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FOUNDATION YEARS JOURNAL 2017

Volume 11

Foundation years journal

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FOUNDATION YEARS JOURNAL 2017

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Foundation years journal

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2 WEEK WAIT DERMATOLOGY CONSULTATIONS: THE INTRODUCTION OF A PROFORMA

V Agarwal, L Bonthala, N Muirhead, C Rodriguez-Garcia

Abstract

Skin cancers are the most common cancers in the UK (1). Melanomas and squamous cell cancers have metastatic potential and are referred to dermatology secondary care via the Two Week Wait (2WW) cancer pathway.

The assessment, documentation and management of 2WW patients in the dermatology outpatient setting needs to be efficient and evidence based. The burden is likely to increase with rising skin cancer incidence (2). In view of this, a closed loop standards audit was designed to review adherence to current evidence based guidelines for assessing 2WW skin cancer referrals and measure the impact of a proforma (Figure 1) to aid in meeting these guidelines. Clinical notes were collected in two cycles from patients referred between September and October 2016 with standard documentation, and from February and April 2017 with a proforma.

Data was collected from 100 patients over both cycles. Our audit showed that adherence to a proforma vastly improved performance in documenting full skin check, lymph node examination and sun care advice. Not only does a proforma aid provision of a streamlined service, it reminds clinicians to give secondary prevention advice.

Introduction

Skin cancers are the most common cancers in the UK (1), they are usually categorized as Non Melanoma Skin Cancers and Melanomas.

Non Melanoma Skin Cancers account for 20% of cancers in the UK. There are two predominant types of Non Melanoma Skin Cancers, basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs). Of these, SCCs represent approximately 23% of Non-Melanoma Skin Cancers. Melanomas account for 4% of all cancers in the UK, and rates are rising, with the incidence rate being projected to rise a further 7% by 2035 (2). More importantly, 86% of cases of melanoma are considered to be preventable, highlighting the importance of early detection and prevention (2).

Both melanomas and SCCs have the potential to metastasize, the subsequent morbidity is increasing the burden on Dermatology and healthcare services (3). Patients seen in Primary Care with suspected Melanoma or SCC are referred to Dermatology 2WW as per national guidance (4). The volume of 2WW referrals per clinic can be high. Many publications on this topic target the training of GPs to improve identification of skin cancer prior to referral (5). Our study targets the quality of secondary care consultations to meet the evidence based recommendations.

A closed loop standards based audit was designed to:

(A) Review adherence to current best practice evidence based guidelines for assessing 2WW skin cancer referrals.

(B) Measure the impact of a proforma to aid in meeting these guidelines.

Current Best Practice Guidelines

The evidence based recommendations used in our audit were Ultraviolet (UV) exposure advice, use of bedside dermoscopy, lymph node examination and full skin check.

With regard to UV ray exposure, a systematic review of 18 observational studies has shown a consistent association with occupational UV exposure and increased risk of squamous cell carcinoma (6). Furthermore, results from a prospective randomized controlled trial on 1,621 randomly selected residents in Australia showed that advice to use sunscreen daily halved the rate of developing melanoma during a ten year follow up (7).

Lymph node examination should form a compulsory part of the examination of a patient referred via 2WW. It is known that squamous cell carcinomas and melanomas have the inherent clinical potential to metastasize to lymph nodes. In addition, early detection of lymphatic invasion aids diagnosis, staging and management (8).

Dermoscopy is the use of a handheld magnifier (typically x 10) with a non-polarised light source to examine skin lesions. The non-polarised light reduces reflection from the surface and deeper skin structures are easier to identify. This has been well evidenced for pigmented lesions. The NICE guidelines (2015) (4) for suspected cancer recognition suggest that for pigmented skin lesions, suspicion of melanoma should be documented with specific diagnostic findings on dermoscopy. Evidence is mounting for the use of dermoscopy in non-pigmented lesions, a recent international study of 2,072 patients demonstrated that appropriate management increased from 78.1% without to 82.5% with dermoscopy (9).

Along with the standards described above, full skin check is equally imperative. Based on the authors' clinical experience, high risk patients may have numerous cancer or pre-cancerous lesions. A head-to-toe skin check allows for early detection and prevention of further high risk skin cancers (7).

Method

Clinical notes from patients referred to a busy district general hospital Dermatology department between September and October 2016 were reviewed. Data was collected from 50 new referrals, limiting it to 10 patients per clinician. This was to ensure the sample was as fair and representative as possible. Data collection was based on documentation of standards from Current Best Practice Guidelines - local skin examination, clinical findings, full skin examination, dermoscopy, lymph node examination and UV/ sun care advice. The results of the first audit were presented at a local departmental meeting.

Based on results from the first loop and suggestions for re-audit, a proforma (please see Figure 1) was then developed and used to complete the audit loop.

2 WEEK WAIT DERMATOLOGY CONSULTATIONS: THE INTRODUCTION OF A PROFORMA

V Agarwal, L Bonthala, N Muirhead, C Rodriguez-Garcia

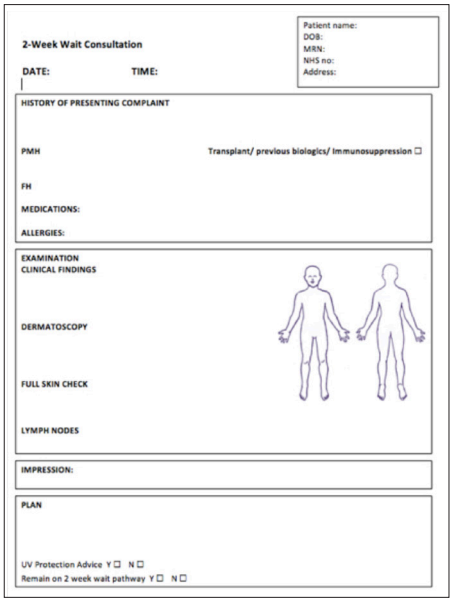

Figure 1

The repeat audit of 50 patients was conducted for patients referred between February and April 2017 via the 2WW skin cancer pathway. It was designed with the intention of signposting clinicians towards assessing and completion of standards in busy, time restricted clinics without comprising on quality of care provided.

Results

The results table (presented in Figure 2) presents a comparison between the first audit findings, and the results of the repeat audit after introduction of the proforma. Pleasingly, improvements were seen in all categories after introduction of the proforma with local skin check and clinical findings completed in 100% of proformas. This was an improvement from 92% completion of local skin check in the first loop of this audit.

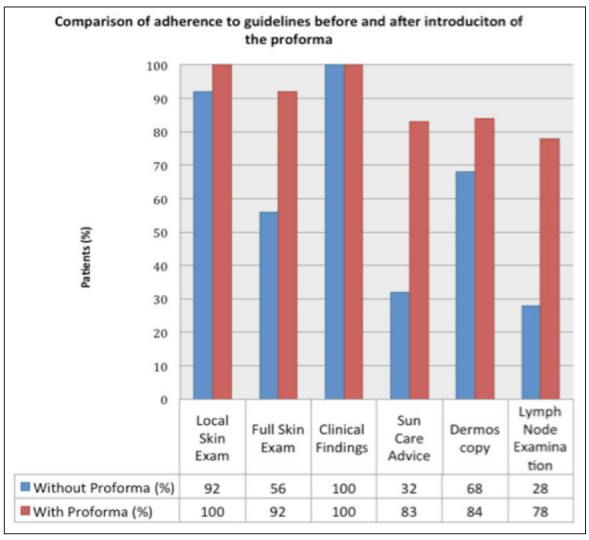

Figure 2

Full skin examination was documented by 94% of clinicians compared to 56% previously, with dermoscopy completed in 84% compared to 68% previously. Lymph node examination was documented in 78% of patients in the repeat audit, compared to 56% previously. Sun care advice was provided for 83% of patients in the repeat audit, which shows significant improvement compared to 32% in the first loop.

Discussion and Conclusion

The improvement between the two audit cycles clearly demonstrates that this proforma (Figure 1) assists clinicians in documentation according to current best practice guidelines. It is also reflective of GMC Good Medical Practice Guidance (10) (Domain 2, Quality and Safety, Contribute to and Comply with Systems to Protect Patients) which states that it is our responsibility to 'take part in regular reviews and audits of your own work and that of your team' and 'responding constructively to outcomes'.

Feedback from clinicians using the proforma was positive, with the overall message being that that it is a useful tool in guiding consultations as well as making documentation easier. It was also perceived to be a useful training tool for trainee doctors in Dermatology. Two specific criticisms were that the proforma did not allow enough space for documenting the history of presenting complaint and the examination findings. As a result, it may have been the case that even though a certain standard was assessed, it may not have been documented clearly due to lack of space on the proforma. This feedback will help us to develop improvements in the layout of the current proforma, for example extending it to two pages and increasing the size of the body diagrams.

In a national survey of Dermatologists the interquartile range of skin cancers diagnosed in all those referred to 2WW clinics as being suspicious was 7-13%. Therefore, one could argue that educating GPs would reduce the burden on secondary care. However, results of a UK study on over 500 referrals revealed that a targeted education module to GPs designed to improve diagnostic accuracy did not improve pick up rate of squamous cell carcinomas and melanomas (5). In our experience many of the referrals have other risk factors identified by the GP including previous personal or family history of skin cancer, fair skin type or a rapidly changing lesion (4). Our proforma is also aiding delivery of secondary prevention by giving these high risk individuals the opportunity for full skin check and sun protection advice.

Electronic documentation is now being introduced in NHS trusts. The scope for integrating the dermatology 2WW proforma into the electronic system of the trust where the audit was conducted has been identified. Should it be integrated, we would be able to make use of technology available to create accurate recordings of examination findings and thus improve the quality of documentation for skin cancer 2WW referral patients using guideline based standards we have assessed in a busy, time challenged environment.

2 WEEK WAIT DERMATOLOGY CONSULTATIONS: THE INTRODUCTION OF A PROFORMA

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References

1. British Skin Foundation Skin Cancer http://www.britishskinfoundation.org.uk/SkinInformation/SkinCancer.aspx. Accessed July 2017.

2. Skin Cancer Statistics. Cancer Research UK http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/skin-cancer. Accessed July 2017.

3. NCIN Data Briefing. Non-melanoma skin cancer in England, Scotland, Northern Ireland, and Ireland. http://www.ncin.org.uk/publications/data_briefings/non_melanoma_skin_cancer_in_england_scotland_northern_ireland_and_ireland. Accessed July 2017.

4. NICE Guideline 2015- Suspected cancer, recognition and referral https://www.nice.org.uk/guidance/ng12/resources/suspected-cancer-recognition-and-referral-pdf-18372680716. Accessed July 2017.

5. Shariff ZI, Roshan A, Williams AM, Platt AJ. 2 – Week wait referrals in suspected skin cancer: does an instructional module for general practitioners improve diagnostic accuracy? Surgeon 2010, 8 (5): 247 – 251.

6. Schmitt J, Seidler A, Diepgen TL, Bauer A. Occupational UV light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta analyses. Br J Dermatol 2011; 164 : 291 – 307

7. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol Off J Am Soc Clin Oncol. 2011 Jan 20;29(3):257–63.

8. Motley RJ, Preston PW, Lawrence. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Br J Dermatol 2002, 146:18-25

9. Sinz C, Tschandl P, Rosendahl C, Akay BN, Argenziano G, Blum A, Braun RP, Cabo H, Gourhant JY, Kreusch J, Lallas A, Lapins J, Marghoob AA, Menzies SW, Paoli J, Rabinovitz HS, Rinner C, Scope A, Soyer HP, Thomas L, Zalaudek I, Kittler H. Accuracy of dermatoscopy for the diagnosis of nonpigmented cancers of the skin. J Am Acad Dermatol. 2017 Dec;77(6):1100-1109.

10. GMC. Good Medical Practice (2013) http://www.gmc-uk.org/guidance/good_medical_practice.asp. Accessed July 2017.

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CASE BASED DISCUSSION: BLISTERS IN BABIES, WHAT TO DO & WHAT NOT TO DO

MD Zaman, I Salvary

Abstract

This is a case based discussion about a new born baby who had presented with a blistering rash, shortly after birth.

Blistering skin conditions are characterized by the presence of fluid filled lesions. Vesicles are small blisters measuring less than 5mm in diameter, and bullae are bigger blisters measuring 5mm or more in diameter. Blistering diseases can be divided into acute and chronic categories and the aetiology varies from common viral infections to rare genetic conditions. Some blistering conditions can be potentially life threatening and may require prompt hospitalization. (1)

Here we will discuss the presentation and management of a relatively rare blistering skin disease.

Case History

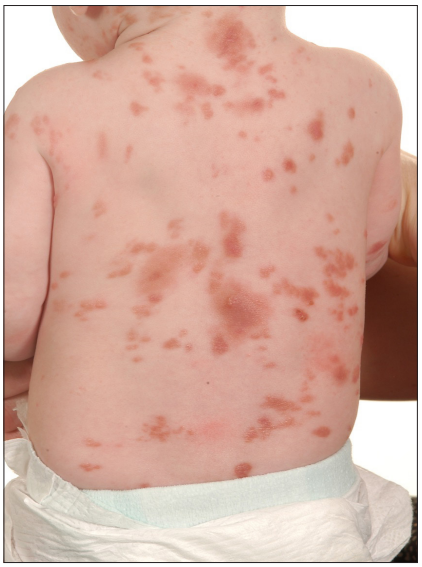
Our patient was referred to the dermatology team aged three weeks, by her paediatrician with a history of generalised blistering rash mostly involving the head, neck and upper torso from day 1.

She was born with blisters and one of the midwives thought she looked a bit slimy and decided to give her a good rub, which resulted in more blisters and increased redness of her skin. There were blisters also on the placenta and initial clinical diagnosis was Varicella Zoster infection.

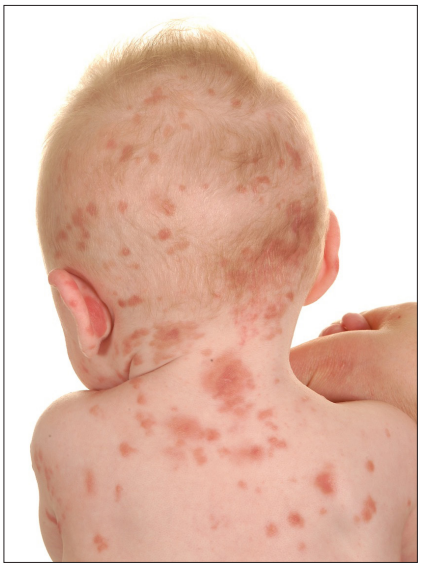
Her mother had a history of chicken pox as a child; however, she came into contact with a person suffering from chicken pox three weeks prior to her delivery. The patient was started on IV Aciclovir and was discharged home after a week when her condition improved to some extent.

However, three to four days following discharge she came up with new crops of blisters, mostly on her head and neck and was re-admitted. She was re-started on Aciclovir and was referred to both the ophthalmology and dermatology teams. Viral and bacterial swabs were also taken during both admissions.

When she was reviewed by the Dermatology team at three weeks, she was systemically well, with normal developmental milestones and taking regular feeds. Despite negative viral cultures she remained on Aciclovir. She continued to have new lesions, starting as a papule, and then developing into a vesicle followed by weeping and scabbing and finally resolving with a brown macule. The Ophthalmology team found no evidence of retinitis. A skin biopsy was planned but her mother was reluctant to consent for this procedure.



Picture 1



Picture 2

Her case was discussed at a joint meeting at the nearest tertiary centre, considering the unusual presentation and negative microbiology findings. The meeting advised a diagnostic skin biopsy with possible differential diagnoses including – Langerhans Cell Histiocytosis and Incontinentia Pigmenti.

CASE BASED DISCUSSION: BLISTERS IN BABIES, WHAT TO DO & WHAT NOT TO DO

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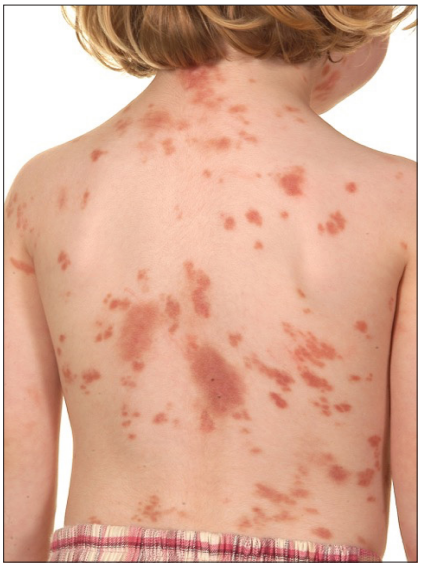
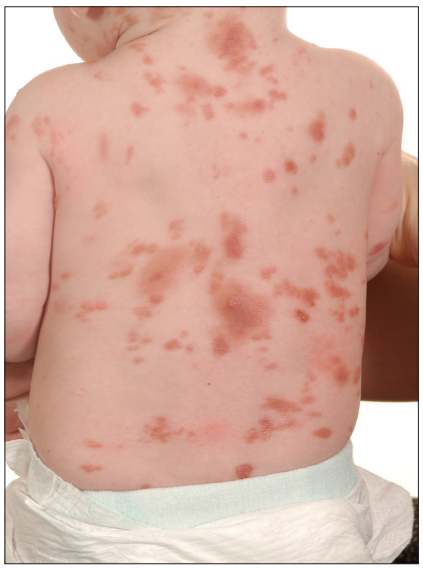
The outcome of the joint meeting was discussed with her parents and finally a skin biopsy was performed under local anaesthesia with written informed consent from the patient's mother. The biopsy was sent for histopathology, immunofluorescence and electron microscopy. Histopathology was reported as showing Urticaria Pigmentosa or Cutaneous Mastocytosis with strongly positive Choloroacetate esterase stain for mast cells. The diagnosis was explained to her parents and they were advised to avoid hot baths, vigorous rubbing, and medications such as – Anticholinergics, Codeine and Opiates as all those can cause massive histamine release from mast cells. Her parents were also provided with a Junior EpiPen® to be used in events of an insect bite to avoid potentially severe anaphylactic reaction.

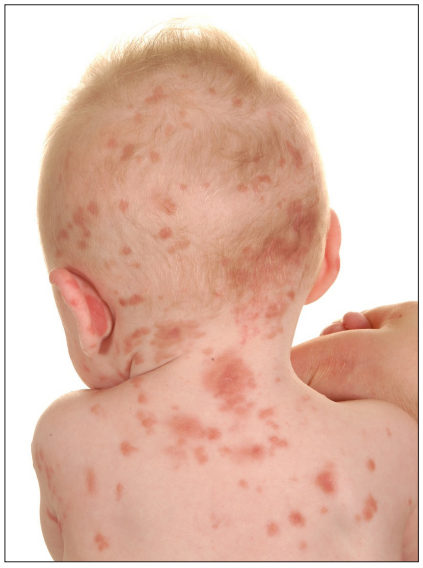


Picture 3

She continued to meet all her developmental milestones and gradually her rash started to improve. She was given regular emollients and antihistamines on as needed basis for pruritus but never needed to use her EpiPen®. She had regular follow up appointments every six to eight weeks to start with and later on two- three times a year. During her last review she had a few residual pigmented patches but no active lesions. At present she is on annual dermatology follow up. She has a reasonable understanding of her condition and is aware of trigger factors.



Picture 4



Picture 5

CASE BASED DISCUSSION: BLISTERS IN BABIES, WHAT TO DO & WHAT NOT TO DO

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Discussion

Blistering diseases can be acute or chronic. Differential diagnoses for acute blistering conditions include infective conditions, such as - Herpes simplex, Herpes Zoster, Varicella Zoster, Erysipelas, Hand foot and mouth disease, Atypical enterovirus infection, Eczema Herpeticum. Also included are inflammatory dermatoses, for example – Acute febrile neutrophilic dermatosis, Contact dermatitis, insect bites, Chilblains, Pompholyx, Erythema Multiforme, Steven Johnson's Syndrome, Drug hypersensitivity syndrome and Necrotising fasciitis.

Most cases are diagnosed from the history, especially history of contact, insect bites reactions, new drugs etc and clinical examination. Investigations include routine haematology, biochemistry for inflammatory markers, relevant microbiological investigations, such as viral and bacterial cultures and PCR.

A chronic blistering disease however, often requires a skin biopsy for histopathology and direct immunofluorescence. Sometime indirect immunofluorescence can be obtained by checking for the presence of a specific autoantibody in a blood sample. Examples of chronic blistering disease include genetic conditions, for example – Epidermolysis Bullosa, Cutaneous Mastocytosis, Hailey Hailey disease and acquired conditions, such as – Bullous Pemphigoid, Chronic Bullous Dermatoses of childhood, Dermatitis Herpetiformis, Pemphigus Vulgaris, Porphyria cutanea tarda. (1)

Urticaria Pigmentosa is a chronic blistering condition of genetic aetiology and is considered the most common form of Cutaneous Mastocytosis.

Mastocytosis comprises a group of rare disorders of excessive mast cell proliferation and accumulation, which can be limited to the skin (Cutaneous Mastocytosis) or involve bone marrow and other extracutaneous tissues (Systemic Mastocytosis). It can affect both sexes equally and can occur at any age.

World health organization classifies Mastocytosis as follows:

1. Cutaneous Mastocytosis

2. Systemic Mastocytosis

3. Mast cell leukaemia

4. Mast cell sarcoma and

5. Extracutaneous mastocytoma

Types of Cutaneous Mastocytosis include Solitary Mastocytoma, Diffuse Erythrodermic Mastocytosis, Paucicellular Mastocytosis or Telangiectasia Macularis Eruptiva Perstans (TMEP), and Urticaria Pigmentosa (UP). (2)

Mast cells express a receptor for Stem Cell Factor on their surface, the receptor tyrosine kinase KIT (CD117). Many of the molecular defects in Mastocytosis show gain-of-function mutations in KIT, the encoding gene for KIT. More than 95 percent of adults with Systemic Mastocytosis (SM) have exon 17 KIT mutations, most commonly D816V. Approximately 40 percent of children with Cutaneous Mastocytosis (CM) have exon 17 mutations, with another 40 percent carrying KIT mutations outside of exon 17. (3, 4)

Two thirds of Cutaneous Mastocytosis occur in children and nearly all cases are characterised by positive Darier's sign [when a lesion is stroked, it becomes urticated (raised), pruritic, erythematous and oedematous]. Lesions most commonly appear as yellow/brown macules but can be papular, nodular or bullous. Usually lesions are pruritic and pruritus can be exacerbated by changes in temperature, exercise, hot showers, local friction, ingestion of hot beverages, spicy food, ethanol, emotional stress, or certain drugs including Aspirin, Opiates, Codeine and Anticholinergics.

