the past 30 years or so, much has been learned about the underlying mechanisms that determine the chemosensitivity for antimetabolites chemotherapy agents in children, most particularly in the context of childhood ALL [4]. Within this context, a greater understanding of the pharmacology at the clinical, cellular and pharmacogenetic level of the principal treatments employed has led to increased insights in to the optimisation of treatment [4] and has helped underpin the considerable improvement for the survival of childhood ALL over this time period [4].

Therefore, this review looks at whether the lessons learned from the ALL can be applied to the treatment of CD and JIA. The antimetabolites considered are methotrexate (MTX) which is employed in the therapy of childhood JIA and 6-mercaptopurine (6-MP) which has a major role in the treatment of childhood CD. Azathioprine (AZA), a prodrug of 6-MP, is considered along with 6-MP in this context, and for each disease a search for evidence of any pharmacological influences on the rate, depth and duration of response will be made and referenced against that known for childhood ALL.

Thiopurines And Crohn's Disease

Cellular pharmacology of 6-MP

6-MP cellular uptake is subject to anabolic reactions to form thioguanine nucleotides (TGNs) which exert cytotoxicity via their incorporation into DNA, or catabolic reactions to form inactive metabolites [1]. Several enzymes are involved in the formation of TGNs from thiopurines (Figure 1). The first step is catalysed by hypoxanthine-guanine phosphoribosyl transferase (HGPRT). An alternative metabolic pathway occurs when thiopurines are metabolised by thiopurine s-methyltransferase (TPMT) to form inactive s-methylated nucleobases. 6-MP is also subject to inactivation by xanthine oxidase (XO) [2]. Genetic polymorphisms for TPMT expression are recognised, and as will be discussed later, influence the tolerability and effectiveness of 6-MP as a therapy for childhood ALL.

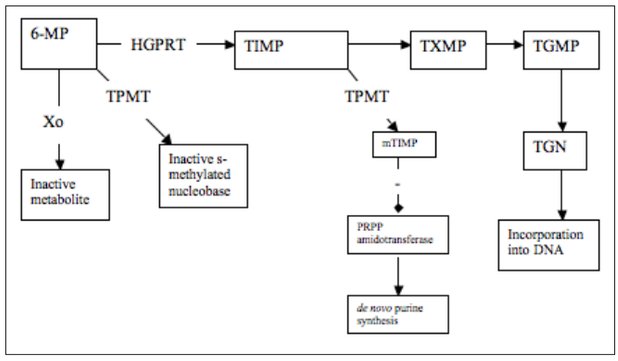


Fig 1: Cellular metabolism of 6-MP [1]

(HGPRT = hypoxanthine-guanine phosphoribosyl transferase; XO = xanthine oxidase; TPMT = S-methyltransferase; TIMP = Thioinosine monophosphate; TGN = Thioguanine nucleotides, TXMP = 6-thioxanthine monophosphate; TGMP = thioguanine monophosphate; mTIMP = methylthioinosine monophosphate; PRPP = phosphoribosyl pyrophosphate; ➔ = inhibits)

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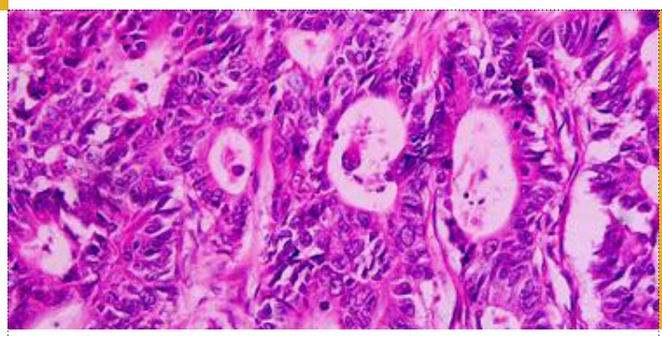

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Pharmacokinetics of 6-MP

Oral thiopurines undergo extensive intestinal and first pass (hepatic) metabolism and their pharmacokinetics are characterised by a wide inter- and intra-patient variability and the following characteristics[1]:

- Oral 6-MP has an average elimination T1/2 of 1 hour [3].
- Peak plasma concentrations within 1-4 hours of an oral dose [1].
- A 7-fold inter-individual variation in the peak/maximum circulating concentrations in the blood or plasma (Cmax) and area under the concentration versus time curve (AUC) [1].
- A considerable intra-individual variation in both plasma AUC and Cmax have also been demonstrated, with a coefficient of variation (CV) of 57.5% for Cmax and 57.9% CV for AUC in an ALL study of 18 ALL children being treated with a 6-MP mean dose of 67mg/m2 (range 50.0-83.3mg/m2) [4].

The absorption of AZA is incomplete and variable leading to the highly variable bioavailability of the drug (16-72%) [5]. However, oral bioavailability is greater for AZA than for 6-MP.

Thiopurine Pharmacogenetics

Bioavailability of thiopurines is influenced by TPMT activity, which shows a trimodal distribution pattern whereby a lack of activity is found for 1 in 300 patients, intermediate activity for 11% of patients and the remaining 89% having high activity. These TPMT activity levels relate to single nucleotide polymorphism (SNP) for which a variety of variants have been characterised [6]. Individuals without polymorphisms have high activity and heterozygous SNP result in intermediate enzyme activity. Homozygous polymorphism results in the rarer null TPMT status and complete loss of function. In general, if TPMT activity is high, less intracellular TGNs will be formed and if lower, more toxicity can result.

Hepatic TPMT activity has been found to be higher in adult males compared to adult females and it has been suggested that variations in first pass metabolism could account for the considerable inter- and intra- patient variability in 6-MP pharmacokinetic parameters [1].