Children with Cutaneous Mastocytosis have an excellent prognosis, with lesions spontaneously resolving by the time they reach puberty. A longitudinal study on 43 children done between 2002 and 2007 has shown no significant effect on quality of life. (5)

In contrast, adults mostly develop systemic disease.

Diagnosis is made mainly through skin biopsy, however, full blood count, histamine level in the blood and urine, Serum Tryptase, Dexa bone scan, bone marrow biopsy can also be considered based on clinical presentations, especially if systemic involvement is suspected. Higher Serum Tryptase level (>20microgram/l) indicates extensive degranulation and therefore requires close observation and further investigations to exclude systemic involvement. (6)

Avoidance of trigger factors and education of parents and care givers are the two main components of overall management. H1 antihistamines are usually the treatment of choice for pruritus. Combined H1 and H2 antihistamines have also been shown to be effective in some cases.

Oral Sodium Chromoglycate has also been used but not commonly as first line treatment. Topical steroids can give some symptomatic relief but long term risks need to be considered. In adult patients with Systemic Mastocytosis, Phototherapy either in the form of narrowband UVB or Photochemotherapy (PUVA) can be useful, although benefits tend to be short lasting. In specific cases laser treatment can be considered for cosmetic purposes. (7)

CASE BASED DISCUSSION: BLISTERS IN BABIES, WHAT TO DO & WHAT NOT TO DO

MD Zaman, I Salvary

Conclusion

Blistering skin conditions can be acute or chronic. In common cases the clinical history and examination are sufficient to make a diagnosis. However, in more unusual cases specialist intervention and investigations may be necessary. A multidisciplinary approach can be useful as other organ involvement, especially eye involvement could be potentially life changing. Communication with the patient/caregiver is a key part of management as it appears very alarming and can cause significant anxiety and stress.

Questions

Q1. Which is not an acute blistering condition?

A) Varicella Zoster infection

B) Eczema Herpeticum

C) Erysipelas

D) Erythema Multiforme

E) Haily Haily disease

Q2. Which of the following is not a trigger factor for Cutaneous Mastocytosis?

A) Vigorous rubbing

B) Hot Bath

C) Spicy food

D) Antihistamine

E) Opiates

Q3. What is the most important diagnostic tool in Cutaneous Mastocytosis?

A) Serum Histamine level

B) Serum Tryptase level

C) Skin Biopsy

D) Viral PCR

E) Skin autoantibodies

Q4. The key factor in managing Cutaneous Mastocytosis is?

A) Education of patients/caregivers

B) Epipen® for emergencies

C) Regular Sodium Chromoglycate

D) Regular Antihistamines

E) Sun avoidance

Q5. If a child comes to A&E with a history of recurrent crops of blisters, we should...?

A) Send home with reassurance

B) Admit under paediatrician for further assessments and investigations

C) Arrange Viral swab and discharge with Aciclovir

D) Send home with topical emollients and mild topical steroids

E) Discharge with GP follow up if observations are stable and baseline bloods are normal

Answers

Q1. Answer: E

Teaching Note: Acute blistering diseases could be of infectious or inflammatory origin. Both viral and bacterial infections can cause blistering rash. Common viral causes include Herpes Simplex, Herpes Zoster and Varicella Zoster. Erysipelas is an acute Staphylococcal skin infection, which affects mostly upper dermis and superficial lymphatics.

Acute inflammatory conditions can cause blisters too, the commonest example being eczema. Occasionally Herpes virus can present as a superadded infection on eczematous rash, causing widespread, potentially serious skin infection, known as Eczema Herpeticum. Other inflammatory conditions presenting with blisters include Erythema Multiforme, Steven Johnson's Syndrome and Necrotising Fascitis.

Q2. Answer: D

Teaching Note: Mast cells can be activated in hot temperatures (also in a lesser extent, by cold temperatures), vigorous rubbing, spicy food, Ethanol and even by anxiety and stress. Insect bites and stings can cause potentially life threatening anaphylactic reactions. Moreover, common viral and bacterial infections and certain drugs, including NSAID, Opiates, Anticholinergics and Dextromethorphan can also activate mast cell degranulation.

CASE BASED DISCUSSION: BLISTERS IN BABIES, WHAT TO DO & WHAT NOT TO DO

MD Zaman, I Salvary

Any procedure under anaesthesia (for example surgery, dental works) and vaccinations need to be carefully planned beforehand. Antihistamines are first line treatment. Both H1 and H2 blockers have been shown to be effective.

Q3. Answer: C

Teaching Note: Mastocytosis is a genetic condition, characterized by pathologic increase in mast cells in cutaneous tissue and other organs, such as the liver, spleen, bone marrow and lymph nodes. Although symptoms of Mastocytosis are mostly Histamine mediated, it is Serum Tryptase which is generally used as an indicator of disease extent. Serum Tryptase level of >20microgram/l in Cutaneous Mastocytosis warrants further investigations to exclude systemic involements.

Skin Biopsy is the primary diagnostic tool. It shows an increased number of mast cells in the papillary dermis. Electron microscopy shows round and spindle shaped mast cells in sheet pattern, which stain with tryptase and chymase. There is no specific skin autoantibody for Cutaneous Mastocytosis and it is not of infective origin.

Q4. Answer: A

Teaching Note: Cutaneous Mastocytosis is a benign condition with excellent prognosis. Therefore, communication to parents/caregivers and later on to patients is the key component of the management. Thorough discussion, verbal and written information about potential triggers and symptom control and specific instructions about how to deal with emergencies, all are very important as an acute presentation can be very frightening. Teachers, school nurses, day care workers, dentists, doctors and nurses in primary and secondary care, all need to be aware of the diagnosis and all surgeries, for example dental works, and vaccinations need to be planned carefully beforehand.

Q5. Answer: B

Teaching Note: Although common viral and bacterial infections can cause a blistering rash and can be treated in the community, recurrent blisters raise possibility of more chronic conditions and need to be assessed properly. A multidisciplinary approach is vital, as mucosal involvement, especially eye involvement can cause potentially serious complications. Therefore, proper evaluation ought to be done to make plan for further investigations in order to reach a final diagnosis.

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References

1. Oakley A. Blistering skin conditions | DermNet New Zealand [Internet]. Dermnetnz.org. 2017 [cited 21 July 2017]. Available from: https://www.dermnetnz.org/topics/blistering-skin-conditions/
2. Mastocytosis: Background, Pathophysiology, Epidemiology [Internet]. Emedicine.medscape.com. 2017 [cited 21 July 2017]. Available from: http://emedicine.medscape.com/article/1057932-overview
3. Berezowska S, Flaig M, Rüëff F, Walz C, Haferlach T, Krokowski M et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. Modern Pathology. 2013;27(1):19-29.
4. Bodemer C, Hermine O, Palmérini F, Yang Y, Grandpeix-Guyodo C, Leventhal P et al. Pediatric Mastocytosis Is a Clonal Disease Associated with D816V and Other Activating c-KIT Mutations. Journal of Investigative Dermatology. 2010;130(3):804-815.
5. Heinze A, Kuemmet T, Chiu Y, Galbraith S. Longitudinal Study of Pediatric Urticaria Pigmentosa. Pediatric Dermatology. 2017;34(2):144-149.
6. Matito A, Morgado J, Álvarez-Twose I, Laura Sánchez-Muñoz, Pedreira C, Jara-Acevedo M et al. Serum Tryptase Monitoring in Indolent Systemic Mastocytosis: Association with Disease Features and Patient Outcome. 2017.
7. Castells M, Metcalfe D, Escribano L. Diagnosis and Treatment of Cutaneous Mastocytosis in Children. American Journal of Clinical Dermatology. 2011;12(4):259-270

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APPROACH TO THE ADRENAL INCIDENTALOMA

E Ahmad, M Haq, D Barnes

Abstract

An adrenal incidentaloma is an asymptomatic adrenal mass lesion discovered on radiological imaging not performed for suspected adrenal disease. The prevalence of adrenal incidentalomas on abdominal CT scans has been reported to be 4.4% (1), and even higher in older patients (10%) (2).

When an incidental adrenal mass lesion is discovered on an imaging study, there are two questions that need exploring;

1. Is it functional?

2. Is it malignant?

This article will highlight the evaluation and subsequent management of this by way of a case study.

Case Study

A 48 year old lady is referred to the Endocrine Clinic after she was discovered to have a 1.9 cm nodule arising from the left adrenal gland on an abdominal CT scan whilst being investigated for possible gallstones. Her only past history consists of depression, for which she is taking Escitalopram.

You are the doctor in the Endocrine Clinic. What specific questions should you ask when taking a history?

The adrenal glands secrete a number of hormones, including cortisol, aldosterone and catecholamines (Figure 1). Approximately 10% of adrenal incidentalomas are functional (3), although the figure varies between studies due to selection bias of patient cohorts

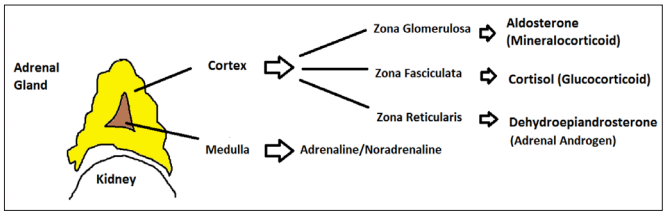

Figure 1: Hormones produced by the adrenal gland.

The two key conditions that should be screened for in all cases are a phaeochromocytoma, and Cushing's syndrome (which may be subclinical) (4). In selected cases, consider screening for primary hyperaldosteronism if there is concomitant hypertension and/or unexplained hypokalaemia. In very rare cases, adrenal androgens and their precursors should be measured if there are clinical features of androgen excess, or imaging features suggestive of adrenocortical carcinoma.

The classic triad of symptoms in patients with a phaeochromocytoma are episodic headache, sweating and palpitations. Approximately 50% of patients have paroxysmal hypertension, and therefore may not be known to be hypertensive.

Common symptoms of Cushing's syndrome include proximal muscle weakness (which may manifest as difficulty rising from chairs, climbing stairs or combing hair), weight gain, and easy bruising. There may be a history of hypertension or osteoporotic fractures. Both Cushing's syndrome and phaeochromocytoma may be associated with diabetes mellitus.

Examination Findings

The patient looked well, and weighed 80 kg, giving a BMI of 27. Pulse rate was 76 bpm and BP 118/74.

What other specific areas should be examined for in this patient?

Specific clinical features of Cushing's syndrome should be looked for. These include facial plethora, a "moon face", "buffalo hump" (dorsocervical fat pad), skin atrophy, purpura, abdominal striae (which is typically reddish-purple in colour), central obesity, thin arms and legs associated with proximal myopathy.

A tachycardia and hypertension may be present in patients with a phaeochromocytoma. Our patient had no clinical features of Cushing's syndrome, and had a normal pulse and BP.

Investigations

Figures 2 and 3 show the CT scan images of the patient's left-sided adrenal incidentaloma.

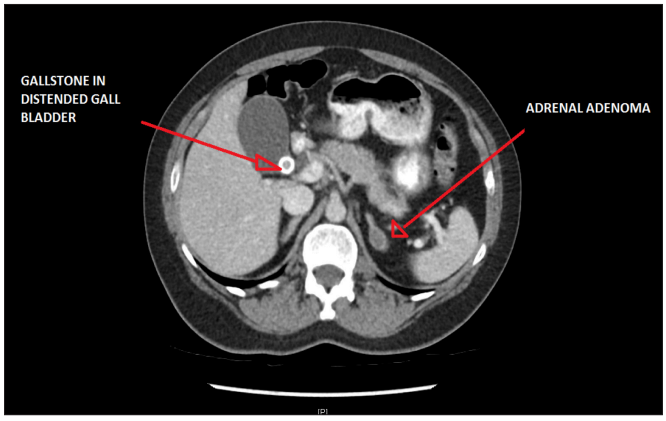

Figure 2: Transverse section of adrenal adenoma on CT scan.

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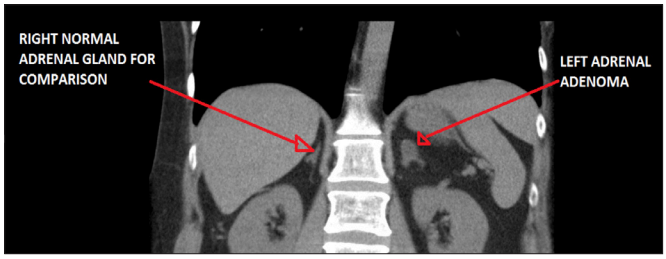

Figure 3: Coronal section of adrenal adenoma on CT scan.

What other investigations would you request, and what additional information do you need from the CT images?

The patient should have her electrolytes checked to look for hypokalaemia. In her case, her serum potassium was 4.5 mmol/l.

The screening test for a phaeochromocytoma is a 24 hour urine collection for metanephrines. For Cushing's syndrome, an overnight dexamethasone suppression test should be arranged. The patient is asked to take a single dose of 1 mg oral dexamethasone at 11 pm, with a view to having a 9 am serum cortisol checked the following morning: a normal result is less than 50 nmol/l. Our patient had normal results for these two investigations.

An adrenal mass which is homogeneous and lipid-rich is consistent with a benign adenoma. The presence of intracytoplasmic fat in an adenoma results in low attenuation on non-enhanced CT scans. The Hounsfield scale is a semi-quantitative method of measuring radiographic attenuation compared with water (which is conventionally allocated a Hounsfield unit (HU) of 0). If an adrenal mass measures < 10 HU on a non-enhanced CT, this is consistent with the density of fat.

Combined with a homogeneous appearance and size less than 4 cm, this would be entirely consistent with a benign adenoma. Our patient's adrenal mass measured minus 20 HU in keeping with a benign adenoma. Other factors which should be taken into account when attempting to differentiate between benign and malignant adenomas are shown in Table 1. PET scans can be helpful in selected cases, especially in those with a previous history of malignancy or when CT scans are indeterminate or suspicious for malignancy.

Lesion	Benign Adenomas	Malignant adenomas
Appearance	Round and homogenous with smooth margins	Heterogeneous density with irregular shape
Size	<4cm	≥4cm
Non-contrast CT	<10 HU	≥10 HU
Contrast enhanced CT	Rapid contrast washout (>50% after 10 minutes of contrast administration)	Delay in contrast washout (<50% after 10 minutes of contrast administration)
MRI	Isointense with liver on both T1 and T2 weighted MRI sequences	Hypointense compared to liver on T1 weighted MRI and intermediate to high intensity signal on T2 weighted MRI

Table 1: Imaging characteristics of adrenal incidentalomas.

Biopsy of an adrenal mass should only be considered if all of the following criteria are met (4):

1. A functional adenoma has been excluded (in particular, a phaeochromocytoma).

2. The lesion has not been conclusively characterised as benign by imaging.

3. Management would be altered on the basis of histology.

What is the management of the adrenal incidentaloma?

The management will primarily depend upon the nature of the adenoma – whether it is likely to be benign or malignant; functional or non-functional. For non-functioning adenomas < 4 cm in diameter with benign features on imaging criteria, no further imaging is required.

For functioning adenomas with clinically significant hormone excess, an adrenalectomy would be definitive therapy. Some patients may have "autonomous cortisol secretion" (ie cortisol levels that do not suppress adequately following the administration of dexamethasone) without exhibiting clinical features of overt Cushing's syndrome (4).

Age, degree of cortisol excess, general health, comorbidities (eg type 2 diabetes, hypertension, obesity and osteoporosis) and patient's preference should be taken into account when determining the management strategy.

For non-functioning adenomas which are suspected of being malignant on radiological criteria, the size of the adenoma and presence or absence of local invasion will affect the surgical strategy. All such cases need to be discussed at a multi-disciplinary meeting.

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For indeterminate lesions on CT scans which are not hormonally active, a multi-disciplinary team would consider additional imaging using an alternative modality, interval imaging (in 6-12 months) or surgery.

In general terms, patients with an adrenal incidentaloma should be discussed at a multi-disciplinary team meeting if any of the following criteria apply:

1. Imaging is not consistent with a benign lesion.

2. There is evidence of hormone excess.

3. Evidence of significant tumour growth during follow-up imaging.

4. Adrenal surgery is being considered.

Summary

1. An adrenal incidentaloma is an adrenal mass, usually greater than 1 cm in diameter, discovered as an incidental finding on imaging not performed for suspected adrenal disease.

2. The prevalence of adrenal incidentalomas increases with age.

3. A phaeochromocytoma and excessive cortisol secretion should be screened for in all cases, whilst primary hyperaldosteronism and excessive adrenal androgen secretion in selected ones.

4. Radiological features on imaging help to characterise the nature of the adenoma (ie benign or malignant).

5. Adrenal surgery is considered for those patients with clinically significant functioning adenomas and those with suspected malignancy.

Questions

Q1. A 55 year old lady undergoes a CT scan for evaluation of urinary symptoms and is found to have a 5 cm left-sided adrenal adenoma. She has no significant past medical history, feels well and has a blood pressure of 100/60 and pulse rate of 78 beats per minute.

The mass is homogeneous in appearance with a density of 44 HU on the unenhanced CT, but with a washout of 37% after 10 minutes of contrast administration on an enhanced CT scan. Which of the following is best next approach in the management of this patient?

A. Request an MRI scan of the adrenal glands

B. Repeat the CT scan in 12 months' time

C. Refer to the surgeons for removal of the adenoma

D. Request an aldosterone:renin ratio

E. Discharge from follow-up as lesion is clearly benign

2. A 65 year old man is referred from the Colorectal Surgery Department to the Endocrine Clinic following an incidental finding of a right-sided 3.5 cm adrenal adenoma. He has a background history of type 2 diabetes and hypertension treated with metformin, ramipril, indapamide and amlodipine.

His blood pressure in clinic is 180/110 with a pulse rate of 108 beats per minute. Blood tests show a serum sodium of 140 mmol/l and potassium of 4.1 mmol/l. What is the next most important step in the management of this patient?

A. Add in a beta-blocker in order to control the tachycardia and hypertensive emergency

B. Request an overnight dexamethasone suppression test in view of the hypertension and diabetes

C. Request a 24 hour urinary metanephrine estimation in view of the hypertension and tachycardia

D. Request a PET scan to exclude a malignant lesion

E. Refer the patient for urgent surgery

APPROACH TO THE ADRENAL INCIDENTALOMA

E Ahmad, M Haq, D Barnes

Answers

Q1. Answer A

The size and CT characteristics in this case are suspicious of a malignant lesion. It would be reasonable to request an MRI scan to assess the characteristics of the lesion via a different modality before making a decision regarding possible surgery. An aldosterone:renin ratio is only indicated in certain cases (eg hypertension, hypokalaemia).

Q2. Answer C

The patient is likely to have a phaeochromocytoma and biochemical confirmation of this is important before proceeding to definitive therapy in the form of surgery. Indeed medical management of a phaeochromocytoma is important in the pre-operative period. However, alpha-blockade must be introduced in the first instance: if a beta-blocker is commenced instead, then unopposed alpha-agonist activity may precipitate a hypertensive crisis.

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References

1. Bovio S, Cataldi A, Reimondo G, et al. Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. Journal of Endocrinological Investigation 2006; 29:298-302

2. Terzolo M, Stigliano A, Chiodini I, et al. AME position statement on adrenal incidentaloma. European Journal of Endocrinology 2011; 164:851-870

3. Cawood TJ, Hunt PJ, O'Shea D, Cole D, Soule S. Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant: time for a rethink? Eur J Endocrinol. 2009; 161:513–527

4. Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. European Journal of Endocrinology 2016; 175:G1-G34

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DIABETIC KETOACIDOSIS: A CASE BASED DISCUSSION

B Anderson, K Shotliff

Abstract

Diabetic ketoacidosis (DKA) is one of the most commonly encountered metabolic emergencies with an incidence of 3.6% in patients with known diabetes and a cost to the NHS of £2,064/admission (1). In a Spanish study, cost was estimated at an average of €1,476/admission (2). It continues to have a significant associated mortality of 2-5% predominantly due to late presentation and delays in the initiation of treatment (3).

Patients present to the Emergency Department and especially in the first 24 hours, are managed by acute medics, due to a lack of access to endocrine/diabetic on call teams on an acute medical admission unit. Guidelines for the careful and rapid correction of ketosis are outlined by The Joint British Diabetes Societies (JBDS) for Inpatient Care Group (4). Foundation doctors in all specialties can expect to see DKA and closely following such a protocol will help reduce patient's time spent in ketoacidosis and also length of hospital stay (5).

The case - Part I

A 51 year old man of East African descent working in IT, presented with a 7 day history of coryzal symptoms including 2 days of a cough productive of green sputum. He had no past medical history nor took any medications but did have a strong family history of type II diabetes with both parents, 1 of 3 brothers as well as several aunts and uncles being diagnosed. On direct questioning, he had 6-8 months of polyuria with 5kg of weight loss despite a current BMI of 31. The patient was a non-smoker and was married with 2 teenage children.

Examination showed a respiratory rate of 28 breaths/minute, pulse of 90 beats/minute, blood pressure 132/94 mmHg and a temperature of 38.0°C. Crackles were auscultated at his left lung base but no other abnormalities detected. Blood glucose was 9.5mmol/L.