Comparison of thiopurine treatment for Crohn's disease and childhood ALL

The single agent studies of 6-MP performed in North America in the 1950's demonstrated the potential for 6-MP to induce a complete remission in 25% of cases of childhood ALL [1] and a partial response in a similar number of patients. However, therapy with agents such as corticosteroids, vincristine and L-asparaginase were found to be much more effective [7], with the latter agents superseding 6-MP for the initial phase of therapy. Similarly, thiopurines are not very effective at remission induction for CD, with many studies finding them to be no better than placebo.

However, the single agents studies of 6-MP in the treatment of childhood ALL did identify the promise of this agent as one for maintaining a complete remission once this had been achieved [1]. Treatment with 6-MP now forms the mainstay of the continuing or maintenance therapy of childhood ALL and considerable pharmacology–based research performed over the past 30 years or more, as highlighted below, has served to define the important principles for treatment in this setting with 6-MP: For children with CD, 6-MP also has an effect to prolong remission, but with a considerable inter-individual variation in the duration of this response (Table 1). The following pharmacological variables are known to be important for the effectiveness of 6-MP in the continuing therapy of childhood ALL, yet there is a paucity of studies from the setting of CD for comparison as follows:

Number of subjects	Disease status	Agent	Dose	Duration of treatment	% staying in remission while on treatment	% in remission without treatment, or on placebo	Study
51	CD, in remission on azathioprine.	AZA	2mg/kg/day	6 months 12 months	100% 95%	75% 59%	O'Donoghue (1978) [15]
63	Aged 15-65, in remission on AZA	AZA	2.5mg/kg od	15 months	47%	7%	Candy (1995) [26]
120	CD, in remission for at least 6 months on 6-MP, without steroids.	6-MP (n=84), 6-MP stopped after 1 yr or more (n=36)	50mg (adjusted according to WCC and platelets)	12 months 24 months 3 years 5 years	71% 55% 45% 39%	64% 29% 15% 15%	Kim (1999) [27]
72	IBD (UC or CD)	6-MP	1.5mg/kg/day	76 weeks	UC: 63.6% CD: 53.3%		Mate-Jimenez (2000) [28]
55[P]	Newly diagnosed moderate to severe CD. Remission achieved on steroids with or without 6-mp.	6-MP	1.5mg/kg/day	18 months	91%	53%	Markowitz (2000) [11]
83	CD in remission on azathioprine for >or= 3.5 years	AZA	1.7 +/-0.4 mg/kg/day	18 months	92%	79%	Lémann (2005) [29]

Table 1. Maintenance with thiopurines only – IBD

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Dosing to a pharmacodynamic endpoint: The UKALL VIII childhood leukaemia trial recommended that all childhood ALL patients receive doses of 6-MP (and MTX) sufficient to induce measurable myelosuppression (i.e. borderline neutropenia). The implementation of this protocol resulted in patients receiving higher cumulative doses of 6-MP and resulted in an 18% increase in the relapse-free survival rate of childhood ALL in the UK [8]. In contrast, none of the IBD/CD studies reported have dosed to this level of myelosuppression. In fact, the majority taper down the dose of thiopurine, or indeed stop it entirely, if the white cell or platelet counts go below a predetermined level.

Importance of dose intensity: For childhood ALL, continuing doses of 6-MP are in the region of 75mg/m2 and daily doses are adjusted to maintain a predetermined level of myelosuppression [1]. A landmark childhood ALL study reported that the single most important determinant of overall event free survival was 6-MP dose intensity (DI) [9]. The average 6-MP DI was found to be lower at all time points (i.e. 30, 60, 90 and 120 weeks) in the group which eventually relapsed compared to the patients that remained in remission.

For CD, standard doses for 6-MP are in the region of 1.5 – 2.0 mg/kg/day (approx 43.5 – 58 mg/m2 for a 29 kg child) [10-12]. There is no dosing to myelosuppression. Thiopurine dosing is altered in order to avoid neutropenia and to minimise side effects and the effect of DI on disease outcome has yet to be determined.

Importance of AUC: Children with ALL who experience relatively low exposure to thiopurines as a result of fast clearance rates are more likely to relapse during maintenance therapy [13], and 6-MP AUC correlates with relapse-free survival [14]. The importance of thiopurine AUC has not been investigated in the setting of paediatric or adult CD.

Importance of duration of treatment: For ALL, children are maintained on 6-MP for 2 years (females) or 3 years (males) and prolonging maintenance therapy beyond three years does not improve outcome [1]. In comparison, duration of treatment is more variable in CD, and studies have suggested that AZA/6-MP is safe and efficacious as a long-term treatment, beyond 3.5 years and even beyond 5 years [15].

Relevance of red blood cell (RBC) TGNS: For children with ALL receiving 6-MP, a positive relationship between RBC TGN levels and relapse-free survival has been described [16]. Similarly, a 5-year study involving patients with IBD study measured serial red blood cell TGN levels and for a steady state group, on similar doses of AZA when compared to the doses of 6-MP for children with ALL , it was found that those who remained in remission had significantly higher mean TGN concentrations than those patients who developed active disease [17]

The influence of TPMT genetic polymorphisms¨ TPMT genotyping is standard prior to antimetabolite therapy across all specialities now, mainly to ensure identification of the NULL phenotype and risk of profound myelosuppression that can result form thiopurine administration in this circumstance. For childhood ALL, the influence of TPMT polymorphisms is under investigation, but has been found to relate to the tolerated dose of 6-MP, with patients with heterogynous genetic phenotype/intermediate TMPT activity more likely to require 6-MP dose reduction [18, 19] and also risk of relapse which may be higher for patients with high TPMT activity [20]. Similarly, for patients with IBD studies have found that the incidence of TPMT gene mutations correlates with increased thiopurine-induced overall 'adverse drug reactions and bone marrow toxicity compared with controls.