Assessing the hyperglycaemic patient

Patients presenting with elevated blood glucose levels may be symptomatic with vague symptoms such as fatigue, confusion, abdominal pain, vomiting and muscle cramps. They may or may not complain of the more classical polyuria and polydipsia nor demonstrate Kussmaul's breathing in DKA. As the degree or duration of hyperglycaemia progresses neurological symptoms (lethargy, focal signs, coma) can be seen.

Following basic observations including a blood glucose, a prompt fluid assessment should be performed. Patients presenting with DKA will appear grossly dehydrated with some or possibly all of the following:

- *Slow capillary refill*
- *Tachycardia with a weak pulse*
- *Hypotension*
- *Dry mucous membranes*
- *Decreased skin turgor*

There are several mechanisms responsible for fluid depletion including osmotic diuresis due to hyperglycaemia, vomiting and reduced oral intake. Cardiorespiratory and abdominal examinations are of use to determine any respiratory compensation of acidosis leading to tachypnoea (Kussmaul respiration), any immediate sources of sepsis or intra-abdominal precipitant. It is important to note that taking a history should not delay the time to treatment.

Diagnosing DKA

DKA is a biochemical triad composed of hyperglycaemia (blood glucose >11mmol/L), ketosis (serum ketones >3mmol/L) and acidaemia (pH <7.30) which usually evolves over less than 24hrs. It results from a deficiency in insulin, up regulating hepatic gluconeogenesis and glycogenolysis and causing severe hyperglycaemia. Lipolysis increases the accumulation of ketone bodies (acetone, 3-beta-hydroxybuytyrate and acetoacetate) causing a raised anion gap of usually >20 meq/L. Without insulin there is also intracellular potassium depletion. The severity of DKA correlates with the blood pH not glucose levels. Therefore multiple blood gases are typically needed to monitor treatment.

The differential diagnosis

In this patient's age group, it is important to differentiate between DKA and a hyperosmolar hyperglycaemic state (HHS) as there are subtle differences in treatment (Table 1). 30-40% of DKA presentations are attributed to infection and therefore it is important to exclude sepsis and to treat accordingly. The remainder of precipitants are usually due to treatment failure – either as the first presentation of diabetes (10-25%), non-compliance with medication (25%) or inappropriate alteration of medications (13%). Stressors such as myocardial infarction (MI), stroke, surgery, pancreatitis and drugs make up the small remainder (3).

	Diabetic Ketoacidosis	Hyperosmolar Hyperglycaemic State
Pathogenesis	Insulin deficiency causes gluconeogenesis, glycogenolysis and severe hyperglycaemia. Lipolysis occurs causing ketone production.	Relative deficiency in insulin. Adequate enough insulin to prevent lipolysis and ketogenesis but not hyperglycaemia.
Causes	Infection (30-40%) Other intercurrent illness Psychological stress Missed insulin doses First presentation of type I DM	Infection (30-60%) Other intercurrent illness First presentation of type II DM Drugs(e.g. steroids, thiazides, beta blockers)
Onset	Acute, less than 24 hours	Chronic, over days to weeks
Symptoms & Signs	Hyperglyaemia (>11mmol/L) Polyuria, polydipsia Abdominal pain and vomiting Severe dehydration (hypotensive and tachycardic) Reduced mental state Kussmaul respiration Ketonuria	Hyperglycaemia (>30mmol/L) Polyuria, polydipsia Gradually reducing mental state Severe dehydration (hypotensive and tachycardic) Seizures
Diagnostic Criteria	Hyperglycaemia >11mmol/L Serum ketones >3mmol/L Acidaemia and pH <7.30	Marked hyperglycaemia of >30mmol/L Negative serum ketones <3mmol/L Lack of acidemia, pH >7.30 Osmolality usually >320mosmol/kg
Interventions	Rehydration with IV fluid Electrolyte replacement IV insulin Treatment of precipitating causes	Rehydration with IV fluid Electrolyte replacement IV insulin Treatment of precipitating causes
Mortality Rates	2-5%	15%

Table 1: Differentiating between DKA and HHS.

DIABETIC KETOACIDOSIS: A CASE BASED DISCUSSION

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Bedside tests should include a urine sample and 12 lead ECG. A urine dipstick will demonstrate marked glycosuria and ketonuria in DKA and aid diagnosis of a UTI. An MC&S should be sent regardless of dipstick results.

A VBG will reaffirm a raised blood glucose and demonstrate metabolic acidosis (i.e. pH <7.30 and low HCO_3) in DKA. There may be a degree of respiratory compensation if the patient is tachypnoeic.

Blood tests to be urgently requested by the laboratory should include:

- *A laboratory glucose (bedside glucose testing can be unreliable)*

- *Capillary ketones (superior to urinary ketones)*

- *FBC (WCC is often raised in DKA, regardless of infection)*

- *U&Es (to determine sodium and potassium levels as well as whether an acute kidney injury (AKI) co-exists)*

- *Other investigations as indicated by the history (e.g. amylase/cardiac enzymes/CK)*

A septic screen and imaging should be considered following immediate resuscitation. A chest X-ray may demonstrate a respiratory infection and a CT/MRI head should be used to investigate continued impaired consciousness or any unexplained focal neurology.

The case - Part II

Initial test results showed normal renal and liver function and HbA1c of 129 mmol/mol (non-diabetic range 20-41mmol/mol). A full blood count was unremarkable except a white cell count of $13.6x10^9$/L (normal 4.2-11.2) with a neutrophilia. Amylase was normal. Venous blood gas showed a pH of 7.05, PaO_2 6.0kPa, $PaCO_2$ 2.6kPa, HCO_3 5.3, base excess of -25.2mmol/L and a lactate of 2.7mmol/L. Arterial gases showed a pH of 7.01, PaO_2 18.5kPa and $PaCO_2$ 1.8kPa on 2L of oxygen via nasal cannulae. Urinary ketones were 4+ with a blood ketone of 5.9mmol/L (normal <1.0mmol/L).

Suspecting DKA and escalating to ITU

Following an A to E assessment, if DKA is suspected, IV fluid replacement should be commenced. Escalation to the medical registrar should be done immediately. Using the SBAR approach, it is particularly useful to inform them of any previous diabetes diagnosis and hypoglycaemic medications currently taken, the results of the VBG, ketone levels and what resuscitation has already been commenced.

Providing the registrar with the above information helps classify severity and determine prognosis. If patients are classified as moderate or severe, they will require higher levels of care, such as ITU (Table 2).

	Mild DKA	Moderate DKA	Severe DKA	HHS
Plasma glucose (mmol/L)	>14	>14	>14	>33
pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum HCO3 (mEq/l)	15-18	10-15	<10	>15
Serum Ketones	Positive	Positive	Positive (often >6mmol/L)	Small
Urine Ketones	Positive	Positive	Positive	Small
Serum Osm (mOsm/kg)	Variable	Variable	Variable	>320
Anion Gap	>10	>10	>12	Variable
Mental State	Alert	Alert/drowsy	Stupor/coma	Stupor/coma
Appropriate Clinical Setting	Medical ward	HDU	ITU	ITU

Table 2: Classifying the severity of DKA and the best clinical environment for these patients to be managed, adapted from Gouveia & Chowdhury (6).

The management of DKA

It has been estimated that 1 in 5 inpatient hospital beds are occupied by a diabetic patient and 1 in 4 of those have been subject to medication prescribing errors in the preceding week (7). One recent study also demonstrated that strictly following a protocol can result in a decrease in mean time spent in DKA – from 22.0 to 10.2 hours (5). The DKA guidance summarised below is widely accepted (4), however also become familiar with local trust guidelines and how they differ.

The management of DKA can be split into:

1. *Fluid replacement*

2. *Electrolyte correction*

3. *Insulin replacement*

4. *Treatment of other conditions present*

1. Fluid replacement

Adults in DKA are often deplete of at least 6L of fluid, in addition to their daily maintenance requirements (3). Fluid replacement is the most important initial management of DKA and therefore depending on the age and cardiac function of a patient, an immediate fluid bolus may be given. At least 4L of fluid replacement should be given in the first 12 hours (Table 3).

Until the blood glucose drops below 14 mmol/L, 0.9% sodium chloride is the fluid of choice. Once below 14 mmol/L, 5% dextrose is used to achieve higher insulin prescription and quicker reversal of ketoacidosis. It is important to be aware that over enthusiastic fluid replacement has a risk of precipitating acute respiratory distress syndrome (ARDS) and cerebral oedema in the young.

DIABETIC KETOACIDOSIS: A CASE BASED DISCUSSION

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Fluid	Volume
0.9% sodium chloride	1L over 1 hour
0.9% sodium chloride	2L over 4 hours
0.9% sodium chloride	2L over 8 hours
0.9% sodium chloride	1L over 6 hours

Table 3: Advised fluid replacement in a 70kg patient.

2. Electrolyte replacement

The first bag of fluid should not contain additional electrolytes as it is given quickly and may cause arrhythmias. However as insulin is replaced, a severe hypokalaemia results if left untreated. There is already up to 700mmol deficit in sodium and potassium and 350mmol in chloride during DKA (3). Therefore 2 hourly monitoring of electrolytes is required. Potassium should be given in additional fluid replacement once it falls below 5.5 mmol/L.

Consideration should be given to checking magnesium and phosphate levels as these may also be low and require replacement. Blood ketones should be monitored hourly to ensure they are falling by approximately 0.5mmol/L/hr, otherwise the rate of insulin replacement may need to be increased.

3. Insulin

Insulin acts to reduce serum glucose levels, prevent gluconeogenesis within the liver and stop production of ketones. Typically, insulin is prescribed as 50 units of Actrapid in 50mls of 0.9% sodium chloride at a fixed rate of 0.1 units/kg/hour.

Due to changing patient demographics where DKA is now more likely to be seen in obese individuals, evidence has led to the re-emergence of a fixed rate IV infusion, based on kilogram body weight to enable rapid blood ketone clearance, rather than a variable rate IV infusion previously used (8). Blood glucose should reduce by 3-5 mmol/L/hr (or >10%) until the pH>7.30 and capillary blood glucose is <14mmol/L. These fixed rates may need to be adjusted in insulin resistance states if the ketone concentration is not falling fast enough.

Once the patient is eating and drinking, is ketone free and the pH is within normal range - the patient can stop the sliding scale. Note that even whilst patients are on IV insulin, their usual basal insulin regime should typically be continued.

4. Treatment of other conditions present

If an infection is suspected or there is no obvious precipitant to the DKA, it is reasonable to commence broad-spectrum prophylactic antibiotics. If the patient is drowsy and vomiting, it may be appropriate to place a nasogastric tube to prevent aspiration. Other precipitants e.g. MI, pancreatitis should involve referral to the relevant specialties.

Classification of ketone-prone diabetics: DKA occurs in Type II Diabetes Mellitus

Type I diabetes is associated with beta-cell autoimmunity and a combination of positive antibody levels (e.g. ICA, GADA and IA-2A). Conversely, Type II diabetes is associated with poor beta-cell secretory capacity but with detectable C-peptide levels. Classically, type I diabetes should be autoantibody positive but beta-cell function negative (A+B-) and type II diabetes autoantibody negative but beta-cell function positive (A-B+).

It has long been assumed that DKA exclusively presents in type I diabetics however, one small study conducted in the USA found that up to 50% of DKA presentations in an older adult population occurred in people with type II diabetes (9). Similar mechanisms were thought to exist, where long-standing type II diabetes patients have a complete loss of beta-cell function. However, some patients present within a few years of diagnosis where complete beta-cell dysfunction is unlikely (10).

It has therefore been suggested that these patients have a relative insulin deficiency arising from constant hyperglycaemia secondary to poor diabetic control and the presence of stressors cause increased lipolysis by counter-regulatory hormones e.g. glucagon (11). Improvement in C-peptide levels following resolution of DKA suggests an improvement in beta-cell function and therefore its measurement could be useful in differentiating type I or II diabetes in those patients, like the case above, first presenting with DKA (9).

Euglycaemic ketoacidosis

This is defined as DKA without marked hyperglycaemia and is considered rare, although this may be as a result of under-recognition and under-reporting. It has been shown to be triggered by food restriction, alcohol intake, inhibition of gluconeogenesis and partial treatment of DKA (8). Sodium-glucose co-transporter 2 (SGLT-2) inhibitors have also recently been described as causing euglycaemic ketoacidosis (12).

The link between SGLT-2 inhibitors and DKA

In 2015, the European Medicines Agency issued a warning about an increased risk of DKA in patients prescribed SGLT-2 inhibitors (12). Whilst SGLT-2 inhibitors are currently only licensed for use in type II diabetes, there have been a few cases of DKA in these patients after initiation of a SGLT-2 inhibitor (12). The majority of cases however, are seen in patients with type I diabetes taking the medication 'off-licence'. The precise factors predisposing individuals to develop DKA remain unknown (13). If patients have a long history of type II diabetes (and possibly a reduced beta cell reserve) and/or if insulin is reduced on initiation of an SGLT-2 inhibitor, clinicians should be wary of DKA.

DIABETIC KETOACIDOSIS: A CASE BASED DISCUSSION

B Anderson, K Shotliff

Conclusion

DKA is a medical emergency that is both costly for the NHS and still has a significant mortality. Adhering to protocols significantly reduces time spent in DKA and length of inpatient stay. Further, attempting to classify diabetes as either type I or II following DKA should aid the optimisation of individual blood glucose control. We hope that summarising the most currently accepted management plan here for foundation doctors will improve future patient care and reduce the burden on both the NHS and patients.

SBA / MCQs

1. The first priority / treatment needed in a person presenting with diabetic ketoacidosis, is:

a. Sodium replacement

b. Potassium replacement

c. Magnesium replacement

d. Fluid replacement

e. Insulin replacement

2. In a patient with suspected diabetic ketoacidosis, the following results confirm the diagnosis of DKA if:

a. Blood glucose, 9 mmol/l, Serum ketones, 0.1 mol/l, Venous pH 7.40

b. Blood glucose, 19 mmol/l, Serum ketones, 2.5 mol/l, Venous pH 7.35

c. Blood glucose, 29 mmol/l, Serum ketones, 3.5 mol/l, Venous pH 7.10

d. Blood glucose, 39 mmol/l, Serum ketones, 1.5 mol/l, Venous pH 7.38

e. Blood glucose, 49 mmol/l, Serum ketones, 2.0 mol/l, Venous pH 7.41

3. Acute fluid therapy used in Diabetic Ketoacidosis, should start with:

a. 5% dextrose

b. Dextrose saline (0.18% sodium chloride, 4% glucose)

c. 0.9% sodium chloride

d. Hartmann's Solution

e. 1.26 % Sodium bicarbonate

4. In a 55 year old overweight Afro-Caribbean man with a family history of type 2 diabetes, presenting with diabetic ketoacidosis and newly diagnosed diabetes mellitus, you would expect to see:

a. Positive islet cell and anti-GAD antibodies, and detectable C peptide

b. Positive islet cell and anti-GAD antibodies, and no detectable C peptide

c. Negative islet cell and anti-GAD antibodies, and detectable C peptide

d. Negative islet cell and anti-GAD antibodies, and no detectable C peptide

5. In a 100 kg 25 year old male, we would expect their fluid (water) deficit during an episode of diabetic ketoacidosis to be:

a. 1 litre

b. 5 litres

c. 10 litres

d. 15 litres

e. 20 litres

Answers:

1. Correct answer is D

Fluid replacement is the first treatment and priority needed in these patients as they are significantly fluid depleted, as they are significantly fluid depleted. Typically, 0.9% sodium chloride with no added potassium is started as soon as DKA is diagnosed. Insulin and potassium replacement are commenced following fluid resuscitation.

2. Correct answer is C

DKA is typically diagnosed with a glucose >11 mmol/L, serum ketones >3.0 mmol/L and a pH <7.30

3. Correct answer is C

Initially give 1 litre of 0.9% sodium chloride over 1 hour, without added potassium. When fluids containing potassium are given rapidly, i.e. in less than 2 hours, there is a risk of causing cardiac arrhythmias. Potassium is added to subsequent bags of fluid depending on the rate and potassium blood test results. Crystalloids like 0.9% sodium chloride, rather than colloids, are preferred initially, due to a potential increased morbidity and mortality seen in this situation with colloid contacting regimens.

DIABETIC KETOACIDOSIS: A CASE BASED DISCUSSION

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4. Correct answer is C

In ketosis prone type 2 diabetes, which is not an unusual finding in this patient group, autoimmune markers such as ICA/islet cell antibodies and anti-GAD antibodies. As these patients have some residual pancreatic tissue and often take oral agents rather than insulin, once over the acute insult causing the DKA, typically they will also have detectable C-peptide levels.

5. Correct answer is C

Typical deficits in an adult with Diabetic Ketoacidosis are:

Water - 100ml/kg

Sodium - 7-10mmol/kg

Chloride - 3-5mmol/kg

Potassium - 3-5mmol/kg

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References

1. Dhatariya, K., Skedgel, C. & Fordham. R. The cost of treating diabetic ketoacidosis in the UK: a national survey of hospital resource use. The Journal of Diabetic Medicine. 2017;34: 1361-1366.

2. Barranco, R.J., Gomez-Peralta, F., Abreu, C., Delgado-Rodriguez, M., Moreno-Carazo, A., Romero, F. et al. Incidence, recurrence and cost of hyperglycaemic crises requiring emergency treatment in Adalusia, Spain. Diabetic Medicine. 2017; 34: 966-972.

3. Shotliff, K. & Fountain, A. Oxford Desk Reference Acute Medicine: Chapter 10 Diabetes and Diabetes coma. Oxford University Press; 2016.

4. Joint British Diabetes Societies Inpatient Care Group. The management of diabetic ketoacidosis in adults: Second edition. http://www.diabetologists-abcd.org.uk/JBDS/JBDS.htm. 2013. Last accessed 14th October 2017.

5. Kempegowda, P., Coombs. B., Nightingdale, P., Chandon, J.S., Al-Sheikhli, J., Shyamanur, B. et al. Regular and frequent feedback of specific clinical criteria delivers a sustained improvement in the management of diabetic ketoacidosis. Clinical Medicine. 2017; 17(5): 389-394.

6. Gouivea, C.F. & Chowdhury, T.A. Managing hyperglycaemic emergencies: an illustrative case and review of recent British guidelines. Clinical Medicine. 2013; 13(2):160-162.

7. Chowdry T.A., Cheston, H. & Claydon, A. Managing adults with diabetes in hospital during an acute illness. BMJ. 2017; 528.

8. Kitabchi, A.E., Umpierrez, G.E., Miles, J.M., Fisher, J.N. Hyperglycaemia crises in adult patients with diabetes. Diabetes Care. 2009; 32:1335-1343.

9. Maldonado, M., Hampe, C.S., Gaur, L.K., D'Amico, S. Iter, D., Hammerle, L.P. et al. Ketosis-Prone Diabetes: Dissection of a heterogeneous syndrome using an immunogenetics and beta-cell functional classification, prospective analysis and clinical outcomes. The Journal of Clinical Endocrinology and Metabolism. 2003; 88(11): 5090-5098.

10. Newton, C.A. & Raskin, P. Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus: clinical and biochemical differences. Archives of Internal Medicine. 2004; 164:1925-2931.

11. Poitout V. Glucolipotoxicity of the pancreatic cell: myth or reality? Biochemical Society Trans. 2008; 36:901-904.

12. European Medicines Agency. Review of diabetes medicines called SGLT2 inhibitors started. http://ema.europa.eu/docs/en_GB/document_library/referrals_document/SGLT2_inhibitors_20/procedure_started/WC500187926.pdf. 2015. [Last accessed 17th October 2017].

13. West, K., Webb, L.A., Fenech, M. & Dhatariya. K. Possible risk factors for the development of sodium-glucose co-transporter 2 inhibitor-associated diabetic ketoacidosis in type 2 diabetes. The British Journal of Diabetes. 2016; 16: 78-81.

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HYPONATRAEMIA & CONFUSION

H Mackay, S Rajbhandari

Abstract

Hyponatraemia is defined as a serum sodium level below 135mmol/L. It is commonly encountered by junior doctors in clinical practice, especially on the wards. It is important to take the correct approach to work out the cause. A full history and examination should be carried out, including all relevant investigations.

Hyponatraemia is divided into hypovolaemic, euvolaemic and hypervolaemic. The treatment varies for each type of hyponatraemia, so it must be assessed carefully. Mismanagement of hyponatraemia can cause coma, seizures and even death. Rapid elevation of serum sodium may cause 'osmotic demyelination syndrome'.

In this article we will cover a case discussion, which highlights the importance of the identification of hyponatraemia and treating the root cause.

Case History

A 55 year old female patient presented to her General Practitioner (GP) with a 2 day history of dry cough and left sided pleuritic chest pain. She was sent to hospital for an urgent chest X-ray. The X-ray was reviewed (Figure 1) and she was advised to go straight to the Emergency Department.

On arrival, she was alert, although appeared a little disorientated. She is an ex alcoholic, with a past medical history of alcoholic liver disease and alcohol related memory impairment. She takes thiamine daily and is on no other medication. She is an ex smoker of 15 pack years.

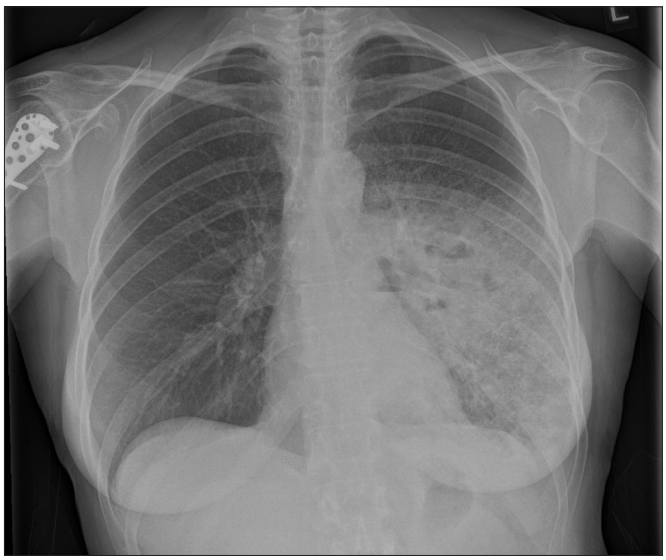

Figure 1: Chest X-ray showing consolidative changes with evidence of cavitation in the left lower lobe.