Methotrexate and juvenille idiopathic arthritis

Cellular Pharmacology of methotrexate

MTX is a classical antifolate that acts at three main cytotoxic loci within a cell, namely; dihydrofolate reductase (DHFR), aminoimidazole carboxymide ribonucleotide (AICAR) and thymidylate synthase (TS) [1] (Figure 2). TS and AICAR are important enzymes in de-novo thymidylate and purine synthesis, respectively. MTX is taken up into cells by the reduced folate carrier (RFC) [1]. Once inside the cell, MTX is converted by folypolyglutamate synthetase to polyglutamated forms (MTXPGs) by the addition of up to 6 glutamate residues with Ð carboxyl linkages [21]. By contrast, the MTXPG are subject to hydrolysis by folylpolyglutamyl hydrolase (FPGH). The polyglutamation of MTX aids its retention within the cell and also increases its potency as an inhibitor of TS and AICAR [1]. The cytotoxicity of MTX is related to polyglutamation and intracellular retention [1].

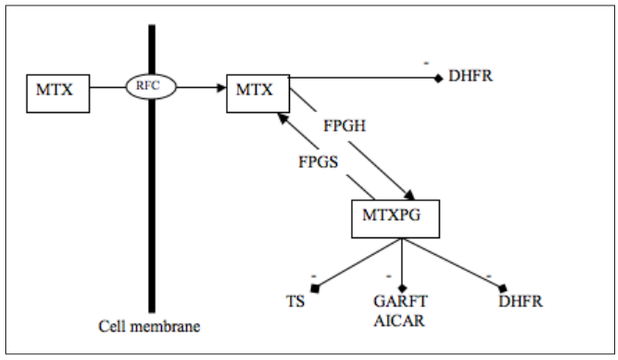

Fig 2: Uptake and metabolism of MTX [1]

MTX = methotrexate; RFC = reduced folate carrier; FPGH = folylpolyglutamyl hydrolase; FPGS = folylpolyglutamyl synthetase; DHFR = dihydrofolate reductase; MTXPG = MTX polyglutamate; TS = thymidylate synthase; GARFT = glycinamide ribonucleotide formyltransferase; AICAR = aminoimidazole carboxymide ribonucleotide formyltransferase;➔= inhibits)

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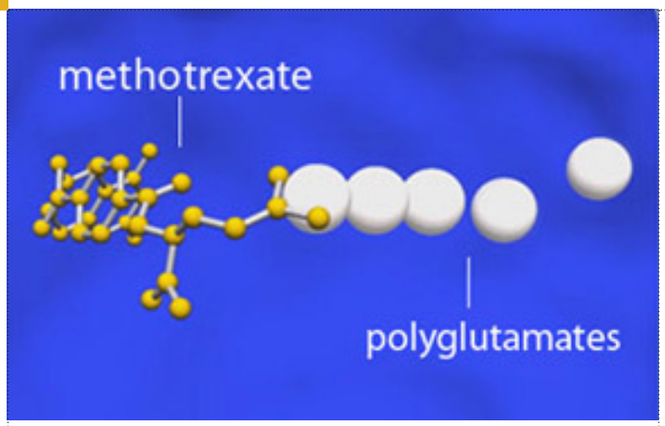

Pharmacokinetics of MTX

The pharmacokinetic characteristics of oral and parenteral MTX have been extensively characterised, including the following findings:

- At the standard initial dose of 7.5mg/m^2 for the treatment of JIA, there is no difference seen between AUC for oral and parenteral routes of administration. However, when patients receive standard maintenance doses of 17.0 mg/m^2 (similar to the 20 mg/m^2 employed for the maintenance therapy of childhood ALL) the AUC is lower following oral administration when compared to parenteral administration [21].

- When the bioavailability of oral and subcutaneous MTX in children with JIA was investigated, it was found that oral MTX had a bioavailability of 11-15% less than subcutaneous MTX of the same dose. A non-linearity in pharmacokinetics was noted for the oral route, but not for the SC route.

- Both oral and parenteral routes produce substantial (3-5 fold) intra- and inter- individual variation in pharmacological parameters, including C_{max} and AUC. Even though intramuscular MTX leads to a higher C_{max} and AUC than the oral route, it does not reduce the variability seen in the oral route [22].

- If MTX is to be given orally, it has been found that it has greater bioavailability when taken in the fasting state.

- Studies of children with ALL have identified sex-related difference in MTX pharmacology between boys and girls Following oral administration of 20mg/m^2 MTX, female children were found to have significantly higher plasma AUC values than male children [23].

Other pharmacological factors influence the pharmacokinetic disposition of MTX. A recent placebo-controlled study in adult patients with rheumatoid arthritis [24] found that folinic acid supplementation led to reduced plasma MTX concentrations 2 and 8 hours after intramuscular MTX administration, with a consequent 20% reduction in AUC. The researchers suggested that folinic acid led to increased intracellular uptake of MTX and promotion of sequestration of MTX intracellularly. It has variably been proposed that, in terms of arthritis management, folate supplementation should only be initiated if side effects appear [25].

Treatment with High-dose MTX (HDMTX), where MTX doses of 1-8 g/m^2 (i.e. more than 100-fold higher than those employed for oral maintenance therapy) with folinic acid rescue is now an established part of the consolidation therapy of childhood ALL [1] and, as will be discussed below, the large inter-patient variability in pharmacokinetics of this schedule of MTX impacts significantly on outcome for childhood ALL.

A comparison of MTX treatments for childhood ALL and JIA

In comparison to 6-MP, the importance of MTX in the remission induction and maintenance therapy of childhood ALL has been less extensively studied, but very good evidence exists for the importance of pharmacokinetic variability in the face of HDMTX therapy for childhood ALL.

However, studies of MTX performed in the 1950's identified that the dose and schedule of MTX was important for inducing and maintaining a remission for childhood ALL, where twice weekly parenteral dose of MTX (30mg/m^2/dose) was more effective than a daily oral dose (3mg/m^2/dose); the different schedules being associated with median remission duration of 17 and 3 months, respectively [1]. However, in the setting of oral therapy for the maintenance of remission for childhood ALL, it has been shown in ALL that there appears to be no relationship between MTX dose-intensity, peak concentration and systemic exposure to event-free survival [14, 22].

There have not been any systematic investigations of the potential importance of parameters such as the DI, peak concentrations or AUC of MTX for JIA. However, this drug is active in the treatment of this disease. For example, a double-blind placebo-controlled trial of oral MTX in resistant JIA concluded that there was a significant therapeutic advantage associated with a MTX dose of 10mg/m^2/week, with 63% of children showing an improvement compared to 32% and 36% for MTX 5mg/m^2/week and placebo respectively [26]. In addition the following information has been learned from clinical studies involving MTX and JIA:

- Changing to an SC or intramuscular (IM) route of administration can be beneficial when using MTX to treat JIA
- MTX concentrations do not correlate with disease activity in rheumatoid arthritis [23][27].
- Individual RBC MTXGlu$_{1\text{-}5}$ can be measured accurately, with low intra-patient variability and could be used effectively for drug concentration monitoring [1]
- Higher concentrations of MTXGlu$_3$ have been associated with reduced disease severity in arthritis [28,29].
- No advantage could be found for continuing maintenance therapy with MTX in the long-term in JIA [30].

The probability of discontinuation of MTX in rheumatoid arthritis patients one year post initiation of treatment is in the region of 30%[24]. The main reason for discontinuation of MTX treatment is its adverse effects, ranging from minor side-effects such as mouth ulcers and gastrointestinal disturbances to major side-effects such as bone marrow toxicity and liver function test abnormalities. These adverse effects are mainly thought to be mediated via folate antagonism, but folate supplementation may reduce the efficacy of MTX and folic acid is not given alongside oral MTX for children with ALL.

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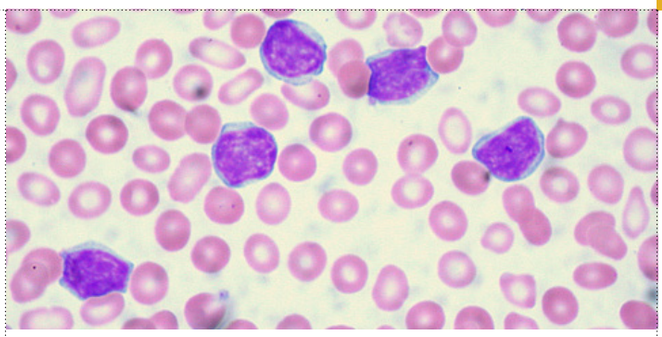
The HDMTX regimens employed for the treatment of childhood ALL recommend MTX doses that are hundreds-fold in excess of those employed for the treatment of JIA, where "high-dose" often signifies a two-fold increase in dose. In the setting of childhood ALL, where HDMTX is generally administered over a period of 24 hours, MTX pharmacokinetic variability (at least 5-fold variations in steady-state plasma MTX concentrations) has been found to relate to outcome and this phenomenon has been circumvented by pharmacologically-guided dosing of the drug [7]. The use of high-dose MTX has not been reported for children with JIA, but it may be important to note that MTX doses of 500 mg/m^2 with folinic acid rescue have given patients with oral MTX-resistant rheumatoid arthritis clinical benefit [31].

Conclusions

Although the antimetabolites 6-MP and MTX have formed an important treatment modality for the treatment of Crohn's disease and JIA, respectively, over the past 40 years, the potential importance of those pharmacological factors that relate to the prognosis of childhood ALL have not been studied extensively for other childhood illnesses. For example, whereas for childhood ALL 6-MP protocol adherence, DI and AUC are of prognostic importance and pharmacogenetic studies are bringing new insights into the optimisation of this therapy, the 6-MP doses employed for therapy in Crohn's disease are lower and the importance of pharmacokinetic variability is largely unknown. In the case of MTX, although pharmacokinetic variability does not seem to impact on prognosis for childhood ALL for the low doses that are used orally for maintenance therapy, the use of HDMTX is effective in the consolidation therapy of this disease and pharmacokinetic variability here is not only important but can be modified. HDMTX as a therapeutic strategy has not been employed for children with JIA.

It may also be important that, for many years, MTX (weekly) and 6-MP (daily) have been administered together for the treatment of childhood ALL, and that recent studies have identified that higher red cell TGNs relate to higher RBC long-chain MTX polyglutamates in the context of maintenance therapy, indicating an increased bioavailability of the "active" metabolites of TGN when MTX is more optimally metabolised [32]. Could MTX and 6-MP be used in combination for other diseases such as JIA and Crohn's disease, where azathioprine for JIA [33] and MTX for Crohn's disease [34], respectively, are known to be active? If this was to be considered, then the experience of decades of treatment of childhood ALL could be incorporated into the prospective study of pharmacological variables as determinants of disease response and duration, and allow the optimisation of such therapy which in turn may limit or avoid the use of the current second line biological agents such as anti-TNFalpha.