Full clinical examination was normal apart from reduced air entry in the left base on chest auscultation. Her oxygen saturation was 97% with respiratory rate of 24/minute. Pulse rate was 100/minute, her blood pressure was 104/57 mmHg and temperature was 35.7°C. Initial laboratory results showed neutrophilic leucocytosis with raised CRP (Table 1).

Test	Value	Ref Range
WBC	25.75 $x10^9$/L	4.00 - 11.00 $x10^9$/L
Hb	118 g/L	115 – 165 g/L
Platelets	620 $x10^9$/L	140 – 440 $x10^9$/L
Neutrophils	22.84 $x10^9$/L	1.60 – 7.50 $x10^9$/L
Sodium	126 mmol/L	133 – 146 mmol/L
Potassium	3.6 mmol/L	3.5 – 5.3 mmol/L
Urea	1.9 mmol/L	2.5 – 7.8 mmol/L
Creatinine	39 µmol/L	45 – 84 µmol/L
eGFR	>90	n/a
CRP	291 mg/L	<5.0 mg/L
Glucose	6.7 mmol/L	3.5 – 6.0 mmol/L
Bilirubin	15 µmol/L	0 – 21 µmol/L
GGT	55 U/L	0 – 42 U/L
ALP	101 U/L	30 – 130 U/L
Albumin	29 g/L	35 – 50 g/L
INR	1.4	1.0
Corr Calcium	2.30 mmol/L	2.20 – 2.60 mmol/L
Phosphate	1.16 mmol/L	0.80 – 1.50 mmol/L

Table 1: Initial investigation results showing raised white cell count, predominantly neutrophilic with raised CRP.

She was diagnosed with a left sided pneumonia with CURB65 score of 2, however due to her marked neutrophilia and hyponatraemia she was admitted to the Medical Unit. She was started on intravenous (IV) antibiotics – coamoxiclav and clarithromycin. She felt better with the antibiotic regime however her inflammatory markers did not improve.

A CT thorax was performed which showed "consolidative changes with evidence of cavitation in the left lower lobe". Bronchoscopy showed irregular mucosa and biopsies taken from that site confirmed small cell lung cancer. She was referred to the multi-disciplinary team, but remained in the respiratory ward for treatment.

Two weeks into her admission she became hyponatraemic. Her sodium had fallen to 112mmol/L. When the junior doctor assessed the patient, she was found to be well hydrated (but not fluid overloaded) and her observations were stable. It was thought that the hyponatraemia was caused by the progression of her lung cancer. She was put on a strict fluid restriction. Despite this, her sodium dropped further to 104mmol/L within another three days, and she became confused.

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She was able to follow commands and engage in conversation, however seemed forgetful. One day she walked to her own home without any warning. At this point a 'Deprivation of Liberty Safeguards' (DoLS) was put in place, as she lacked the mental capacity for the decision to accept treatment and stay in hospital. Her hyponatraemia improved with treatment. She was discharged when she was stable and chemotherapy for the small cell lung cancer was planned as an outpatient. However, she has had frequent admissions for hyponatraemia since.

Hyponatraemia

Hyponatraemia is defined as a serum sodium below 135mmol/L (1). It is found in 15-30% of acute hospital admissions and is particularly prevalent in intensive care and in the elderly. It is common in patients with respiratory tract infections, alcohol excess and those on thiazide diuretics (2). Hyponatraemia is caused either by the inability of the kidney to excrete water, or due to excess water intake. Therefore, it is important to clarify the exact type and the cause of the hyponatraemia so that appropriate treatment can be started.

Approach to Hyponatraemia

Treatment of hyponatraemia will take into account the cause, the volume status of the patient and the severity of symptoms. When approaching a patient with hyponatraemia, the following must be considered:

1. Potential for artefact: has the sample been taken from a site near IV fluids?

2. Ensure the correct sample has been tested for the correct patient

3. Repeat the sample if in doubt (send as urgent)

Once hyponatraemia is confirmed, the volume status of patient should be assessed. History of vomiting or diarrhoea, diuretic use, state of mucous membrane, skin turgor, dependent oedema, blood pressure, fluid balance chart and renal function will give clue to the hydration status of the patient. The patient can be hypovolaemic, hypervolaemic or euvolaemic. The most efficient methods of assessing fluid balance are:

- *Clinical examination: assessing oedema (peripheral, pulmonary), the JVP (jugular venous pulse), tissue turgor and mucous membranes (moist/dry). This is relatively quick and easy to do, however lacks specificity as it is difficult to quantify.*

- *Input/output chart: this is normally completed by nursing staff on request by the medical team. It takes into account measures such as IV and oral fluids (including medications), urine output, vomiting and fluid lost through drains. It is easy to quantify volume however does not take insensible losses into account (sweating, loss from burns etc.).*

Symptoms of Hyponatraemia

Symptoms of hyponatraemia can be classified into moderate and severe. Moderate symptoms are:

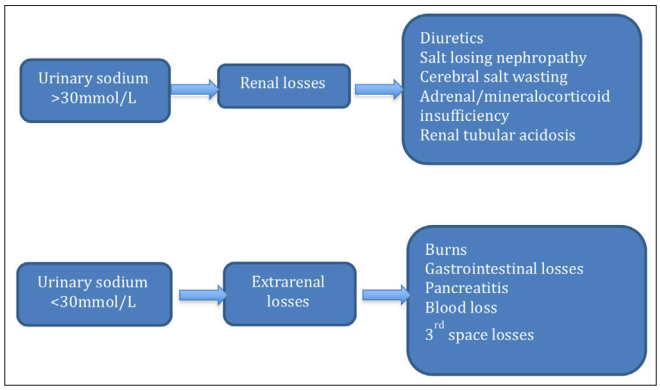
- *Headache*
- *Nausea and vomiting*
- *Marked confusion*

Severe symptoms are:

- *Vomiting*
- *Mood changes*
- *Seizures*
- *Decreased level of consciousness/coma*

Hypovolaemic (reduced extracellular fluid) Hyponatraemia

Hypovolaemic hyponatraemia is most often due to sodium loss through either the renal system (use of diuretics) or gastrointestinal system (vomiting or diarrhoea). Patients often have low blood pressure, reduced skin turgor, dry mucous membranes and disproportionally raised blood urea. In difficult cases the source of sodium loss can be confirmed by measuring spot urinary sodium. The result of this (Box 1) will show whether the hyponatraemia is due to the renal loss of sodium, or extrarenal loss (3).



Box 1: Spot urinary sodium excretion measurement to confirm source of sodium loss in Hyponatraemia with a urine osmolality >100mOsm/kg.

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How to perform fluid restriction

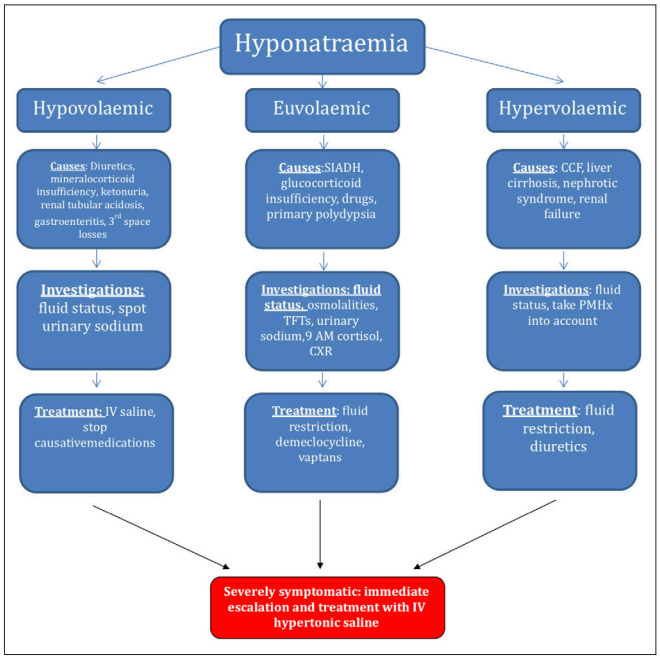
- Give patient their allowed fluid (eg 1000 ml) as water in a jug in the morning.
- They are instructed to drink only that amount in 24 hours.
- If the patient is confused, drinks should be given when requested/ required and the total volume added up on the fluid balance chart.
- Fluid input and output chart should be accurately maintained and monitored.
- It is vital that fluid administered intravenously is taken into account on the fluid balance chart.
- Daily weight measurement should be performed.
- Monitor urea and electrolytes daily.

Box 2: Fluid Restriction is commonly advised but often poorly performed. Effective fluid restriction can be achieved as above.

Bedside Osmolality Calculation

- 2 x (Na (mmol/L) + K (mmol/L)) + Urea (mmol/L) + Glucose (mmol/L).
- Eg: Calculated serum osmolality from table 1 will be 2 x (126 + 3.6) + 1.9 + 6.7 = 267.8 mOsm/kg

Box 3: Bedside calculation of serum osmolality. Values below 275 are abnormal. This should be confirmed with laboratory measurement of serum osmolality.



Box 4: Hyponatraemia causes & treatment.

Treatment of hypovolaemic hyponatraemia is with intravenous normal saline. This should be given slowly (eg 2 litre of normal saline in 24 hours) in the presence of heart failure or renal failure. On the other hand, if there is Acute Kidney Injury or low blood pressure, it should be given rapidly as a bolus (eg 250 ml of normal saline per hour) with hourly observation of urine output and hydration status.

Hypervolaemic (increased extracellular fluid) Hyponatraemia

Hypervolaemic hyponatraemia is caused by a marked increase in total body water, which creates a dilutional effect on total body sodium. There will usually be peripheral oedema present. Causes of hypervolaemic hyponatraemia are:

- *Congestive cardiac failure (CCF)*
- *Liver cirrhosis*
- *Nephrotic syndrome*
- *Renal failure*

Treatment of this condition is fluid restriction (Box 2) and cautious use of diuretics (2).

Euvolaemic (normal extracellular fluid) hyponatraemia:

This is defined as hyponatraemia with expanded intracellular fluid. There is no oedema present. Causes include:

- *Thiazide diuretics*
- *Hypothyroidism*
- *Adrenal insufficiency*
- *Excessive beer consumption/tea and toast diet*
- *SIADH (syndrome of inappropriate antidiuretic hormone secretion)*

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Occasionally, serum sodium can be low due to marked increase in lipid, protein or other solutes. The osmolality will be normal or slightly raised when directly measured. This is called pseudohyponatraemia. The most common example in clinical practice is hyperglycaemia. Recognition and treatment of the underlying disorder improves hyponatraemia in such cases. Treatment of euvolaemic hyponatraemia is usually with fluid restriction to 1000 ml per day (Box 2) or hypertonic saline in patients with moderate to severe symptoms.

Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH)

There are many causes of SIADH. This causes the body to excrete inappropriately concentrated urine. It is characterised by normal renal and adrenal function, with no oedema or hypovolaemia. Hyponatraemia in this case is the result of excessive ADH release, which increases renal water reabsorption.

The diagnosis of SIADH is usually one of exclusion. Pituitary, adrenal, thyroid and renal pathology must be excluded, the patient should not be on diuretics and should be clinically euvolaemic. To confirm diagnosis, the serum and urinary osmolarities must be tested. The diagnostic criteria are as follows:

- *Serum osmolarity <270mosm/l (low)*

- *Urinary osmolarity >100 mosm/l (high)*

Typically urinary sodium concentration is >30 mmol/L in SIADH. Serum osmolality can be calculated at bedside using a simple equation (Box 3) but for accurate measurement the sample must be sent to the laboratory. Investigations such as thyroid function tests (TFTs), 9 AM cortisol and a chest X-ray will help to exclude other causes of euvolaemic hyponatraemia (4). The causes of SIADH are outlined in Table 2 (5).

Malignant	Lung cancer is most common but other malignancies such as that of the pancreas, ureter, stomach, testicles
Pulmonary	Pneumonia, abscess, empyema, ventilation
Central Nervous System	Tumours, abscess, meningitis, encephalitis, intracranial haemorrhage, traumatic brain injury, demyelination
Drugs	Many drugs can cause SIADH. The most common drugs in daily practice are: SSRIs, Tricyclic antidepressants such as amitryptiline, haloperidol, illicit drugs such as ecstasy, oxytocin, carbamazepine, chemotherapeutic agents such as Vincristine and cyclophosphamide.
Post-operative	Most common following pituitary surgery but may occur following any surgical stress.
Other	HIV, idiopathic, iatrogenic

Table 2

Management of Hyponatraemia

The management of hyponatraemia is treatment of the cause (Box 4). Low blood pressure, acute kidney injury and neurological manifestations need close monitoring and urgent treatment. Severe hyponatraemia is a life threatening condition and can cause cerebral oedema. Once the volume status of the patient has been assessed (hyper, hypo or euvolaemic) then the appropriate treatment regime can be commenced (Box 4).

A thorough assessment of the patient's medical and drug history is important, as causative medications should be stopped. If the symptoms are severe then urgent senior assistance should be sought immediately from the medical registrar, renal team or intensive care team. The treatment for severely symptomatic hyponatraemia is IV hypertonic saline (Table 3).

If symptoms are mild to moderate then medical interventions can be used on the ward such as fluid restriction, diuretics, demeclocycline and IV normal saline (Box 4). Assistance should still be sought from a senior colleague, as often these cases can be complex to manage.

Method	Notes
Fluid Restriction	Restrict the patient to 1000mls of fluid per day, taking into account oral and IV fluids.
Normal Saline	This is useful if the patient is dehydrated (hypovolaemic).
Hypertonic Saline	In severe hyponatraemia (Na < 125) with severe symptoms or neurological manifestation, an infusion of 150ml 3% hypertonic saline should be given over 20 minutes. Serum sodium should be checked after 20 minutes, with an aim to increase the sodium by 5 mmol/L. Cycles are to be repeated so serum sodium increases by 5mmol/L, and stopped when this has been achieved. Serum sodium should increase by <10mmol/L in 24h and <18mmol/L in 48hrs
Demeclocycline	A tetracyclic antibiotic that causes nephrogenic diabetes insipidus by impairing action of ADH in the kidney. This is rarely used in clinical practice due to uncertainties over its safety.
Vaptans	Vasopressin receptor antagonist. It acts on vasopressin receptors in the collecting duct therefore increasing solute free water excretion by the kidneys. Serum sodium should be closely monitored. This is rarely used in practice due to concerns over its safety. Vaptans commonly increase sodium by too rapidly, which is also dangerous for the patient.

Table 3: The methods that can be used in the management of hyponatraemia are outlined in the table below.

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Abbreviations

ADH – Antidiuretic Hormone

CURB 65 – measure of severity in pneumonia: Confusion (yes or no), Urea (>7mmol/l), Respiratory rate (>30), Blood pressure (systolic <90mmHg or diastolic <60mmHg), Age (>65). Score 1 point for each criteria fulfilled.

- *Score 0 -1: low risk, consider home treatment*
- *Score 2: consider hospital treatment or close supervision*
- *Score >3: inpatient management, severe pneumonia, high mortality risk*

DoLS – deprivation of liberty safeguards

ABCDE – airway, breathing, circulation, disability, exposure

There have been concerns over the safety of demeclocycline and vaptans, therefore they should only ever be used under specialist advice.

Neurological Manifestation of Hyponatraemia

Neurological manifestation of hyponatraemia depends upon the cerebral adaptation to the serum sodium. If there is acute hyponatraemia (< 48 hours) the brain cells swell due to osmotic effect, which causes cerebral oedema. In mild cases it manifests as confusion and drowsiness, but may lead to fits and coma. As the skull is a compact structure, if the cerebral oedema is severe, it can cause death due to brain herniation.

The use of party drugs containing NMDA (eg Ecstasy) can cause mild SIADH and if compounded with excess water intake, it causes acute hyponatraemia and can lead to seizures, coma and death. Acute hyponatraemia is also seen in the postoperative state where stress causes a mild SIADH. It is often worsened by giving intravenous dextrose as fluid replacement. On the other hand, patients can adapt very well to chronic hyponatremia.

In such cases sudden correction in serum sodium with overzealous therapy can cause osmotic demyelination (8). Osmotic Demyelination Syndrome is a serious condition caused by the rapid increase of sodium in the blood. It can lead to confusion, cranial nerve defects, quadriplegia, coma and death. Correction of serum sodium levels should never exceed 0.5mmol/L/hr (i.e. 12mmol in 24 hours). (6)

Management of our Case

Our patient was diagnosed with SIADH and started on chemotherapy for small cell lung cancer. Due to her being haemodynamically stable and not having a renal team on site, the following treatment pathway was followed on the respiratory ward:

1. The patient was fluid restricted to 1litre. This had no effect on her sodium levels and was difficult to observe due to her marked confusion. She did not understand the need for the restriction and was filling her own water jug up in the ward bathroom.

2. Demeclocycline was tried first as use of tolvaptan is restricted by our local health authority due to cost. Despite several days of treatment there was no effect on her sodium levels.

3. Lastly, tolvaptan was tried. A single dose brought her sodium up from 113mmol/L to 127mmol/L, which is dangerously fast. Tolvaptan was stopped immediately and the sodium levels remained at a satisfactory level and the patient was discharged.

Since then, the patient has had frequent readmissions for confusion and feeling unwell due to hyponatraemia. As the root cause of her hyponatraemia is the small cell lung cancer, causing SIADH, the only way to prevent further episodes is to treat the cancer with chemotherapy, which she is now receiving.

Hypertonic saline treatment could have been given for euvolaemic hyponatraemia with moderate to severe symptoms caused by SIADH if it is available and close monitoring is possible:

- *Give 150ml infusions of 3% sodium chloride over 20 minutes.*
- *A 5mmol/L increase in the serum sodium may be enough to improve symptoms.*
- *Infusions should be repeated until serum sodium has increased by 5mmol/L.*
- *Infusions should be given in intensive care or a high dependency unit.*
- *After the increase in sodium has been achieved, cause-specific treatment should be commenced.*
- *Serum sodium should increase by <10mmol/L in the first 24 hours and <18mmol/L in the first 48 hours.*
- *Urea and Electrolytes should be monitored daily once this has been achieved. (6)*

HYPONATRAEMIA & CONFUSION

H Mackay, S Rajbhandari

Test Yourself

1. Which of the following conditions would lead to a hyponatraemia with urinary sodium >20mmol/L?

a. Pancreatitis

b. Dehydration

c. Liver cirrhosis

d. CCF

e. Diuretic use

2. Which of the following is the first line treatment for hypervolaemic hyponatraemia?

a. Tolvaptan

b. Fluid restriction/diuretics

c. Demeclocycline

d. IV saline

e. ACE inhibitors

3. You are called to see a patient who is confused and vomiting. Observations: BP 93/64, HR 96, sats 99%, temperature 36.9C. Blood tests reveal the patient is hyponatraemic with a sodium of 118mmol/L. What is the most appropriate first line treatment for this patient's hyponatraemia?

a. IV 0.9% saline

b. Diuretics

c. Tolvaptan

d. Hypertonic saline

e. Haemodialysis

4. What is the target rate for increasing serum sodium in the treatment of hyponatraemia?

a. >0.5mmol/L/hr

b. 5mmol/L per day

c. <0.5mmol/L/hr

d. 12mmol/L/hr

e. 20mmol/L per day

5. Which of the following drugs is most likely to cause hyponatraemia?

a. Paracetamol

b. Amlodipine

c. Salbutamol

d. Carbamazepine

e. Prednisolone

HYPONATRAEMIA & CONFUSION

H Mackay, S Rajbhandari

Answers to Questions

1. E

Diuretic use. Use of diuretics (especially thiazide diuretics) causes a renal loss of sodium. Therefore when urinary sodium is measured it will be >20mmol/L.

2. B

Fluid restriction/diuretics. Always aim to cause a negative fluid balance. This must be closely monitored and includes oral and IV fluid intake.

3. A

IV 0.9% saline. This patient is hypovolaemic (likely due to vomiting) and will need rehydration therapy to rectify the sodium. Always remember to use ABCDE approach to a sick patient and manage life threatening conditions promptly.

4. C

<0.5mmol/L/hr. If the serum sodium is increased any faster than this, there is a risk of osmotic demyelination syndrome. This can lead to coma, seizures and death. Check the U+Es at least every 6 hours to try and avoid this.

5. D

Carbamazepine. Carbamazepine increases ADH release (1), therefore creates a state of SIADH, causing euvolaemic hyponatraemia.

Appendix

When to call the registrar:

1. If the patient is symptomatic e.g. acute confusion, seizures

2. If the serum sodium decreases/increases by > 12mmol/L per day

3. If the patient has not responded to first line treatment e.g. fluids/fluid restriction

4. If the patient has not responded to omission of causative medications.

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References

1. Niceorguk. 1. Niceorguk. [Online]. Available from: https://cks.nice.org.uk/hyponatraemia [Accessed 10 August 2017].
2. Biswas, M, Davies, J.S. Hyponatraemia in Clinical Practice. Postgrad Med J. 2007;83(980): 373-378.
3. Reynolds, R.M, Seckl, J.R. Hyponatraemia for the clinical endocrinologist. Clinical Endocrinology. 2005;63(1): 366-374
4. Schwartz, W.B, Bennett , W, Curelop, S, Bartter, F.C. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med. 1957;23(4): 529-542
5. Thompson, C.J, Crowley , R.K. Hyponatraemia. J R Coll Physicians Edinb. 2009;39(1): 154-7.
6. Spasovski G et al; Clinical practice guideline on diagnosis and treatment of hyponatraemia. European Journal of Endocrinology 2014; 170: G1 – G47)

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NERVE BLOCKS IN PALLIATIVE CARE

V Potter, D Feuer

Abstract

Although the majority of patients with advanced cancer have their pain well controlled with the use of analgesic medications, there remains a subset for whom this is not the case. This may be because their pain is resistant to analgesics and/or because escalating doses of opioids are leading to intolerable side effects or toxicity. In these circumstances, interventional pain techniques should be considered. This article looks at what nerve blocks are, when to refer and discusses a case study focusing on a specific example of the coeliac axis block.