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ANTIMETABOLITE THERAPIES IN PAEDIATRICS – DO THE LESSONS LEARNED FROM THE CLINICAL PHARMACOLOGY OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA APPLY TO THE TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS AND PAEDIATRIC CROHN'S DISEASE?

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Number of subjects	Disease status	Dose	Concomitant therapy	Duration of treatment	Improvement	Improvement with placebo	Comments	Study
127	JIA. Systemic (n=32)	10 mg/m^2 of body surface area (n=46), 5mg/m^2 (n=40), Placebo (n=41)	Indomethacin (26%), Naproxen (18%), Tolmetin sodium (17%) Diclofenac (16%), Aspirin (16%). Other NSAIDs (6%)	6 months	63% (10mg) 32% (5mg)	36%		Gianni (1992) [30]
88	Persistent active, despite NSAIDs and steroids. Systemic (n=45), extended oligoarthritis (EOA) (n=43).	15mg/m^2 (or placebo)	Prednisolone, NSAIDs	4 months (followed by two months wash out), crossed over with the same for placebo.	48% EOA 25% Systemic	18% 16%	Crossover trial	Woo (2000) [31]
595	Polyarticular-course JIA.	8.0-12.5mg/m^2/week, po	Stable dose of no more than one NSAID. Stable low-dose of prednisone.	6 months	72% ACR paediatric30* 61% ACR paediatric50* 38% ACR paediatric70* 12% complete			Ruperto (2004) [32]
	Those patients who failed to improve on above treatment (n=133)	15mg/m^2/week, SC or IM		6 months (in addition to 6 months above)	62.5% ACR paediatric30* 57.5% ACR paediatric50* 45% ACR paediatric70* 12.5% complete			
		30mg/m^2/week, SC or IM			57.3% ACR paediatric30* 55% ACR paediatric50* 47.5% ACR paediatric70* 10% complete			

Table 2. Remission induction with Methotrexate - JIA

*The ACR Paediatric 30 criteria define improvement of ≥ 30% in at least three of the six core set variables, with no more than one of the remaining variables worsened by >30%. Patients can be evaluated using more stringent definitions of 50%, 70% or 90% improvement (ACR Paediatric 50, ACR Paediatric 70 and ACR Paediatric 90 respectively). Core Variables: Physician global assessment of disease activity, patient/parent assessment of overall well-being, functional ability, number of joints with severe arthritis, number of joints with limited range of movements, Erythrocyte sedimentation rate (ESR)

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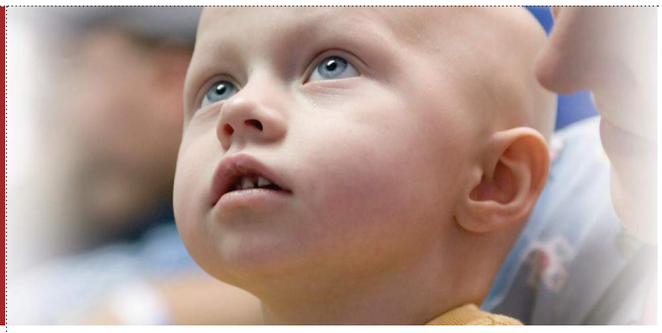

Clinical Pharmacology and Outcomes For Children with Cancer
Patient Management.

Abstract

With the introduction of combination chemotherapy agents over the past 60 years, the prognosis for children's cancers has improved dramatically. However, there is considerable intra- and inter-patient variation in the pharmacokinetic disposition of many of the cytotoxic chemotherapy agents employed in the first-line therapy of childhood cancers. For childhood acute lymphoblastic leukaemia in particular, pharmacology-based studies of dose intensity, pharmacokinetic variability and the pharmacogenetic influences for drug metabolism have helped to inform and develop therapies that have improved the therapeutic index of anticancer agents such as 6-mercaptopurine and methotrexate, with resulting impact on pharmacodynamic end points such as toxicity, tumour response and survival. In this review, the key pharmacologic parameters of anticancer agents are defined and their importance for the outcomes of childhood cancers are discussed

Introduction

The prognosis for childhood cancer has improved steadily over the past forty years with the introduction and refinement of combination chemotherapy agents. Research in the field of pharmacology has allowed the identification of inter-individual differences in drug disposition following their administration (pharmacokinetics) that can relate to differences in pharmaco-dynamic outcomes such as toxicity, disease response and survival. The pharmacokinetic disposition of anti-cancer drugs can allow effective monitoring of their dosage, the design of optimum treatment schedules and as will be discussed below, the optimisation of a therapeutic window in certain circumstances.

The aim of this review is to introduce the important terms that define the pharmacokinetic disposition of anti-cancer agents in children, describe their inter- and intra-patient variability following administration and give examples of how the knowledge of pharmacokinetics can inform outcomes such as toxicity, efficacy and second cancers.

Pharmacokinetic Parameters

Clinical pharmacokinetics is the discipline that describes the absorption, distribution, metabolism and elimination of drugs in patients requiring drug therapy. Cytotoxic chemotherapy agents can be administered orally where factors that influence absorption to the systemic circulation must be considered. In general the pharmacological effect of a drug is delayed when it is given extra-vascularly because of the time taken for the drug to be absorbed into the body.

After the drug reaches the systemic circulation it can leave the vasculature and penetrate the various tissues or remain in the blood. If the drug remains in the blood it may bind into endogenous proteins such as albumin or alpha 1-acid glycoprotein. In most cases this binding is reversible and equilibrium between the protein bound drug and unbound drug exists. Unbound drug in the blood provides the driving force for distribution of the agent of body tissues.