Introduction

The World Health Organisation (WHO) defines palliative care as ''an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual'' (1).

In clinical practice, whether in the hospital, hospice or community setting, one of palliative care's main roles from the medical perspective is pain control. This is achieved with the use of non-pharmacological techniques (for example, radiotherapy, surgical procedures, massage) and pharmacological approaches, as well as addressing any contributing psycho-social factors.

Not all palliative care patients, whether they have a malignant or non-malignant condition, experience pain. However, a large proportion do and it has been reported that pain occurs in up to 70% of patients with advanced cancer and about 65% of patients dying of non-malignant disease (2).

Looking specifically at cancer, it is estimated that in those with an advanced malignancy who do have pain, this can be managed in 80-90% of patients using conventional analgesia and adjuvant medications (table 1). Prescribing should be according to the principals of the WHO analgesic ladder (figure 1).

Step 1 analgesics include paracetamol, step two, the weak opioids such as codeine preparations and tramadol and step three, the strong opioids such as morphine, oxycodone and fentanyl. However, this leaves approximately 10% of patients who have pain which remains difficult to control (3). At this point, we need to consider interventional techniques which include nerve blocks.

Conventional analgesia	*Adjuvant agents*
Paracetamol	Antidepressants
NSAIDs	Anticonvulsants
COX2 inhibitors	Corticosteroids
Opioids	Bisphosphonates
	Muscle relaxants
	Anasesthetic agents

Table 1: Examples of conventional and adjuvant analgesia.

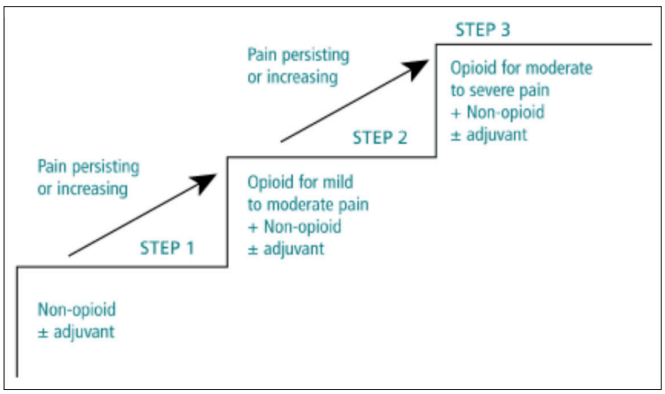


Figure 1: WHO ladder.

Nerve blocks

A nerve block is any deliberate interruption of a signal travelling along a nerve, often for the purpose of pain relief. One way they can be classified is on the basis of length of the effect (table 2).

Type of block	Length of block	Mechanism
Short term	Hours to days	Injection of agent
Long term	Weeks to months	Injection of agent
Permanent	Several months – indefinite	Division of nerve or removal of nerve, injection of agent, physical damage e.g. heat

Table 2: Classification of nerve blocks.

Nerve blocks may also be thought of in terms of the type of nerve being targeted. Local or regional nerve blocks affect a specific area of the body e.g. a femoral nerve block to anaesthetise the leg. These blocks also include epidural and spinal blocks (4).

Sympathetic nerve blocks are for neuropathic pain with a sympathetic component. Sympathetic nerves control involuntary bodily functions whereas the somatic nervous system is responsible for voluntary skeletal muscle control and reflexes. In disease sympathetic nerve can send signals causing pain.

Blocking these nerves involves interrupting nerve transmission over a large area and are performed at the ganglion or plexus. Commonly used agents include an opioid and local anaesthetic and sometimes a steroid. If permanent damage is desired, the nerve is destroyed often with alcohol or phenol and sometimes hypertonic saline5. Examples of nerve blocks are given in table 3.

NERVE BLOCKS IN PALLIATIVE CARE

V Potter, D Feuer

Peripheral nerve/plexus block examples
Femoral nerve block
Sciatic nerve block
Suprascapular nerve block
Lumbar plexus nerve block
Intrapleural nerve block
Autonomic nerve block examples
Coeliac plexus block
Stellate ganglion block
Lumbar sympathetic block
Superior hypogastric plexus block
Ganglion of impar block

Table 3: Examples of nerve blocks.

When To Consider Referring A Palliative Care Patient For A Nerve Block

Patients with pain who are not responding to their analgesic medications despite up-titration of the doses and the addition of adjuvant medications require consideration for nerve blockade. Often such patients will have already been referred to the palliative care team (or pain team) for advice regarding their pain control and despite this specialist input, their pain is not improving.

Patients who are intolerant to the side effects of their analgesic regimen should also be considered for referral for interventional pain techniques as the side effects they are experiencing will limit any further dose escalation or may mean cessation of the drug.

In addition, the pain the patient has should be localised or appear to be within the distribution of a nerve, although it is important to bear in mind referred pain which may confuse the clinical picture. Accumulating evidence highlights the opioid-sparing qualities and other benefits afforded by interventional techniques which include decreasing medication-induced side effects, reducing the economic burden of poor analgesia and overall improvement in quality of life of the patients with painful malignant disease (6).

Case Study

Mr L is a 42y gentleman with a diagnosis of metastatic pancreatic adenocarcinoma. He has been under the oncologists for 1 year and his disease has progressed through multiple lines of chemotherapy. He now has multiple liver and peritoneal metastases. Mr L is experiencing symptoms of nausea, fatigue but most debilitating of all, severe upper abdominal pain. There is a constant background pain scored at 5 to 6 out of 10 in severity with unprovoked episodes of more severe pain scored at 9 to 10 out of 10. The pain is described as burning, sharp and radiating though to the back.

Mr L's pain has worsened over the last few months. Two months ago the pain had been reasonably well controlled on co-codamol prescribed by his GP. However this then stopped being effective. When an inpatient in hospital under the oncologists, he had been referred to the palliative care team for a pain review and oral morphine had been commenced and the co-codamol stopped.

This was initially effective but then the dose needed to be up-titrated due to increasing pain levels. Unfortunately Mr L developed opioid toxicity necessitating the morphine being opioid switched to oxycodone. However, side effects including drowsiness and myoclonic jerks continued to be problematic.

Adjuvant medications were added including gabapentin and dexamethasone. This partially eased his symptoms but Mr L still remained in significant pain. After discussion with Mr L and his family, he was referred to the anaesthetic team for a coeliac nerve block. This was performed with a dramatic reduction in Mr L's pain and although he still required opioid analgesia, it was at a much lower dose which was not associated with any side effects.

The coeliac axis nerve block

A coeliac plexus block inhibits the autonomic supply to the upper gastrointestinal tract (figure 2) and can provide effective analgesia for patients with pancreatic and other upper gastrointestinal malignancies e.g. stomach, gallbladder, liver.

The technique of chemical ablation of the coeliac plexus was first described in 1914 and performed as an intraoperative procedure. Subsequently, it has been carried out under radiographic, fluoroscopic, computed tomography (CT) and ultrasonography imaging guidance. An endoscopic ultrasound-guided technique has most recently been introduced (7).

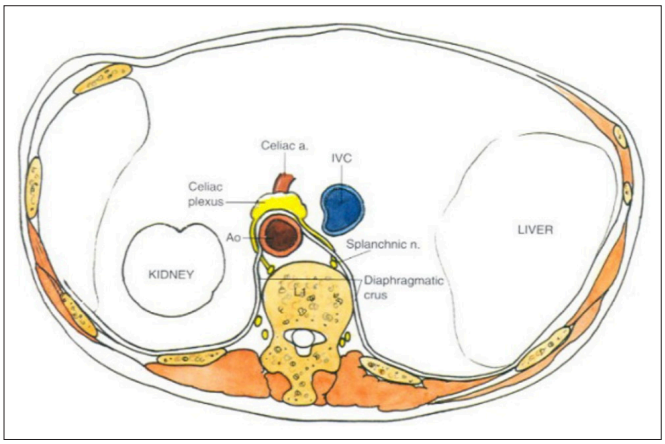


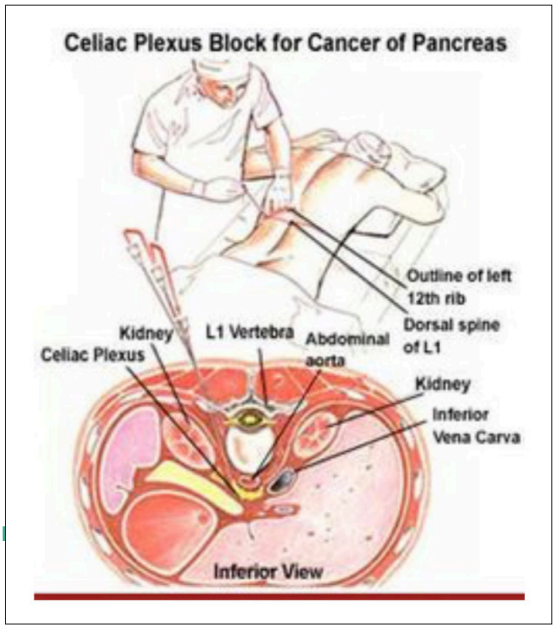
Figure 2: Anatomy of the coeliac plexus.

NERVE BLOCKS IN PALLIATIVE CARE

V Potter, D Feuer

The procedure when performed percutaneously is done under imaging guidance and may be undertaken by an interventional radiologist or an anaesthetist. The patient lies in the prone position and has local anaesthetic injected into the skin, with or without sedation. One or two fine needles are inserted just under the bottom of the ribcage and directed forward to lay just either side of the aorta in the area of the plexus (figure 3).

An alternative technique involves the deliberate passage of the needle through the aorta to end up just in front of it. Radio-opaque dye is injected though one of the needles to confirm the correct position followed by a local anaesthetic and then alcohol to first anaesthetise and then destroy the nerves.



The endoscopic procedure, involves passing an endoscopic ultrasound down the oesophagus whilst locating the aorta and tracing this to the coeliac trunk. At this point, the coeliac axis or plexus is located just above this area. Once in the coeliac area, a needle is passed though the scope into this region and the anaesthetic agents injected. The procedure usually takes approximately 15–20 minutes (8).

Contraindications to a coeliac axis block include bleeding and infection risk, where the source of the pain is no longer being transmitted through the autonomic nerves and in the presence of a large aortic aneurysm. However, some of these are relative contra-indications only, as in the palliative population, particularly for those with a limited prognosis and where improving quality of life is of paramount importance, it may well be that the potential benefits outweigh the risks. This highlights the need for assessing such patients on a case by case basis.

Risks and complications

Overall, particularly with the advent of image guided techniques, a coeliac axis block is a relatively safe procedure with major complications reported in less than 2% of patients (9).

Most of the complications are transient rather than permanent in nature. Hypotension can occur due to the blockade of sympathetic and parasympathetic nervous systems. For this reason intravenous fluids are administered before, during and after the procedure. Transient diarrhoea can be a problem due to the same mechanism.

Other risks include infection, bleeding due to aorta or inferior vena cava injury by the needle, intravascular injection (which should be prevented by checking the needle position with the dye) and upper abdominal organ puncture with abscess/cyst formation. Rare complications include paraplegia from injecting phenol into the arteries that supply the spinal cord (again, prevented by checking the needle position with dye), sexual dysfunction (due to injected solution spreading to the sympathetic chain bilaterally), intramuscular injection into the psoas muscle and lumbar nerve root irritation (secondary to injected solution tracks backwards towards the lumbar plexus) (10).

The procedure success rates differ from centre to centre. One paper quotes the successful relief of the pain of patients with pancreatic cancer and other abdominal malignancies can be expected in as many as 85% and 73% respectively (11). Some patients will experience total pain relief enabling their opioids to be weaned and stopped whilst in others their dose can at least be reduced. Unfortunately a small proportion will not have any benefit and this is a possible outcome of the procedure. The block can be repeated if necessary. The nerves will start to regenerate and so if appropriate, the procedure may need to be performed again in 6-9 months (8). However in disease progression of pancreatic cancer this is often not required.

Summary

In patients whose pain is proving difficult to control despite pharmacological and other measures, nerve blocks are an interventional technique to be considered. Palliative care patients often have a limited prognosis making effective pain control, thereby leading to improved quality of life, all the more important. An awareness of these procedures and when to refer for a specialist opinion is necessary knowledge when looking after individuals with symptoms secondary to progressive, advanced disease.

NERVE BLOCKS IN PALLIATIVE CARE

V Potter, D Feuer

MCQs

Q1. Which one of the following drugs is at step 2 of the WHO analgesic ladder?

1. Paracetamol

2. Codeine

3. Diamorpine

4. Gabapentin

5. Fentanyl

Q2. The autonomic nervous system is responsible for all of these functions except which one?

1. Heart rate

2. Respiratory rate

3. Visual accommodation

4. Gastrointestinal tract motility

5. Patellar reflex arc

Q3. Which one of these would be an indication for referral for a nerve block procedure?

1. 'all over' body pain described by patient

2. Patient is on step 2 of the WHO analgesic ladder and pain is starting to improve but is still present

3. Patient is on maximal doses of a number of analgesics including an opioid but with worsening pain

4. Patient's pain has been reviewed by the general medical team but not the palliative care or pain team

5. Patient is on step 1 of the WHO ladder with worsening symptoms

Q4. Which one of these statements is true?

1. A nerve block is guaranteed to last for the lifetime of the patient.

2. There is a 100% success rate in achieving good pain control for patients undergoing a nerve block.

3. A patient has to have a prognosis of at least 1 year to be considered for a nerve block.

4. The patient needs to understand the possible risks involved prior to undergoing a nerve block procedure.

5. Pain in palliative care patients with a malignancy is always due to the direct effect of the tumour(s).

Q5. In a coeliac axis block, which one of the following is NOT a contraindication?

1. Presence of a large aortic aneurysm

2. Markedly deranged coagulation studies

3. Presence of an active infection in the upper abdomen

4. A severe thrombocytopenia

5. Intolerable opioid side effects from current analgesic regimen

Answers

Q1. Answer 2

Paracetamol is a step 1 analgesic, diamorphine and fentanyl are strong opioids therefore step 3 and gabapentin is classified as an adjuvant.

Q2. Answer 5

The patellar reflex arc is controlled by the somatic nervous system which is responsible for voluntary skeletal muscle control and reflex arcs. The autonomic nervous system is responsible the remainder.

NERVE BLOCKS IN PALLIATIVE CARE

V Potter, D Feuer

Q3. Answer 3

This patient has been escalated on opioids and adjuvant analgesics to the maximum dose that is safe but has on-going pain; a nerve block should be considered in this case. Pain should be relatively well localised, the doctor needs to have trialled strong analgesia first to see if this is effective and ideally, the patient should have received a pain assessment from a member of the palliative care or pain team.

Q4. Answer 4

As with all procedures the patient needs to give informed consent which includes awareness of the risks involved. A nerve block often needs repeating after a period of time due to regenerating nerve fibres, the success rate is good in improving pain control but is not 100% and unfortunately in some patients, very little benefit is gained.

A prognosis of less than 1 year should not be a barrier to interventional pain techniques and it is important to maximise comfort in those with a short life expectancy. Pain in palliative care patients may be due to direct effects of the tumour but may be secondary to a range of different factors (e.g. post radiotherapy, post operatively, co-morbidities, psychosocial distress).

Q5. Answer 5

This would be an indication for a block, i.e. that the dose of the patient's opioid cannot be up-titrated any further. The others are all contraindications for undergoing the procedure, although each case needs to be considered individually particularly in palliative care patients.

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References

1. http://www.who.int/cancer/palliative/definition/en/

2. Colvin L, Forbes , Fallon M. Difficult pain. BMJ 2006; 332(7549):1081-1083

3. Chambers, WA. Nerve blocks in palliative care. Br J Anaesth 2008; 101 (1): 95-100

4. Hochberg U, Elgueta MF, Perez J. Interventional Analgesic Management of Lung Cancer Pain. Front Oncol 2017; 7 (17): doi:10.3389/fonc.2017.00017.

5. Koyyalagunta D, Engle MP, Yu J, Feng L, Novy DM. The Effectiveness of Alcohol Versus Phenol Based Splanchnic Nerve Neurolysis for the Treatment of Intra-Abdominal Cancer Pain. Pain Physician 2016; 19 (4): 281-92

6. Candido KD, Kusper TM, Knezevic NN. New Cancer Pain Treatment Options. Curr Pain Headache Rep 2017; 21 (12): doi:10.1007/s11916-017-0613-0

7. Yasuda I, Wang HP. Endoscopic ultrasound-guided celiac plexus block and neurolysis. Digestive Endoscopy 2017; 29: 455–462. doi:10.1111/den.12824

8. Gress F. Endoscopic ultrasound-guided celiac plexus block and neurolysis. Am J Gastroenterol 2001; 96(2):409-16.

9. Wong GY, Schroeder DR, Carns PE et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA 2004; 291(9):1092-9

10. Wang PJ, Shang MY, Qian Z, Shao CW, Wang JH, Zhao XH. CT-guided percutaneous neurolytic celiac plexus block technique. Abdom Imaging 2006; 31(6):710–718

11. Mercadante S, Nicosia F. Celiac plexus block: a reappraisal. Reg Anesth Pain Med 1998; 23(1):37-48

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PALLIATIVE CARE FOR PATIENTS WITH FRAILTY

R Benbow, F Hakkak

Abstract

We describe the case of a frail elderly lady, initially admitted to hospital acutely unwell, who was later transferred to a hospice for end of life care. This case illustrates the frailty illness trajectory and the difficulties with prognostication, and the supportive management required for common symptoms seen at the end of life.

Case History

An 89 year old lady, with a background of hypertension, chronic kidney disease stage 3, glaucoma, previous polymyalgia rheumatica and severe kyphoscoliosis, was admitted to hospital with new onset atrial fibrillation with rapid ventricular rate. Her medications included furosemide, morphine sulfate modified release, lercanidipine, mirtazapine, alendronic acid, and brinzolamide eye drops. She reported a general decline in health during the preceding year, and had moved into sheltered accommodation closer to her family 3 months prior to admission.

She had found it increasingly difficult to mobilise, with pain in her back and hips, and had had a number of falls which had led to decreased confidence in mobilising. She was currently able to mobilise short distances with the help of a frame. She had also suffered multiple urinary tract infections. Her appetite had decreased with subsequent weight loss, and she had recently had a computerised tomography (CT) scan of thorax/abdomen/pelvis investigating this which showed no sign of malignancy (see Image 1).

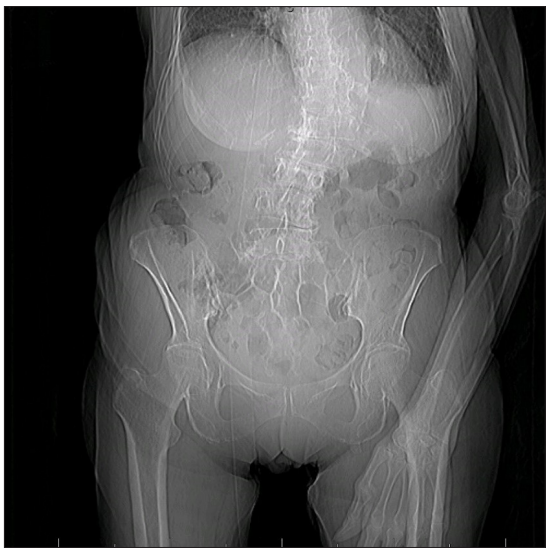

Image 1: CT prior to admission; reported as showing marked lumbar kyphoscoliosis and marked degeneration in lumbar spine and bony pelvis.

On admission, she was started on digoxin which was successful in controlling her heart rate. Following this she was deemed medically fit for discharge, but was unable to mobilise, managing only to transfer with assistance of two. Her mobility was limited by significant joint pain, which limited rehabilitation efforts. She was treated with an increasing dose of oral opioids for pain, but these were ineffective.

She reported a persistent low mood and her mirtazapine was increased. Due to her continued weight loss, she had an oesophago-gastro-duodenoscopy (OGD) which showed gastritis and presence of Helicobacter pylori, for which she was given eradication therapy. There was no change in symptoms or oral intake following this.

6 weeks after admission, she suddenly deteriorated, with her Glasgow Coma Scale (GCS) dropping to 8/15. No reversible cause was found for this and she was felt to be dying. Her medications were rationalised and she was started on a continuous subcutaneous infusion (CSCI) of morphine for ongoing analgesia.

She was transferred to the local hospice inpatient unit 2 weeks after her sudden deterioration for end of life care. In the intervening days, her clinical condition significantly improved, with her GCS returning to 15. On examination her pulse was 132 and irregular. She had significant sarcopenia. She reported that her joint pain had resolved following the introduction of CSCI analgesia, and she was keen to try to mobilise again. Her greatest wish was to return home mobile; but she accepted that she may not return to her baseline level of health. She felt that if she deteriorated again, she would not want to be transferred to hospital under any circumstances, and would want to die in the hospice.

Given her improved clinical condition, she was restarted on digoxin which was successful in rate controlling her atrial fibrillation. Her CSCI was stopped and she was converted to a fentanyl patch, which was successful in maintaining control of her background pain. She was reviewed by physiotherapy, but was unable to progress beyond standing with assistance for very brief periods, pain and confidence being the main barrier to mobility. She was given laxatives for troublesome constipation.

2 weeks after transfer to the hospice, she deteriorated again, with episodes of vomiting and abdominal pain. It was felt she had an element of mechanical bowel obstruction secondary to constipation, and she was given further bowel intervention and antiemetics. Despite this, she continued to deteriorate, becoming agitated at times.