Certain organs such as the liver and lungs possess enzymes that metabolise drugs and the resulting metabolite may be inactive or have a pharmacological effect of its own. Drug metabolism usually occurs in the liver and can be classified into two categories. Phase I reactions generally make the drug molecule more polar and water soluble so that it is prone to elimination by the kidney. These chemical modifications include oxidation, hydrolysis and reduction. Phase II reactions involve conjugation to form glucuronides, acetates or sulphates.

Most drugs follow linear pharmacokinetics which describes the relationship between serum drug concentrations and drug dosing where change in plasma concentration exhibits a proportional relationship to the amount of drug given. When a drug is given by continuous intravenous infusion serum concentrations increase until equilibrium is established and serum concentrations level off and remain constant when the rate of drug administration equals the rate of drug elimination (Figure 1). In pharmacokinetics description of drug disposition, certain parameters are most frequently and importantly described as follows:

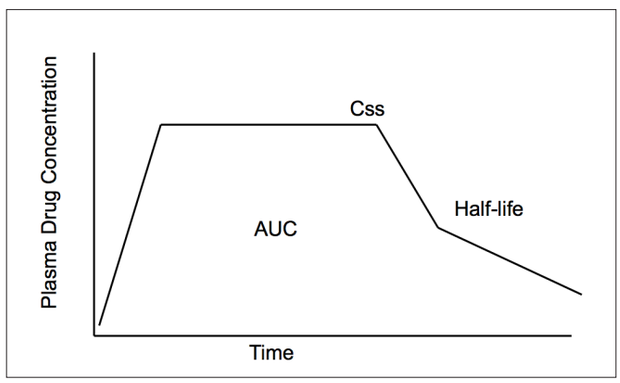

Figure 1: Schematic representation of key pharmacokinetic variables.

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• Clearance – This is the most important pharmacokinetic parameter because it determines the steady state concentration of a drug at a given dosage rate. Clearance describes the sum of the various means to eliminate a drug from the circulation, including renal elimination and hepatic metabolism. Clearance is described by the formula Cl = D/AUC.
• AUC designates the area under the concentration-versus-time curve for a given drug and dosage administration. It is a measure of the systemic exposure to any given agent.
• Half-life – This is the unit of time taken for a drug concentration to halve in the plasma and helps to determine the frequency of dosing.

The relationship of clinical pharmacokinetics to drug schedule and optimum administration and modulation of pharmacodynamics is now an established practice for the treatment of children with cancer (1), with pharmacologically-guided therapies as discussed below, designed to modulate toxicity and also optimise the therapeutic window of drug administration.

Determinants of the pharmacokinetic disposition of anti-cancer drugs in children

For the majority of anti-cancer agents in current clinical use in children, there is a wide intra- and inter-patient variation in pharmacokinetic disposition. The relationship of this phenomenon to pharmacodynamic parameters such as toxicity and response will be discussed later. However, firstly we will discuss the various reasons for this variability and how this can influence paediatric drug dosing and administration.

The developmental pharmacology of children can influence drug disposition, action and therapy (2). Drug disposition in children can differ than that found for adults and the following parameters are taken into account when designing a dose or schedule for administration of anti-cancer agents.

• Generally, the rate at which most drugs are absorbed following oral administration is slower in neonates and young infants than older children. Thus, the time required to achieve maximal plasma levels is prolonged in the very young.
• Age-dependent changes in body composition alter the physiologic spaces into which a drug may be distributed. The relatively larger extra-cellular and total body water spaces in neonates and young infants as compared with adults and older children, coupled with adipose stores that have a higher ratio of water to lipid result in lower plasma levels of drugs in these compartments when the drugs are administered in a weight-based fashion. The influence of age on the apparent volume of distribution is not as readily apparent for lipophilic drugs that primarily are distributed in the body tissues.
• Developmental differences in the activity of intestinal drug-metabolising enzymes and efflux transporters can markedly alter the bioavailability of drugs. For example, the intestinal activity of cytochrome P450 enzymes can increase with age.
• The renal elimination of drugs is also age dependent as maturation of renal function is a dynamic process that begins during foetal organogenesis and is complete by early childhood. The renal glomerular filtration rate increases rapidly during the first two weeks of life and then rises steadily until adult values are reached at eight to twelve months of age.

The differing physical-chemical constitution of children, along with age-dependent differences in their renal and hepatic functions mean that drug doses may be modulated (generally by reduction) for use in the very young. Although anti-cancer agents are generally prescribed according to body surface area based on weight in children (3). Age-related differences in the pharmacokinetics of drugs such as Methotrexate mean that higher doses of drug has to be given to children under four years of age to achieve a similar systemic exposure as that achieved for older children (4). In addition, recent work to characterise the pharmacokinetic disposition of the akylating agent Carboplatin and the topoisomerase II inhibitor Etoposide have shed more light upon the difficulty of predicting absolute clearance values for children under 12 kg in weight for the drug Carboplatin and also question the need for dose modification for the drug Etoposide in this age group (5).

As we have discussed, cancer chemotherapy is often limited by significant inter-individual variations in responses and toxicities. Such variations are often due to genetic alterations in drug metabolising enzymes or drug receptor expression (6). Indeed, the study of pharmaco-genetics in relation to cancer aetiology and the effectiveness of chemotherapy is an important and ongoing area of research in oncology (7).

Pharmacokinetic disposition of the commonly employed cytotoxic agents in paediatric oncology

When administered either by the oral, intramuscular or intravenous route chemotherapy agents demonstrate significant intra and inter patient variability in pharmacokinetic parameters such as clearance and AUC. These have now been characterised for the conventional cytotoxic agents that are employed in paediatric oncology practice but surprisingly the characterisation of agents that have been long in use such as actinomycin-D has only recently been achieved. Most drugs demonstrate at least a 3-5 fold variation in pharmacokinetic parameters and these are highlighted in the Table.

Agent	Category	Pharmacokinetic parameter	Range of variation (n-fold)	Reference
oral 6-MP	antipurine	AUC	80	8
oral MTX	antifolate	AUC	18	9
i.m. MTX	antifolate	AUC	3	9
vincristine	Tubulin-binding	Cl	3	10
actinomycin-D	Antitumour antibiotic	C max	30	18
Actinomycin-D	Antitumour antibiotic	AUC	4	11
HDMTX	antifolate	Css	5	12
ifosfamide	Alkylating agent	AUC	4	13
cyclophosphamide	Alkylating agent	Cl	8	14
carboplatin	Alkylating agent	AUC	3	15
etoposide	Topoisomerase I	AUC	5	16
cisplatin	Alkylating agent	AUC	3	17

The pharmacokinetic variability of selected anticancer agents in children (Css = steady state plasma, concentrations, Cl = clearance, Cmax = maximum concentration achieved in the plasma, AUC = area under the concentration-versus-time curve).

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The Pharmacokinetic characteristics of a drug can be used to guide dosing. For example, pharmacokinetically-guided dosing has successfully been achieved for children enabling more successful guidance of high-dose carboplatin (19). For children receiving high-dose carboplatin fractioned over three or five days, with the initial dose based on renal function to achieve a set target AUC, dose adjustment was carried out based on observed individual daily AUC's and this was found to allow an achievement of carboplatin exposures within 80-126% of target AUC, values as compared to estimated exposures of 65-213% of target values when carboplatin was administered without dose adjustment.

Pharmacokinetically guided dosing of carboplatin has allowed successful treatment of patients with Wilms' tumour who have experienced a bilateral nephrectomy (20) and studies have characterised the safety and necessary discard volumes from central lines for children undergoing pharmacokinetic studies (21).

Relationship between pharmacokinetic parameters and patient outcomes

The dose and schedule of many of the anti-cancer agents have been related to tumour response for a variety of childhood cancers and in particular the toxicity of agents such as actinomycin D. For example, the dose and schedule of actinomycin-D has been related to the development of the complication of veno-occlusive disease for children receiving this treatment as part of the therapy for Wilms' tumour (22). However, there has been a systematic study of the importance of key pharmacological parameters for the outcomes of certain childhood cancers over recent years and studies involving childhood ALL have led the way here.

Firstly, increasing the dose intensity of chemotherapy agents can improve survival for some childhood cancers. Without measuring any plasma drug concentrations or other pharmacological parameters, dose intensity, defined as the administration of a standardised amount of drug over a unit period of time (e.g. mg/m2/week), can serve as a crude measure of an increase in systemic exposure to drug. For the treatment of children with Stage IV neuroblastoma, the intensification of induction chemotherapy with agents such as cisplatin, vincristine, carboplatin, etoposide and cyclophosphamide has been related to an increase in event-free survival at three years in a randomised setting, an effect that may relate to the more rapid induction regimen enabling myeloablation to be given much earlier in the treatment pathway for these children (23). In addition, an analysis of prescribed dose intensity for methotrexate has been related to outcome for patients with high-grade osteosarcoma (24). However, experience of increasing dose-intensity of chemotherapy agents, such as vincristine, doxorubicin, cyclophosphamide and ifosfamide for Ewing's sarcoma and osteosarcoma have failed to show a positive relationship between prescribed dose-intensity and prognosis (25-28).

However, if the actual dose intensity that is actually received within a given treatment regimen is studied then there has been a general finding that a poorer prognosis will ensue when dose-intensity values are lower.

For example, the received dose-intensity for vincristine and actinomycin D related to survival and the risk of metastases for patients with localised Ewing's sarcoma (29) and a more detailed description of this phenomenon is described for patients with osteosarcoma of the extremity treated with neo-adjuvant chemotherapy with methotrexate, cisplatin and doxorubicin (30). Due to delays or dose reductions, only 12% of patients received the treatment exactly as scheduled by the protocol. 46% received a dose-intensity between 90 – 99% of the intended value and 42% received a dose-intensity between 63 – 89% of the intended. For patients with higher-dose intensity a 76% survival was compared with less than 60% for those with lower chemotherapy dose-intensity (30).

A similar finding has been described for children with acute lymphoblastic leukaemia, where patients who were ranked in the approximate middle and lower tertiles of drug exposure to Vincristine, L-asparaginase and anthracycline were three- to five-times more likely to have a subsequent relapse of the disease (31). Moreover, for children with infant ependymoma the 20% of children who achieved the highest relative dose-intensity of a multi-agent chemotherapy regimen had the highest post-chemotherapy five year survival of 76% compared with 52% for the 30% of patients who achieved the lowest relative dose-intensity (32).

Thus, both the prescribed and dose intensity of chemotherapy actually received can be an important predictor of prognosis. However, the actual measurement of systemic exposure or AUC within the patients themselves when receiving chemotherapy drugs, has often been found to relate to factors such as toxicity or outcome. For example, a clinical pharmaco-dynamic study of continuous infusion teniposide identified systemic exposure as a determinant of response in a Phase I study of this anti-cancer agent (33), and systemic exposure to 6-mercaptopurine when measured in children was found to be an independent prognostic factor for the treatment of acute lymphoblastic leukaemia, following its administration via the oral route (34).