Her oral medications were stopped as she became unable to swallow, and she was recommenced on a CSCI with levomepromazine 10mg for nausea, and midazolam 5mg for agitation. She was catheterised after developing urinary retention. Midazolam was gradually titrated up to 15mg due to persistent agitation. She died peacefully with her son present 2 weeks after the deterioration in her health. Her cause of death was given as 1a) Old Age.

PALLIATIVE CARE FOR PATIENTS WITH FRAILTY

R Benbow, F Hakkak

This lady's health gradually deteriorated in the last year of her life. There were various points of significant decline- falls at home, urinary tract infections, development of symptomatic atrial fibrillation and subsequent hospital admission- but this was set against a background of gradual decline, with decreased mobility and oral intake. Even when a reversible problem was found and treated, her overall health did not improve. She had been concerned that she had cancer in the months prior to her hospital admission, due to her loss of appetite and weight loss.

Subsequent investigations showed no signs of malignancy. In the two weeks prior to her death, she was treated with increased laxatives as it was felt constipation was causing an element of bowel obstruction, but despite her bowels opening her clinical condition did not improve. As a gradual decline in general health had been observed for a long period, and there was no identifiable disease or injury that caused the death, her cause of death was given as solely Old Age.

During her hospital admission, unable to walk and uncertain whether she would be able to return home, her mood became low and she repeatedly expressed a wish to die, feeling she had "had enough". On admission to the hospice, her mood had improved somewhat. Her pain, which had been a source of distress, had significantly improved with the change to parenteral analgesia, and she was hopeful of her mobility improving as a result. She remained very clear that if her condition deteriorated she would not want any escalation of treatment. Her wishes were respected, and when it was clear she was approaching the end of her life she remained at the hospice for supportive care.

The trajectory of disease and progression to death varies significantly dependent on the underlying disease process, with four distinct disease trajectories clearly defined: sudden death, cancer, organ failure and frailty/ dementia (see Figure 1) (1). Studies have shown the vast majority of deaths follow these defined trajectories (2).

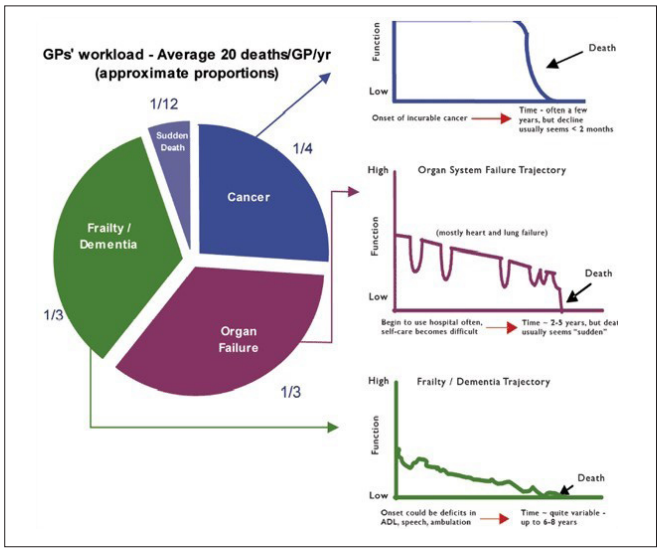

Figure 1: Taken from Gold Standards Framework (GSF) Proactive Identification Guidance (1)

The disease trajectory for frailty is of a slow, steady decline from an already low functional baseline. Onset can be marked by decreased ability to complete activities of daily living (ADLs), or by changes in speech, cognition, or oral intake. (3) As functional reserve decreases, seemingly minor physical or psychosocial events can lead to further rapid decline. When acute physical events occur, such as infections, it can be difficult to predict whether there will be a response to treatment. These events may cut short the disease trajectory, making the timeframe variable.

Palliative care for non-malignant conditions

Despite the recognition that palliative care can provide benefit for all patients, regardless of diagnosis, patients with cancer remain more likely to receive palliative care input than those with other illnesses (4).

The unpredictable disease trajectories for organ failure and frailty pose a challenge in delivering palliative care for these patient populations. In order to tackle this, the Gold Standards Framework devised Proactive Identification Guidance (PIG) to help clinicians identify patients likely to be in their last year of life (1). The PIG consists of 3 steps:

1. The "Surprise Question" – would you be surprised if the patient died in the next year?

2. Presence of General Indicators of Decline e.g. increasing dependence, repeated hospital admissions

3. Specific Clinical Indicators related to the three disease trajectories. For organ failure, this is further broken down into specific diseases e.g. heart failure, Parkinson's disease

For the frailty disease trajectory, Specific Clinical Indicators are broad, but include consideration of walking speed, deteriorating performance score and weight loss.

Following identification of patients who may be in their last year of life, clinicians can then assess patients' current and future clinical and personal needs, and with the patient plan their care.

For patients with frailty, gradual physical or cognitive decline often leads to increased dependence and social isolation. Patients who feel they have lost their dignity or sense of self can experience significant psychological or spiritual distress. This can be reduced by anticipating and planning for deteriorating health in older age. (4,5)

PALLIATIVE CARE FOR PATIENTS WITH FRAILTY

R Benbow, F Hakkak

End of life care

Regardless of the underlying disease process, for patients in the last few days of life symptoms of pain, nausea, agitation, and respiratory secretions are common (6). Because of this, it is recommended that all patients felt to be at the end of their life have "anticipatory" or "just in case" medications prescribed – pro re nata (PRN) subcutaneous medications to quickly treat these symptoms.

The specific medications prescribed vary by region, but commonly used medications are summarised in Box 1. The subcutaneous route is preferred when the oral route is unavailable, as intravenous injections are invasive and no more effective the subcutaneous injections, and intramuscular injections are often painful (7).

†Consider dose reduction if eGFR below 30

Commonly prescribed anticipatory medications			
Pain	Nausea/vomiting	Agitation	Respiratory secretions
Morphine sulfate 2.5-5mg†	Levomepromazine 5-6.25mg†	Midazolam 2.5-5mg†	Hyoscine butylbromide 20mg
Diamorphine 2.5-5mg†	Haloperidol 0.5-1.5mg	Haloperidol 0.5-1.5mg	Hyoscine hydrobromide 400 micrograms†
			Glycopyrronium 200 micrograms

Box 1

"Old Age" as cause of death

Old age (or similar terms such as frailty) should only be given as the sole cause of death in limited circumstances (8):

- *You have personally cared for the decreased over a long period*
- *You have observed a gradual decline in your patient's general health*
- *You are not aware of any identifiable disease/injury that contributed to the death*
- *You are certain there is no reason the death should be reported to the coroner*

The ONS Death Certification Advisory group recommends that deaths certified as due to old age alone should be referred to the coroner, unless the deceased was aged 80 or over.

As a junior doctor, you should always consult with the named consultant caring for the patient prior to certifying a cause of death.

Best of five MCQs

1. Mr A is a 77 year old gentleman with a background of congestive cardiac failure (CCF) secondary to ischaemic heart disease (IHD), previous myocardial infarctions (MIs), osteoarthritis and basal cell carcinoma of his left cheek. In the last year, he has become increasingly breathless on minimal exertion, and has been admitted to hospital 4 times with pulmonary oedema requiring intravenous diuretics. Following the last admission, he was discharged to sheltered accommodation as he had been struggling with his ADLs at home. What disease trajectory best describes this?

A. Cancer

B. Organ failure

C. Frailty

D. Sudden death

E. None of the above

2. Mr A has a further hospital admission with pulmonary oedema. Despite further treatment with intravenous diuretics, his condition continues to deteriorate, becoming more breathless. After discussion with himself and his family, the decision is made to stop active treatment as it is no longer giving benefit, and to manage his symptoms supportively.

His conscious level begins to deteriorate, and he is no longer able to take his oral medications, including morphine sulfate modified release 15mg twice daily. It was proposed by the nursing staff that commencing a CSCI with analgesia would be beneficial in maintaining control of his pain.

What would you prescribe as a CSCI for pain relief in the first instance?

A. 40mg morphine sulfate/24 hours

B. 20mg morphine sulfate/24 hours

C. 15mg morphine sulfate/24 hours

D. 30mg morphine sulfate/24 hours

E. 60mg morphine sulfate/24 hours

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3. Mr A has a CSCI with analgesia set up with initial good effect. After 8 hours, he is noticed to have some increased pain. What would be a suitable PRN dose of analgesia to treat this breakthrough pain?

A. 2.5mg morphine sulfate oral solution

B. 2.5mg morphine sulfate subcutaneous injection

C. 1mg morphine sulfate oral solution

D. 1mg morphine sulfate subcutaneous injection

E. 5mg morphine sulfate oral solution

4. Mr A begins to develop some nausea, and levomepromazine 5mg is added to his CSCI to good effect. Which of the following is NOT a symptom commonly experienced at the end of life?

A. Pain

B. Nausea

C. Respiratory secretions

D. Epistaxis

E. Agitation

5. 3 days after admission, Mr A dies peacefully surrounded by his family.

1) What would be the most suitable option for cause of death on Mr A's death certificate?

A. 1a) Heart failure

B. 1a) Heart failure
1b) Ischaemic heart disease

2) Basal cell carcinoma

C. 1a) Heart failure
1b) Ischaemic heart disease

D. 1a) Myocardial infarction
1b) Ischaemic heart disease

E. 1a) Ischaemic heart disease
1b) Heart failure

Answers

1. B – Organ failure

Within the disease trajectory for organ failure, patients are often ill for many years, with intermittent acute severe exacerbations, usually associated with hospital admission and more intensive treatment. In between exacerbations there is usually a gradual decline in function. Death may occur during any exacerbation, though the patient may survive many episodes, making the timing of death uncertain.

2. C – 15mg morphine sulfate/24 hours

The recommended conversion of morphine to a parenteral dose (subcutaneous, intramuscular, intravenous) is half that of the oral dose (9). When converting to a CSCI, it is important to use the total daily dose of oral morphine as a starting point – in this case, 30mg total oral morphine. When halved this then gives the subcutaneous dose over 24 hours.

3. B – 2.5mg morphine sulfate subcutaneous injection

As it has already been mentioned that Mr A is no longer able to take oral medications, the subcutaneous route is the most appropriate first line treatment for PRN analgesia. The recommended breakthrough dose for opioid based analgesia is 1/6 of the total daily dose (9,10). In this case, 15mg morphine sulfate divided by 6 gives 2.5mg as a breakthrough dose. If Mr A was still taking 30mg oral morphine, then E – 5mg morphine sulfate oral solution – would be the most appropriate first line medication.

4. D – Epistaxis

A variety of symptoms can occur in patients approaching the end of their life, with pain, nausea, agitation, and respiratory secretions recognised as being particularly common. Bleeding is less common but still can occur, particularly in patients with advanced cancer. It can be related to the underlying tumour, treatments such as steroids causing gastric erosion, or due to thrombocytopaenia or hepatic insufficiency. Treatment for bleeding includes oral tranexamic acid (though this comes with a risk of hypercoagulation), radiotherapy, and topical tranexamic acid and adrenaline soaks (9).

Catastrophic terminal haemorrhage may occur if a locally invading tumour causes erosion of a major artery, though fortunately this is very rare. For patients at risk of a catastrophic haemorrhage, "crisis packs" can be prepared in anticipation – dark towels to hide the visual impact of bleeding, and fast acting anxiolytics e.g. intramuscular/buccal midazolam (10).

PALLIATIVE CARE FOR PATIENTS WITH FRAILTY

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5. C – 1a) Heart failure 1b) Ischaemic heart disease. Information on cause of death on death certificates should be as follows:

1a) Disease or condition leading directly to death

1b) Disease or condition, if any, leading to 1a)

1c) Disease or condition, if any, leading to 1b)

2) Other significant conditions contributing to death, but not related to the disease or condition causing it

There is guidance given on how to complete certificates within the booklets of certificates themselves, and online (8).

When certifying organ failure as a cause of death, it is imperative to specify the underlying disease or condition that led to the organ failure. If no natural disease responsible for the failure is specified, the death will have to be referred to the coroner. Option A is therefore not specific enough.

Only conditions that contributed to the death should be included on the death certificate. Option B lists basal cell carcinoma as having contributed to death, and is therefore not appropriate. Basal cell carcinomas very rarely cause systemic morbidity, and there is no mention of this in the history given.

There is no mention in Mr A's history of a recent MI leading directly to death. Option D is therefore not appropriate. The previous MIs are accounted for in the death certificate under the umbrella term of ischaemic heart disease.

In Mr A's case, ischaemic heart disease has led to heart failure, and he has died during an episode of decompensated heart failure. Option C is therefore the best answer. Option E gives the sequence of cause of death in the wrong order.

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References

1. The Gold Standards Framework. Proactive Identification Guidance 6th edition, 2016. [Online] Available at URL: http://www.goldstandardsframework.org.uk/PIG [Accessed 17.06.2017]

2. Lunney JR, Lynn J, Hogan C. Profiles of older Medicare decedents. J Am Geriatr Soc 2002; 50(6):1108-1112

3. Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. BMJ 2005; 330:1007-11.

4. Murray SA, Kendall M, Mitchell G, Moine S, Amblàs-Novellas J, Boyd K. Palliative care from diagnosis to death. BMJ 2017; 356:j878

5. Lloyd A, Kendall M, Starr JM, Murray SA. Physical, social, psychological and existential trajectories of loss and adaptation towards the end of life for older people living with frailty: a serial interview study. BMC Geriatrics 2016; 16(1); 176

6. Fürst CJ, Doyle D. The terminal phase. In: Doyle D, Hanks G, Cherny N, Calman K eds. Oxford Textbook of Palliative Medicine, third edition. Oxford University Press 2004. Pages 1119-1133

7. NHS Lanarkshire. Guidelines for the Use of Subcutaneous Medications in Palliative Care. Reviewed 2011. [Online] Available at URL: http://www.nhslanarkshire.org.uk/Services/PalliativeCare/Documents/Guidelines%20for%20the%20use%20of%20Subcutaneous%20Medications%20in%20Palliative%20Care.pdf [Accessed 06.06.2017]

8. Office for National Statistics Death Certification Advisory Group. Guidance for doctors completing Medical Certificates of Cause of Death in England and Wales. Revised 2010. [Online] Available at URL: http://www.gro.gov.uk/images/medcert_July_2010.pdf [Accessed 06.06.2017]

9. Joint Formulary Committee. British National Formulary, 72nd edition. London: BMJ Group and Pharmaceutical Press 2016

10. West Midlands Palliative Care Physicians. Guidelines for the use of drugs in symptom control, 5th edition. Revised 2012. [Online] Available at URL: http://wmpcg.co.uk/ [Accessed 17.06.2017]

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A COMPLEX CASE OF DECOMPENSATED LIVER DISEASE IN A PATIENT PRESENTING WITH ACUTE UPPER GI BLEED

GE Sheehan-Dare, R Hubbard, M Foxton

Abstract

A 48 year old gentleman with alcoholic liver disease (ALD) presents with an acute upper gastro-intestinal (GI) bleed following a recent diagnosis of hepatocellular carcinoma (HCC). This is his third admission for an upper GI bleed in the last two years; he has previously undergone a transjugular intrahepatic portosystemic shunt (TIPS) procedure to relieve portal hypertension.

After treatment of the bleed, a recent computerised tomography (CT) scan is reviewed which demonstrates that the TIPS is no longer patent; a tumour thrombus is the cause of the blockage. This case discussion explores the various complications of liver disease and the evidence-based medicine behind providing good patient care in decompensated liver disease.

Case History

Presenting complaint: Vomited 100-200mls fresh red blood, shortness of breath at rest
History of presenting complaint: May 2015 oesophageal variceal bleed with subsequent banding, Dec 2015 variceal bleed leading to high dependency unit admission, banding x2 and TIPS procedure, Nov 2016 grade 1 oesophageal varices seen on surveillance endoscopy, no further action required
Past medical history: Recent diagnosis of HCC with vascular invasion on a background of alcoholic liver disease with known cirrhosis and ascites, type 2 diabetes mellitus, mild pulmonary fibrosis with recently diagnosed right sided pleural effusion, calcified coronary arteries
Drug history: Chemotherapy agent Sorafenib, Sitagliptin 100mg once daily (OD), Gliclazide 80mg twice daily (BD), Metformin 1000mg BD, Thiamine 100mg BD, Vitamin B OD.
Family history: Not known
Social history: Previous alcohol excess over 150 units/week, ex-smoker: 15 pack-year history for 20 years
Observations: Respiratory rate 26, saturations 96% on 15 litres (L) O_2, heart rate (HR) 139, blood pressure (BP) 145/70, temperature 38.6, glasgow coma score (GCS) 15/15
Investigations: Haemoglobin 109 (previously 135), platelets 148, white cell count (WCC) 12, c-reactive protein 42, urea 3.7, creatinine 69, albumin 35, bilirubin 27, alanine transaminase 49, alkaline phosphatase 115, international normalised ratio (INR) 1.1
Arterial blood gas (ABG) results on air: PH 7.49, $PaCO_2$ 2.9, PaO_2 6.9, bicarbonate 16.8, lactate 3.6, base excess -6.5
Chest x-ray: Opacification in right lower zone with loss of costophrenic angle
Electrocargiogram (ECG): sinus tachycardia

This patient was a 48 year old gentleman brought in by ambulance to Accident and Emergency with haematemesis.

The patient was assessed using the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach: his airway was patent, his respiratory rate was elevated at 26 breaths per minute with saturations of 76% on room air rising to 96% on 15L of oxygen via a non-rebreathe mask (NRBM). The trachea was central, chest wall movement symmetrical, but auscultation revealed reduced air entry at the right lung base.

The heart rate was regular at 139 beats per minute (bpm), normal heart sounds were heard and his blood pressure was 145/70 mmHg. Despite the patient having cool peripheries, his capillary refill rate was less than 2 seconds.

The abdomen was distended but soft and non-tender; shifting dullness was present. There was no evidence of hepatic encephalopathy; GCS was 15/15, pupils were equal and reactive to light. His temperature was 38.6°C and the blood glucose 7.6 mmol/L.

The impression following initial assessment was:

1. Haematemesis secondary to a variceal bleed (known varices)

2. Hypoxia of which the differential diagnosis included the known pleural effusion, potential overlying infection and a pulmonary embolism

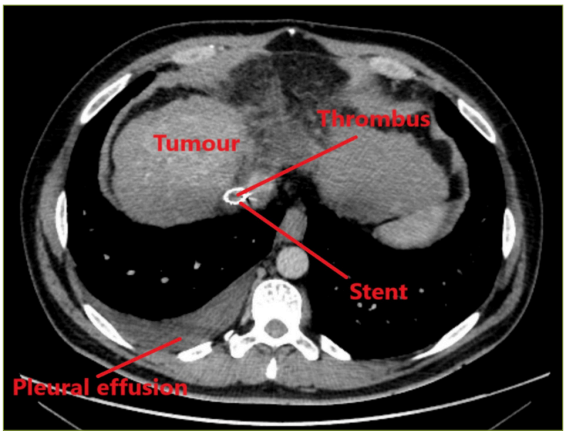
3. Sepsis of which the differential diagnosis included both chest and abdomen as the source

The following plan was made: immediate intravenous (IV) access, blood cultures, blood tests including a cross-match of 4 units, an ABG, IV fluids and a digital rectal examination. The initial ABG demonstrated hypoxia and a raised lactate. A subsequent ABG 2 hours later demonstrated a Hb drop from 10^9 to 91 g/L.

Digital rectal examination revealed melaena. In view of the hypoxia, tachycardia and recent diagnosis of HCC as a risk factor for pulmonary embolism, this gentleman underwent a CT pulmonary angiogram (CTPA). The CTPA was negative for emboli but demonstrated the previously known right-sided pleural effusion. The patient was started on empirical IV antibiotics and was also given 2 mg IV terlipressin.

An urgent oesophago-gastro duodenoscopy (OGD) under general anaesthetic was organised. In view of the patient's severe hypoxia, he was optimised overnight with non-invasive ventilation. Following further episodes of malaena and a continued drop in Hb prior to OGD, the patient was transferred to the intensive treatment unit (ITU) where 2 units of blood were transfused and the abnormal clotting corrected under the advice of haematology: 2 units of cryoprecipitate and 2 units of fresh frozen plasma (FFP) were given.

This patient underwent an OGD which demonstrated four columns of grade 2 oesophageal varices and one well-covered small gastric varix. There was one oesophageal red sign suggesting recent oesophageal haemorrhage. Four bands were applied to the oesophageal varices.



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The patient had undergone a CT scan prior to admission which was now sourced and reviewed. The scan demonstrated HCC disease progression and occlusion of the TIPS stent by a tumour thrombus. Based on these findings it was decided that there was no scope for further TIPS or revision.

The patient was treated with terlipressin for 72 hours and completed 5 days of broad-spectrum antibiotics. The beta-blocker carvedilol was restarted having been stopped on admission. Once the patient's oxygen requirements reduced to a safe level, he was discharged from ITU on long-term oxygen; a subsequent outpatient echo was suggestive of hepatopulmonary syndrome. The patient declined any futher doses of the chemotherapy agent sorafenib, and elected to have best supportive care. He died 2 months later.

Acute Upper GI Bleed – Initial Management

- ABCDE assessment including a full set of observations
- 15L O_2 NRBM may be required
- Insert adequate venous access – 2 large bore cannula
- Take bloods: full blood count, urea & electrolytes, liver function studies, clotting studies, cross-match, venous blood gas
- A low BP and raised HR indicate hypovolaemia and a requirement for a 250 ml (or 500 ml if no cardiac history) fluid bolus. Reassess the patient following the bolus
- Transfuse blood, platelets and clotting factors as per local guidelines. Do not over-transfuse (Target Hb 70-90 g/L)
- If variceal bleeding is suspected, give 2mg terlipressin IV and prophylactic IV antibiotic cover as per local guidelines
- Calculate Blatchford score after initial management is implemented

Discussion

This gentleman presented with an acute upper GI bleed on a background of known oesophageal varices and a history of previous bleeds. Oesophageal varices are formed as a result of portal hypertension. The commonest cause of portal hypertension is liver cirrhosis but it can also occur in the setting of portal vein occlusion caused by a thrombosis or tumour.

Varices have the potential to rupture and this usually occurs with increases in portal pressure. Patients having a variceal bleed have a high mortality related to the severity of the underlying liver disease. Although the origin of the bleed (in this case variceal) was suspected, clinicians must remain open-minded and initially assess every critically ill patient using a methodical ABCDE approach.

There were several important aspects to the management of this patient:

1. The patient's hypoxia was of concern and most important to address initially. This was treated with high flow oxygen; 15L via a NRBM. Potential causes of the hypoxia were a progression of the right-sided pleural effusion, pneumonia and hepatopulmonary syndrome.

Hepatopulmonary syndrome is a rare consequence of chronic liver disease caused by dilatation of pulmonary veins and should be considered in a patient with cirrhosis and hypoxia with no other identifiable cause. Treatment options are limited to long-term oxygen therapy or liver transplantation. The patient left ITU with a long-term oxygen requirement and later investigations suggested an element of hepatopulmonary syndrome.

The sepsis six[1]

To be delivered within 1 hour:

- High-flow oxygen
- Take blood cultures
- Administer empiric intravenous antibiotics
- Measure serum lactate and send full blood count
- Start intravenous fluid resuscitation
- Commence accurate urine output measurement

2. The patient's raised temperature, heart rate and respiratory rate fit the systemic-inflammatory response syndrome (SIRS) criteria, leading the medical team to suspect sepsis. Management of this patient therefore included that for sepsis as well as an acute upper GI bleed.

The sepsis six was covered in 1 hour with high flow oxygen, an IV fluid challenge, broad-spectrum antibiotics according to local policy, a lactate measurement (ABG), blood cultures and urine output monitoring. (1)

Spontaneous bacterial peritonitis (SBP) is a well-known complication of decompensated chronic liver disease and in this patient could have been the source of the infection. SBP carries a mortality of 31.5% at one month which can be reduced with the timely administration of antibiotics. (2) It is worth noting that sepsis can be a trigger for variceal bleeding. (3)

Had this patient not demonstrated signs of sepsis, he still would have received prophylactic antibiotics in view of the suspected variceal bleed as recommended by the British Society of Gastroenterology UK guidelines. (4) Antibiotics in cirrhotic patients with upper GI bleeding have been shown to reduce the relative risk of rebleeding by 47% and reduce the relative risk of mortality by 21%. (5)

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3. This patient was delivered 2mg Terlipressin IV. In line with the British Society of Gastroenterology UK guidelines; if chronic liver disease is known or suspected and there is a high clinical suspicion of variceal bleeding, administering terlipressin is recommended. (4) Terlipressin is a vasopressin analogue which lowers portal pressure. Studies have shown a 34% relative risk reduction in failure to control bleeding and mortality for patients treated with terlipressin in acute variceal haemorrhage. (6)

Unstable patients with severe acute upper GI bleeding should be offered endoscopy immediately after resuscitation.

All other patients with upper GI bleeding should be offered endoscopy within 24 hours of admission.[8]

4. Once the patient had been stabilised with oxygen, fluids, antibiotics and terlipressin, the next stage of management was to optimise homeostasis by correcting clotting and replacing blood products. This is important in view of the urgent need for endoscopy; a patient's condition must be optimised to minimise the risk of undergoing sedation and an interventional procedure. It is important not to over-transfuse patients during this period.

A study in the New England Journal of Medicine demonstrated that patients who had a post-transfusion Hb target of 90-110 g/L had a higher risk of rebleeding, adverse events and a poorer probability of survival at 6 weeks compared to those with a post-transfusion Hb target of 70-90 g/L. A post-transfusion target Hb of 70-90 g/L is therefore recommended. (7) Discussion with a haematologist is recommended on how best to correct deranged coagulation.

When should I call my registrar?

An upper GI bleed is considered an emergency. Due to the risk of rapid deterioration in patients with upper GI bleeding, particularly those with variceal bleeding, patients should be discussed with the registrar immediately.

What will the endoscopist want to know?

The endoscopist will want to know:

1. Presenting history

2. Clinical signs

3. Co-morbidities: liver, cardiac, renal, respiratory

4. Drug history: non-steroidals (NSAIDs), anti-platelet agents, anti-coagulants

5. Blood pressure and heart rate

6. Other clinical signs eg. stigmata of chronic liver disease (see box)

7. Blood results: full blood count, clotting screen, renal and liver function

8. What management you have implemented so far eg. fluids, blood transfusion, terlipressin, correction of clotting

9. How has the patient responded?

10. When did the patient last eat?

Blatchford Scoring System

Blood Urea (mmol/L)	
6.5-8.0	2
8.0-10.0	3
10.0-25	4
>25	6
Haemoglobin (g/L) for men	
12.0-12.9	1
10.0-11.9	3
<10.0	6
Haemoglobin (g/L) for women	
10.0-11.9	1
<10.0	6
Systolic blood pressure (mmHg)	
100-109	1
90-99	2
<90	3
Other markers	
Heart rate > 99 bpm	1
Malaena at presentation	1
Syncope at presentation	2
Hepatic disease	2
Cardiac failure	2

Score of 0 = low risk
Score of > 0 = high risk for needing intervention and inpatient management recommended

What are the common causes of an acute upper GI bleed?

The common causes of an upper GI bleed include peptic ulcer disease, variceal bleed, Mallory-Weiss tear and upper gastrointestinal tumours. This patient had a previous history of variceal bleeding and this was therefore the most likely cause, however patients with liver disease also commonly have peptic ulcer disease. NSAIDs, aspirin and a history of alcohol excess are all risk factors for peptic ulcer bleeds. Following endoscopy, patients with peptic ulcer bleeds and high-risk stigmata requiring endoscopic therapy should have a 72 hour PPI infusion. (8)

Stigmata of chronic liver disease

- Clubbing
- Palmar erythema
- Asterixis
- Spider nevi
- Jaundice
- Gynaecomastia
- Caput medusae
- Abdominal distension (ascites)

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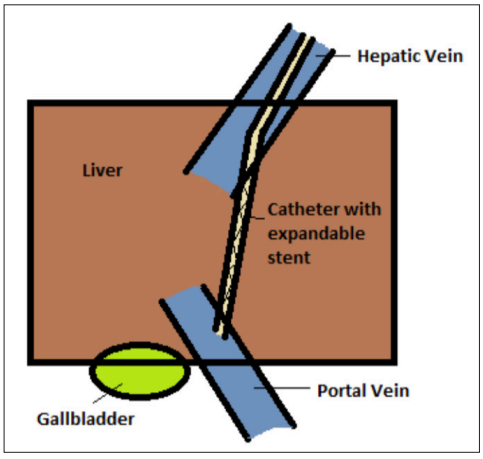
What is a TIPS Procedure?

A TIPS procedure is performed by an interventional radiologist to relieve pressure in the hepatic-portal system. Using x-ray imaging the interventional radiologist inserts a thin hollow wire down the jugular vein towards the hepatic vein. A catheter is then guided over the wire and a needle inserted through to create a connection between the hepatic systemic vein and the portal vein. The needle is withdrawn and the stent expanded.

The stent will remain in for the rest of the patient's life, however they must attend regular ultrasound scans to confirm the patency of the stent. Evidence suggests that cirrhotic patients with acute upper GI bleeding who undergo a TIPS procedure within 72 hours have a significant risk reduction in treatment failure (97% vs 50%) and mortality (86 vs 61%) at one year compared to those who are not offered TIPS. (9)



Other aspects to managing a patient with decompensated liver disease

Decompensated liver disease can come in the form of any of the following complications: variceal bleeding, ascites, jaundice and hepatic encephalopathy.

Studies have shown that acute on chronic liver disease has a high mortality rate (often exceeding 50%). (10,11) A 2013 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) found that less than half of patients who died from ALD received 'good care', and identified several avoidable deaths. Recommendations are for early aggressive treatment of complications to improve mortality. (12)

Child-Pugh Classification for Severity of Cirrhosis

Total bilirubin (µmol/L)	
<34.2	1
34.2-51.3	2
>51.3	3
Albumin (g/L)	
>35	1
28-35	2
<28	3
INR	
<1.7	1
1.7-2.2	2
>2.2	3
Ascites	
Absent	1
Mild to moderate	2
Severe	3
Encephalopathy	
Absent	1
Grade 1-2	2
Grade 3-4	3

Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

In response to the 2013 NCEPOD, a 'care bundle' for patients with decompensated cirrhosis has been developed to ensure optimal management is initiated in the first 24 hours. (13) Here we discuss several aspects of the care bundle, excluding GI bleed which has been discussed above:

Investigation & management of infection

All patients with decompensated liver disease should have a septic screen performed on admission. Mortality at one month is as high as 30% for patients with bacterial infections. (2) Patients with chronic liver disease do not always display the typical inflammatory response of infection. In patients with ascites, a diagnostic paracentesis should be conducted and sent to biochemistry for WCC and to microbiology for microscopy, sensitivity and culture (MC&S).

A polymorph cell count of >250 per mm^3 is diagnostic for SBP. If SBP is suspected, broad-spectrum antibiotics should be initiated in line with local antibiotic guidelines whilst awaiting sensitivities. Patients should also have fluid resuscitation in the form of human albumin solution (HAS): 1.5 g/kg on the day of SBP diagnosis and 1 g/kg 48 hours later. (13) Following an episode of SBP, all patients should be given long-term prophylactic antibiotics as per local guidelines.

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Ascites

As well as WCC and MC&S, ascitic fluid can be sent for albumin analysis and to cytology for assessment of malignant cells. The albumin value can be used to calculate the serum-ascites albumin gradient (SA-AG). This is calculated as follows: serum minus ascitic albumin.

A value below 11 g/L is suggestive of an exudative process. A high value suggests a transudative process; fluid is forced under pressure into the peritoneum due to portal hypertension.

An ultrasound scan (USS) to assess for portal vein thrombosis and HCC is important for patients with ascites. Management of ascites involves abstinence from alcohol, a low salt diet, use of diuretics including oral furosemide and spironolactone and therapeutic paracentesis.

Platelets should be checked prior to therapeutic paracentesis in some cases and HAS 20% should be infused alongside the drainage of ascitic fluid as per the 2012 AASLD guidelines; 100mls of 20% HAS is normally given for every 2-3 litres drained. (14) Due to risk of introducing infection, therapeutic paracentesis drains should be removed strictly after 6 hours.

Hepatorenal syndrome

Kidney function should be monitored closely in patients with cirrhosis. Hepatorenal syndrome (HRS) can occur acutely (Type 1) or insidiously (Type 2). The cause of HRS is multifactorial but involves renal vasoconstriction. Treatment is with HAS to expand intravascular volume, to stop nephrotoxic drugs, treat underlying sepsis and administer terlipressin; 0.5 mg four times a day initially. (15)

Hepatic encephalopathy

Hepatic encephalopathy can result in coma if not recognised early. Initial symptoms include disruption of the sleep cycle, confusion, asterixis and personality changes. Common precipitants are constipation, dehydration, GI bleeding and sepsis.

The underlying cause should always be sought and treated. Encephalopathy is treated with laxatives such as lactulose and phosphate enemas aiming for 2 soft stool per day which helps rid the body of excess nitrogen. (13)
For patients with recurrent encephalopathy, rifaximin should be considered. Other causes of confusion need to be considered and investigated as clinically appropriate eg. sepsis, trauma, intra-cerebral bleeds and drugs. (13)

Other considerations

Cirrhotic patients are at risk of deep-vein thrombosis whilst in hospital and their need for venous thromboembolism prophylaxis should be assessed. Prophylactic light-weight molecular heparin is only withheld if the patient is actively bleeding or platelets are less than 50. (13)

If the patient is suspected to have a current history of excess alcohol consumption, Pabrinex should be prescribed to prevent Wernicke-Korsakoff syndrome. These patients should also be assessed using the Clinical Institute Withdrawal Assessment–Alcohol scale (CIWA) for the first 48 hours to guide use of chlordiazepoxide administration to prevent the consequences of withdrawal. (13)

Cirrhosis & long-term consequences

Ninety five percent of all HCC develops in patients with cirrhosis and chronic liver disease. The mortality of patients with HCC is dependent upon the stage at which it presents. The 5 year survival ranges from 60% in patients at the earliest stage (BCLC stage A) to 0% (BCLC stage D). (16)

However, early detection through surveillance with USS at 6-monthly intervals has been demonstrated to improve early detection and survival. (17) Curative options include surgical resection and liver transplantation. Loco-regional therapies such as radio-frequency ablation and trans-arterial (chemo)embolization have been shown to prolong survival. All patients who may be suitable for these treatments should be offered surveillance.

Causes of Cirrhosis		Associated signs
Alcohol		Raised ALT, AST, GGT, serum IgA and MCV. Low vitamin D and folate
Infective	HBV	Hepatitis B surface antigen positive
	HCV	Anti-HCV antibody
Non-alcoholic Steatohepatitis		Steatohepatitis and fibrosis on biopsy
Autoimmune	Autoimmune	Raised serum IgG
	Primary Biliary Cirrhosis	Antimitrochondrial antibodies; specifically M2
	Primary Sclerosing Cholangitis	Raised ALP and GGT. Can also be associated with ANA, ANCA, aCA and raised serum immunoglobulins
Genetic	Alpha1 Antitrypsin deficiency	Low levels of serum α-1 antitrypsin
	Wilson's Disease	Low serum copper and caeruloplasmin
	Haemochromatosis	Raised serum iron and ferritin, HFE genotype
Drugs	Amiodarone	Exclusion of other causes
	Methotrexate	

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Questions

1. What is the commonest cause of chronic liver disease in the UK

a) Hepatitis C virus

b) Alcohol

c) Alpha-1 antitrypsin deficiency

d) Methotrexate

e) Haemochromatosis

2. What was this patient's Blatchford score at presentation?

a) 3

b) 9

c) 7

d) 1

e) 4

3. What was this patient's Child-Pugh score at presentation?

a) 5

b) 6

c) 0

d) 15

e) 7

4. Which is not a common complication of chronic liver disease

a) Jaundice

b) Ascites

c) Variceal bleeding

d) Hepatopulmonary syndrome

e) Hepatic encephalopathy

5. In acute upper GI bleeding, which one of these interventions has not been shown to reduce rebleeding or mortality?

a) Administration of terlipressin in patients with variceal bleeding

b) Administration of antibiotics in patients with variceal bleeding

c) Administration of a PPI infusion for 72 hours following endoscopy demonstrating high risk stigmata and receiving endoscopic therapy

d) Administration of PPI before endoscopy

e) TIPS insertion in patients with variceal bleeding

Answers

1 b)

Alcohol is the most common cause of chronic liver disease in the UK. However, although alcohol may be the clear aetiological agent causing the liver disease, it is important to ensure that other treatable causes for chronic liver disease are screened for and identified.

2 c)

This patient's serum urea was 3.7 = 0 points, Hb 109 = 3 points, systolic BP 145 = 0 points, HR 139 = 1 point, malaena at presentation = 1 point, No evidence of syncope = 0 points, known hepatic disease = 1 point and no known cardiac failure (despite calcified coronary arteries) = 0 points. This patient's total score was therefore 7 indicating high risk for requiring intervention. Inpatient management is recommended.

3 d)

This patient's bilirubin was 27 = 1 point, albumin 36 = 1 point, INR 1.1 = 1 point, mild ascites = 2 points, absent encephalopathy = 1 point. This patient's total score was therefore 6 (grade A).

4 d)

Hepatopulmonary syndrome is a rare consequence of chronic liver disease. The incidence of jaundice, variceal bleeding, ascites and hepatic encephalopathy are much more common.

5 d)

Administration of terlipressin, antibiotics and administration of a PPI infusion for 72 hours following therapeutic endoscopy in patients with high risk stigmata have all been shown to reduce the risk of rebleeding and mortality. A PPI infusion prior to endoscopy is not recommended.

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References

1. Daniels R, Nutbeam T, McNamara G, Galvin C. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. Emerg Med J. 2011 Jun;28(6):507-12.
2. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010 Oct;139(4):1246-56.
3. Goulis J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. The Lancet. 1999 Jan 9;353(9147):139-42
4. British Society of Gastroenterology. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. Available from: http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/liver/gutjnl_2015_309262.pdf [Accessed 30th May 2017]
5. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding— an updated Cochrane review. Aliment Pharmacol Ther 2011;34:509–18
6. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database Syst Rev 2003;(1):CD002147.
7. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, et al. Transfusion Strategies for Acute Upper Gastrointestinal Bleeding. N Engl J Med. 2013;368:11-21.
8. NICE Evidence. Acute upper gastrointestinal bleeding overview. Available from: https://pathways.nice.org.uk/pathways/acute-upper-gastrointestinal-bleeding
[Accessed 30th May 2017]
9. García-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, Abraldes JG, et al. Early Use of TIPS in Patients with Cirrhosis and Variceal Bleeding. N Engl J Med 2010;362:2370-2379.
10. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology, 2013 Jun;144(7):1426-37
11. Jalan R, Gines P, Olson JC, et al. Acute-on-chronic liver failure
J Hepatol, 2012 Dec;57(6):1336-48
12. NCEPOD. "Measuring the Units"-a review of patients who died with alcoholic related liver disease. National Confidential Enquiry into Patient Outcome and Death (UK); 2013:1–25.
13. McPherson S, Dyson J, Austin A, et al. Response to the NCEPOD report: development of a care bundle for patients admitted with decompensated cirrhosis—the first 24h Frontline. Gastoenterology. 2016;7:16-23.
14. Runyon B from American Association for the Study of Liver Diseases. Management of Adult Patients with Ascites Due to Cirrhosis:Update 2012. Available from: https://www.aasld.org/sites/default/files/guideline_documents/adultascitesenhanced.pdf [Accessed 30th May 2017]
15. International Club of Ascites. Guidelines: Hepatorenal Syndrome. Available from: http://www.icascites.org/about/guidelines/[Accessed 30th May 2017]
16. Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, Lok AS. Prognosis of Hepatocellular Carcinoma: Comparison of 7 Staging Systems in an American Cohort. Hepatology. 2005;41:707-716
17. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, Marrero JA. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther. 2009 Jul;30(1):37-47.

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ACUTE LIVER FAILURE (ALF): WHAT DO THE FOUNDATION YEAR DOCTORS NEED TO KNOW?

ZA Hashim, C Watters, S Singh

Abstract

The low incidence rate of ALF presents a challenge among clinicians in its diagnosis and management. However, the modern definition of ALF has made it easier in identifying the disease and its phenotype. The interval between the initial symptom and encephalopathy being the main determinant, acute liver failure is classed into hyperacute, acute, subacute presentations. Drug induced liver injury, in particular paracetamol-induced hepatotoxicity is now the leading cause of ALF in the developed world.

However, concurrent viral infections especially Hepatitis A, Hepatitis B and Hepatitis E need exclusion in all cases. Other rarer causes are also discussed. Identifying the underlying cause plays a vital role in improving patient outcomes. After the initial clinical manifestations of coagulopathy, jaundice and encephalopathy, the disease may progress to multiple organ failure within a few hours. Hence, early recognition and escalation of care is paramount in obtaining the best outcome in this patient cohort.

Management of complications are best done in the critical care setting ideally in a liver unit. Increasing rates of spontaneous survival of patients with advances in critical care management evidences this. For early recognition of patients who may go on to require emergency liver transplant Kings College criteria is gold standard. The definitive treatment of ALF remains liver transplantation.

Introduction

Acute liver failure (ALF), a life threatening condition, is most commonly defined as the onset of coagulopathy (INR ≥ 1.5) and encephalopathy in a patient without pre-existing liver disease. Despite this being a rare condition it has accounted for 6% of liver related deaths annually, in the US.(1)

The clinical presentation includes elevated transaminases, hyperbilirubinaemia, coagulopathy, encephalopathy with an increased risk of multi organ failure and death in patients. Early detection of this condition and its possible aetiology with prompt escalation of care plays a vital role in the survival rates of these patients. Advances in critical care management and the use of emergency liver transplantation have improved the survival rates in patients with ALF.(2)

This review outlines the main clinical features, causes, epidemiology, indicators of poor prognosis and management of acute liver failure and is aimed to increase knowledge base of foundation year doctors.

Definition & Clinical Features

Acute Liver failure ensues when the primary liver function viz. coagulation and toxins excretion are affected, provided there is no pre-existent cirrhosis and the duration of the illness < 26 weeks. Terms used to signify length of illness (from jaundice to encephalopathy) such as hyperacute (<7days), acute (7-21 days) and subacute (> 21 days and < 26 weeks) have been used before but they do not have prognostic significance distinct from the cause of the illness. For example, hyperacute cases may have a better outcome largely because most cases are due to paracetamol overdose.(3)

The clinical features of ALF are systemic however the clinical finding of hepatic encephalopathy (HE) is crucial for the diagnosis of ALF. As mental alterations may be subtle initially, intensive screening for the first sign of HE is of paramount importance. The West Haven criteria are used to classify HE.(4)

Aetiology & Epidemiology

The two main causes of ALF are viral infections and drug-induced liver injury. The improvement in public health measures such as vaccination and sanitation, in developed countries like the United Kingdom and USA, has resulted in drug-induced liver injury becoming the leading cause of ALF in these countries.

Paracetamol

Paracetamol-induced hepatotoxicity is relatively common in the UK, approximately 57 % in the UK and requires prompt recognition and management. (5) It is characterized by marked elevations in serum aminotransferases (often >10,000 IU/L) with relatively normal bilirubin levels. (6) Metabolic acidosis, lactic acidaemia, hypoglycaemia and renal dysfunction are all frequent sequelae and tend to occur early in the clinical course. (6)

On initial presentation, history should elicit the amount and method of ingestion (rapid or staggered) and how long before assessment had this occurred. Toxicology screening with serum paracetamol level measurements should be done at initial assessment, although levels are often falsely reassuring, particularly in those who have taken a staggered overdose.