Perhaps serving as a paradigm for the design of an anticancer therapy that seeks to take into account inter-patient pharmacokinetic variability and control for this, the identification of inter-individual variations in high-dose methotrexate clearance and steady-state plasma levels by the St Jude Children's Research Hospital team for the treatment of acute lymphoblastic leukaemia has led to the design and implementation of pharmacokinetic-guided therapy for high-dose methotrexate. With this approach, a 10% improvement in event-free survival was achieved for children with pharmacokinetically-guided post-remission induction therapy with methotrexate as compared with conventional dosing based on body surface area (34).

Polymorphisms affecting certain genes that influence the metabolism, pharmacokinetic disposition and pharmacodynamic effects of anticancer agents have now been characterised. Thus, the study of pharmacogenetics in children with cancer has also identified a further influence that can relate to patient outcome. From the adult cancer setting, variant alleles for doxorubicin transport and cyclophosphamide metabolism have been identified as an important determinant of response and toxicity for breast cancer patients (36).

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In the paediatric cancer setting, the genetic polymorphisms that relate to thiopurine S-methyltransferase (TPMT) have now been extensively studied. The enzyme TPMT metabolises the purine analogue 6-mp and there are drifts within the population genetic polymorphisms, with some 11% of patients having intermediate expression because of heterozygous mutations and homozygous mutant individuals having very low TPMT activity. The latter group of patients are markedly intolerant of this chemotherapy agent and need to be identified to avoid severe toxicity. However, the patients with intermediate activity of the enzyme have been found to tolerate less 6MP during maintenance therapy than patients with wild type gene expression (37). The TPMT genotype with heterozygous expression has also been found to have a better response to early treatment in terms of minimal residual disease status (38).

In addition, a more extensive genetic analysis for polymorphisms has examined the role of factors such as the multi-drug resistant gene and these have been shown to associate with outcome (39). TPMT expression can also relate to the risk of a second malignant neoplasm for children with acute lymphoblastic leukaemia with children with lower TPMT activity more at risk of cancer (40).

Finally, the examination of polymorphisms from the DNA of children with neuroblastoma, examining the polymorphisms for three broad gene categories, including cytochrome P450, glutathione-S-transferase and N-acetyltransferase have identified polymorphisms that may relate to a more favourable outcome for children with neuroblastoma (42). In addition, polymorphisms in genes that are associated with tumour response and survival have been associated with clinical outcome for patients with osteosarcoma (43).

Summary

The science of pharmacology has allowed us to gain insight into the ways that drug disposition can affect both toxicity and survival for children with cancer, allowing a more individualised approach to treatment in some circumstances (Figure 2). The increasing knowledge of pharmacogenetic variables may help with the application of individualised therapy on a wider basis and will be an essential tool for the understanding and optimal usage of novel agents in the area of children's cancer treatment.

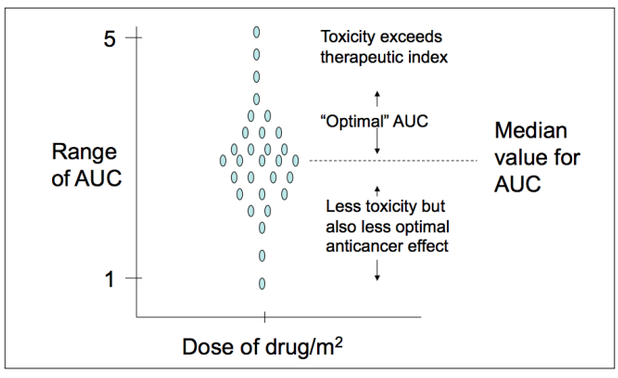

Figure 2: Schematic representation of relationship between the pharmacokinetic variable AUC and the pharmacodynamic effects of toxicity and outcome.

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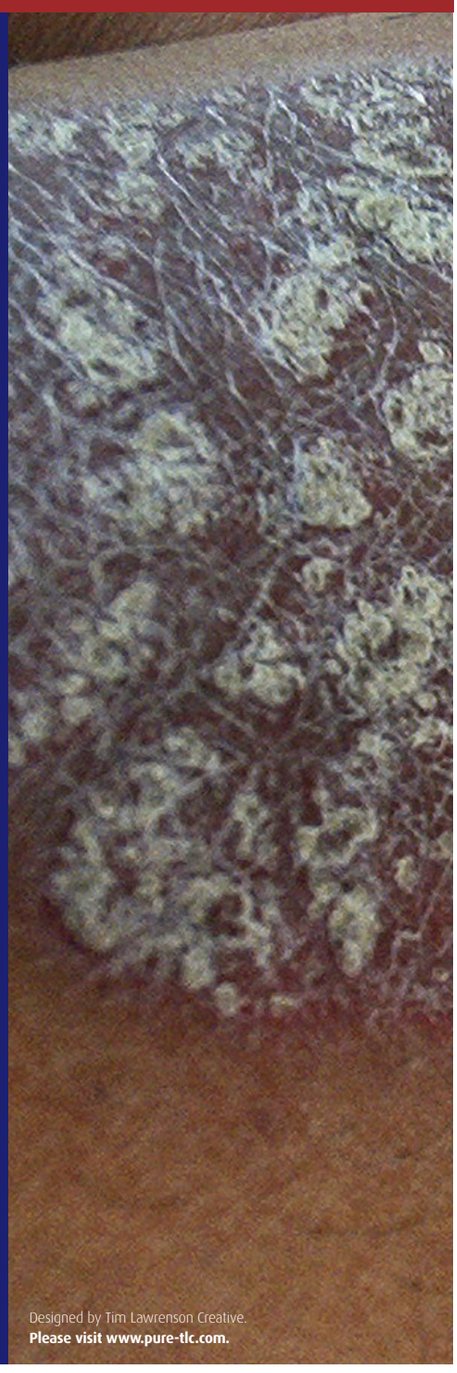

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