Patients who do not meet criteria for emergency liver transplant do have a relatively good prognosis provided they receive appropriate therapy which consists of fluid resuscitation and N-acetylcysteine (NAC).(7) Renal replacement therapy may be required, particularly to treat acidosis.(8) The patient's clinical status can deteriorate rapidly (within hours) so an appropriate care setting should be organized early on.

NAC has repeatedly been shown to reduce progression of liver injury if given early enough following overdose.(7) The mechanism is thought to be related to its anti-oxidant, anti-inflammatory and microcirculatory vasodilatory effects.(8) It is advisable to limit administration of NAC to a maximum of five days due to its anti-inflammatory and immune-paretic effects increasing the risk of developing sepsis.(10)

Non-Paracetamol Drug-Induced Liver Injury (DILI) and ALF

ALF is not as common as in paracetamol overdose (11% in UK) but should progression occur there is higher likelihood of emergency liver transplant or death. DILI tends to occur more often in older patients (>60 years).(11) Often grouped into 'cholestatic' or 'hepatocellular' DILI, with the former tending to run a more subacute course.

Concurrent viral infection should always be considered and excluded in patients with DILI as occurs not infrequently and can acts as trigger for DILI.(3)

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Anti-tuberculosis drugs, certain antibiotics (eg. nitrofurantoin), anti-epileptics and NSAIDs most commonly cause ALF but the list of causative agents is extensive.(12) Patients with DILI may only become symptomatic several weeks after ingestion, which can complicate matters so detailed history of all ingested drugs, vitamin supplements and herbal remedies taken in the previous six months should be taken.(13)

Viral Hepatitis

Hepatitis B, A and E can cause ALF, with the former being the most common (+/- delta superinfection). (14,15) Sexual and social history are important to stratify the risks of HBV infections in individuals presenting with liver disease. Vaccination protocols have led to a significant reduction in the incidence of such cases and early antiviral therapy has also improved outcomes. Less than 4% of acutely infected individuals will develop ALF but mortality rates in that group are higher than with HAV or HEV infection.

Reactivation of HBV in immunosuppressed individuals or those undergoing immunomodulatory therapy can occur and confers a higher mortality risk than with de novo infection.(14) Screening is therefore vital prior to commencing such therapies. A travel history is important as HAV and HEV infection are most commonly seen in those who have recently visited endemic areas. HEV infections have worsened outcomes in older and pregnant patients, as well as those with pre-existing underlying liver disease.(15)

Other viruses, including Herpes Simplex (HSV), Varicella Zoster (VZV), Epstein Barr (EBV) and Cytomegalovirus (CMV) are rare causes and should be screened should the aetiology be unclear.

Autoimmune Hepatitis (AIH)

Consider autoimmune hepatitis if the aetiology is unclear in patients with other autoimmune comorbidities. Autoantibodies are often, but not exclusively positive and other causes should not be overlooked, simply based on positive serological testing.(16) Liver biopsy may be required to confirm diagnosis and will reveal hepatic necrosis accompanied by interface hepatitis and plasma cell infiltration in typical cases. Steroids are often given in AIH and may be effective, particularly if given at an early stage but they tend to be ineffective and potentially damaging in ALF secondary to the above.(16) If commenced on steroids, this should be for a trial period of no longer than seven days before reassessment of effectiveness and suitability for transplant should still be considered at an early stage.(17)

ALF in Pregnancy

The majority of aetiologies of ALF are the same as in non-pregnant individuals. Fulminant hepatitis E infection tends to have worse outcomes in pregnancy but the cause for this is unclear.(18) Haemolysis, elevated liver tests and low platelets (HELLP) is a complication of severe pre-eclampsia and presents in the third trimester, as does acute fatty liver of pregnancy. Foetal delivery is the only definitive treatment alongside seizure prophylaxis and control of hypertension and disseminated intravascular coagulopathy (DIC).(19)

The occurrence of liver failure in pregnancy should lead the clinician to consider liver rupture associated with pre-eclampsia. This presents with right upper quadrant pain and quite often pulmonary embolism needs to be excluded. Management is generally conservative but occasionally surgical intervention with packing may be required if capsular rupture results in significant bleeding. Extensive subcapsular bleeding can result in ischaemic injury to the liver and rarely compression of the hepatic veins, resulting in a clinical picture similar to Budd-Chiari syndrome.(20)

Others

Below are several miscellaneous conditions that can lead to acute liver failure. If the aetiology is indeterminate after thorough assessment and investigations, liver biopsy (usually transjugular) may be helpful.

- *Budd-Chiari Syndrome (acute hepatic vein thrombosis)– characterised by abdominal pain, ascites and hepatomegaly. Diagnosis is confirmed on imaging of the liver +/- venography and venous decompression or transplantation is indicated in significant liver failure. Conditions causing a hypercoagulable state and screening for underlying malignancy must be performed as an underlying malignancy may preclude transplant.*

- *Wilson Disease – tends to present differently depending on age and can occasionally cause ALF. In those under 20 years, hepatic encephalopathy, Coombs negative haemolytic anaemia and a high bilirubin:ALP ratio are seen. Kayser-Fleischer rings will be present in about half of patients and renal dysfunction is often seen. Decompensated liver disease often gives rise to presenting symptoms in the older age group. Early detection is vital as progression to fulminant liver disease is uniformly fatal without liver transplantation. Penicillamine therapy is not recommended in ALF as there is a risk of hypersensitivity.*

- *Mushroom poisoning –ingestion of mushrooms (commonly Amanita phalloides) is a rare but significant cause of ALF. There is no routine diagnostic test to confirm presence of the toxin so clinical assessment is essential. Profuse diarrhoea and vomiting is often seen within 24 hours of ingestion. If ingestion did occur recently, gastric lavage is beneficial.*

- *Acute Ischaemic Injury ('Shock Liver') – often occurs after a period of hypovolaemia, cardiac arrest or in significant biventricular cardiac failure.(21) Blood testing will reveal markedly elevated aminotransferases, which will respond rapidly to normalisation of circulation and tissue perfusion. Monitor for extra-hepatic manifestations such as renal dysfunction or muscle necrosis.*

- *Malignant Infiltration – marked infiltration of the liver will cause ALF. Massive hepatomegaly will be apparent and diagnosis confirmed with imaging and biopsy if appropriate. Transplantation will not be an option in this cohort. Acute severe hepatic infiltration is more commonly seen with small cell lung cancer, breast cancer, lymphoma and melanoma.(22)*

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Aetiology	Initial Assessment	Investigations	Specific Treatments	Liver Transplant	Complications
Paracetamol-induced	Staggered or single ingestion	Marked rises in aminotransferases	N-acetylcysteine	See Kings College criteria	
Drug-induced (non-paracetamol)		Often not as significant rise in aminotransferases. Greater rises in bilirubin		See Kings College Criteria	Less extrahepatic organ dysfunction vs paracetamol
Ecstasy-induced	Identical clinical picture to heat shock related liver injury – hyperacute presentation with severe hyperthermia			Rarely required and often won't alter the outcome	Multi-organ involvement, profound coagulopathy and severe rhabdomyolysis
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	Rare Consider if fever, marked cutaneous rash and lymphadenopathy – often associated with sulphur-containing compounds, some anti-convulsants and antimicrobials	Eosinophilia	High-dose corticosteroid therapy		
Ischaemic hepatic injury (including cocaine induced		Marked elevation of aminotransferases and LDH. Rapidly progressive rise in PT and creatinine	Often improve with establishing haemodynamic stability/medical management		
Viral Hepatitis (HAV, HBV, HEV)			Hep B vaccination Antiviral Hep B therapy		
Autoimmune Hepatitis	PMHx of autoimmune disease	Autoantibodies Liver biopsy	Steroids given but often ineffective in ALF	Consider at early stage	

Table 1: Summary of aetiology of ALF.

Investigations

Investigations to guide accurate identification of aetiology are a crucial determinant of prognosis. Initial tests should include all routine blood tests including Full Blood Count (FBC), Urea & Electrolytes (U&E), Liver Function Test (LFT), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), coagulation profile, arterial blood gas, blood and urine cultures. Imaging including chest radiograph (CXR), abdominal ultrasound with Doppler of hepatic vessels, ECG and echocardiogram also needs to be considered.(23)

In addition to early recognition of the extent of liver injury , these tests help in initiating immediate and specific treatment of various causes of liver failure. Renal dysfunction with subsequent metabolic acidosis and impaired liver function (raised INR) remain the best prognostic markers. Hence serial arterial pH, coagulation profile and renal function tests needs to be done. Additional tests specific to different causes are listed in table 2. Liver biopsy may be required in certain cases like malignant infiltration and autoimmune hepatitis to confirm diagnosis.

Aetiology	*Investigation*
Hepatitis A (HAV)	IgM anti-HAV
Hepatitis B+D (HBV, HDV)	HbsAg, IgM HBcAb, HBV DNA
Hepatitis E	Anti-HEV
Other virology tests	Hepatitis C Ab, Cytomegalovirus (CMV), HIV, Herpes simplex virus (HSV), Ebstein Barr Virus (EBV)
Paracetamol	Plasma levels
Toxicology screen	e.g. Opiates, Barbiturates, Cocaine, Alcohol
Autoimmune Hepatitis	Antinuclear antibody Antismooth muscle antibody Immunoglobulins Anti liver/kidney microsomal Ab
Pregnancy related syndromes	
Fatty Liver	Ultrasound, Uric acid, Histology
HELLP syndrome	Platelet count
Wilson's Disease	Serum cerulosplasmin, Urine copper
Budd-Chiari syndrome	Doppler ultrasound or venography
Malignancy	Imaging and histology
Ischaemic hepatitis	Transaminases, septic screen

Table 2: Summary of investigations of ALF

Indicators of poor prognosis

Given the limited organ availability and lack of other definitive treatments, early recognition of patients who fail medical management is paramount in survival of patients with ALF. The evaluation system widely followed in UK and other European countries is The King's College criteria. It takes into account the patients age and severity of liver injury, as assessed by the presence of coagulopathy or jaundice and HE, which is the main indicator. Meta-analyses confirm a clinically acceptable specificity but more limited sensitivity of its criteria.(3) Early discussion with a liver unit is crucial in this setting. The criteria are shown below in Table 2.

ALF due to paracetamol	ALF not due to paracetamol
Arterial pH <7.3 after resuscitation and >24hrs since ingestion	INR >6.5 or
Lactate > 3mmol/L or	Three out of the five following criteria ▪ Aetiology: indeterminate aetiology, hepatitis, drug-induced hepatitis ▪ Age <10 years or >40 years ▪ Interval between jaundice to HE >7 days ▪ Bilirubin > 300micromol/L ▪ INR>3.5
Three of the following criteria: ▪ > Grade 3 Hepatic encephalopathy ▪ Serum Creatinine > 300 micromol/L ▪ INR > 6.5	

Table 3: King's College Criteria

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General management and of specific complications

The management of acute liver failure (ALF) is largely governed by the underlying aetiology as well as the confirmation/exclusion of significant prognostic factors such as cirrhosis, malignant infiltration etc. but there are general measures that should be employed, especially concerning the potential complications of the condition. Early discussion with specialist units/transplant centres is highly recommended, particularly if there is evidence of complication and the outcome is likely to be poor with medical therapy alone.

Prompt recognition of the condition can often be difficult as initial symptoms tend to be non-specific (e.g. fatigue, malaise, anorexia) prior to features such as coagulopathy or hepatic encephalopathy developing. Hence a thorough physical examination must include careful assessment of mental status and looking for any signs of bruising or bleeding, jaundice and stigmata of chronic liver disease. Right upper quadrant tenderness may be present and the liver span may be small (e.g. shock liver) or large (e.g. viral hepatitis). Careful assessment for any ascites must also be carried out. Signs of increased intracranial pressure like papilloedema, hypertension and bradycardia need to be searched for.

However, once appropriate specific therapies are initiated management is supportive. High dependency units should be employed/aware of the patient from the onset as the clinical picture is often rapidly changeable.(4) Any patient with altered mental status would warrant review for admission to intensive care (preferably in a tertiary centre) for this very reason.

Multi-organ failure and sepsis are the most common causes of mortality in this group and the clinician must be vigilant for the early signs associated with such complications.(4) The complexity of the condition requires a multidisciplinary approach, including hepatologists, liver transplant surgeons, intensivists, dietitians and psychiatrists.

Specific complications

Neurological

The rate of progression and severity of hepatic encephalopathy does have prognostic importance (24). High levels of ammonia and other toxins are thought to play a role in altered cerebral function +/- swelling.

The most serious consequence of ALF is cerebral oedema and intracranial hypertension, which predisposes to uncal herniation and death. Cerebral oedema predisposes the patient to ischaemic and hypoxic brain injury and can therefore lead to long-term neurological sequelae even if the patient recovers from the acute episode.(24)

The development of cerebral oedema is thought to be related to intracranial osmotic disturbances and loss of cerebrovascular autoregulation. There is a recognised correlation with severity of encephalopathy and cerebral oedema which rarely occurs in patients with Grade I or II encephalopathy. Grade I can often be managed at ward-level with regular neurological observations. Patients with Grade II or above should be considered for intubation and ventilation due to the risks of respiratory compromise.

The aim of treatment is to reduce the amount of ammonia reaching the blood brain barrier. Lactulose is commonly used in but can be deleterious, causing ileus. Sedatives should be avoided wherever possible. Patients with Grade III or IV encephalopathy should be intubated with the patient ideally positioned at 30 degrees. This will allow for closer observation (clinical or invasive monitoring) for markers of raised intracranial pressure.

Seizures are not uncommon and can dramatically worsen the clinical picture by furthering the development of raised intracranial pressure and cerebral hypoxia. Phenytoin had traditionally been used for seizures. However, newer agents such as levetiracetam confer less risk of hepatotoxicity and are being utilised more.

Haematological/coagulopathy

Liver-related coagulopathic changes do not necessarily confer a higher risk of bleeding. There tends to be a fairly balanced derangement in both the anti- and procoagulant factors and individuals may even have predominance towards coagulation. (25)

See table 4.

Renal/metabolic/haemodynamics

Appropriate fluid resuscitation should be accompanied by monitoring of haemodynamic status, fluid balance and metabolic parameters. Fluid status can be difficult to assess as low systemic vascular resistance, which is seen in liver failure, results in hypotension.

Hyponatraemia is seen in ALF and there is a correlation between serum sodium levels and intracranial pressure. Dramatic changes in the sodium level should be avoided, aiming for serum levels of 140-145mmol/L with care taken to avoid inducing hypernatraemia. (26)

Acute renal dysfunction despite adequate fluid resuscitation does occur and differentials would include acute tubular necrosis and hepatorenal syndrome. Higher rates are seen with overdoses of paracetamol and other toxins due to their direct nephrotoxic effects, as well as the presence of SIRS and infection.(26)

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Gastrointestinal/nutrition

Gastrointestinal bleeding is a common complication of ALF. In the Intensive Care setting mechanical ventilation for over 48 hours is a significant risk factor, in conjunction with coagulopathy. H2-receptor antagonists are often given (as are PPI agents) for gastric protection from stress-induced bleeding.(27)

Safe enteral nutrition should be commenced at the earliest possible stage as this cohort are often hypocaloric secondary to poor oral intake as well as the catabolic processes which occur secondary to liver dysfunction. Parenteral feeding is an alternative but does not improve outcome and will predispose these patients to infection (including fungal). Hyperglycaemia should be avoided, as it will impair intracranial pressure control.

System	Sequelae	Management
Neurological	Hepatic encephalopathy Cerebral oedema Intracranial hypertension Coma Uncal herniation	• It is important to exclude other pathology such as intracranial haemorrhage with patients presenting in this way. Imaging of the brain parenchyma is therefore often employed once the patient is deemed to be sufficiently stable.
Haematological	Coagulopathy Thrombocytopenia	• Reduced synthesis of anti- and procoagulant factors with increased consumption of platelets • Fresh Frozen Plasma if bleeding or for procedure. Not given routinely as can worsen raised ICP and underlying clotting is a good marker of progression of liver disease • Platelet transfusion as per local and national policy • Vitamin K given to replace any nutritional deficiencies
Renal/metabolic	Acute Kidney Injury Acute Tubular Necrosis Hepato-renal Syndrome Metabolic acidosis Hyperlactataemia Hyponatraemia Hypoglycaemia	• Adequate initial fluid resuscitation as often intravascularly deplete • Pulmonary arterial catheterization can be used to guide fluid resuscitation but would only ever be performed in Intensive Care setting • Should dialysis be required, continuous haemofiltration is considered to be better than intermittent as tends to result in improved cardiovascular and intracranial parameters. • Vasopressin and its derivatives should only be used with extreme caution as it can worsen intracranial hypertension.
Gastrointestinal/nutritional	UGIB – stress ulcer Hypomagnesaemia, hypokalaemia, hypophosphataemia Pancreatitis	• GI bleeding relatively common • H2-receptor antagonists (and PPI) used for gastric protection in such patients • PPI use in particular, should be weighed against the risks of developing ventilator associated pneumonia of Clostridium difficile infection. • Be vigilant for features suggestive of pancreatitis and consider cross-sectional imaging if there is high clinical suspicion. • The management is the same as for acute pancreatitis in non-ALF but severe pancreatitis is a relative contraindication to emergency liver transplant.
Infection/inflammation	Infection (NB risk of bacterial, viral or fungal infection) SIRS	• Prophylactic antibiotics reduce incidence but not overall outcome/mortality • Regularly survey for evidence of infection (CXR, cultures (blood, urine, ascites) and in progressive encephalopathy or SIRS • Ensure asepsis for procedures, regular assessment of indwelling devices and good hand washing etc
Cardiovascular	Low systemic vascular resistance with vasodilation => reduced effective central blood volume Hypotension with tissue hypoperfusion	• Initial hypervolemia (often with hyperlactataemia) tends to respond to volume repletion • Persistent high lactate often secondary to sepsis or due to severity of liver failure • Vasopressors can be used if hypotension persists despite volume resuscitation
Respiratory	Hypoxia ARDS Pleural effusions Pulmonary haemorrhage	• Respiratory dysfunction not commonly seen in early stages - tends to occur with hepatic regeneration or development of sepsis • Consider invasive airway management for protection in progressive hepatic encephalopathy • Hypoxia, hypercapnia and risk of raised intracranial pressure must be carefully balanced • Non-invasive ventilation should be avoided as can worsen neurological dysfunction and increase risk of aspiration and poor compliance

Table 4: Summary of sequelae and management.

Liver transplant

Liver transplant is really the only definitive management in patients who are unable to achieve sufficient regeneration of hepatocytes to sustain life. ALF accounts for up to 12% of liver transplant activity.(28) Outcome of liver transplantation is dependent on the pre-transplant condition of the patient and quality of the graft used. 1-year survival following emergency transplant is slightly worse (80%) than routine transplants and this is mainly due to emergent nature of the condition.

This has however improved tremendously from an overall survival rate of 15 % in the pre-transplant era.(29) Co-morbid cardiovascular, respiratory and systemic conditions have a deleterious impact on patient outcomes. Psychosocial and family support for compliance and substance abuse play an important role in pre transplant assessments. Urgent liver transplants are therefore indicated when poor prognostic indicators are met in the right patient therefore early discussions with liver units is crucial.

Summary

ALF poses challenges due to its rarity, rapid progression and frequently poor outcomes. Causes are generally obvious but clinicians need to be aware of other less common causes especially if the clinical picture does not fit. Patients are particularly prone to infections, bleeding and cerebral oedema when advanced hepatic injury is sustained. Clinicians should be mindful of poor prognostic indicators and an early discussion with liver units is encouraged. Management is largely supportive short of liver transplantation. Multi disciplinary approach with close linkage with hepatologists and liver unit is important to provide the best outcome for patients.

We hope clinicians especially junior doctors benefit from this review translating into the best clinical care based on current evidence.

MCQ's

1) Which among the following statements regarding ALF is true?

1) It is diagnosed when coagulopathy complicates acute liver injury.

2) It is commonly caused by alcohol.

3) A normal blood paracetamol levels precludes paracetamol-hepatotoxicity as the etiology.

4) Intracranial haemorrhage is a recognised complication of ALF.

5) Hepatitis E infection has worsened outcomes in pregnancy.

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2) Which hepatitis infection rarely proceeds to ALF?

1) Hepatitis A

2) Hepatitis B

3) Hepatitis C

4) Hepatitis D

5) Hepatitis E

3) A 45 year old lady presented with history of migraine headaches to the emergency department and altered mental status over the last several hours. Her husband found her to be confused and somnolent early in the day. On examination she had scleral icterus, mild right upper quadrant tenderness and asterixis.

Blood tests showed ALT 6498 units/L, total bilirubin of 105 micromol/L and INR of 7. Her husband reports that she has been consistently taking pain medications including cocodamol for back pain and started taking additional paracetamol 500 mg for her headaches several days ago. Given the diagnosis, which among the following statements below is incorrect?

1) Prognosis would be poor if she doesn't meet the criteria for emergency liver transplant.

2) NAC reduces progression of liver injury by its anti-oxidant and microcirculatory vasodilator effect.

3) Renal replacement therapy may be required to treat acidosis.

4) NAC infusion is not recommended for more than 5 days.

5) Metabolic acidaemia, lactic acidosis and hypoglycaemia are frequent complications.

4) As part of the initial investigations for the etiology of ALF, which of the following test is not required.

1) INR

2) HBsAg

3) IgG anti-HAV

4) Ant-HEV

5) HIV

5) Which of the following patients would be considered for liver transplantation after paracetamol overdose?

a) PT 120 seconds, creatinine 270 umol l-1, grade III encephalopathy

b) PT 90 seconds, creatinine 374 umol l-1, grade II encephalopathy

c) PT 120 seconds, creatinine 317 umol l-1, grade III encephalopathy

d) PT 120 seconds, creatinine 270 umol l-1, grade IV encephalopathy

Answers

1. Correct answer: 5

Hepatitis E infections have worsened outcomes in older and pregnant patients. ALF is acute liver injury complicated by coagulopathy and encephalopathy. Alcohol is the common cause of chronic liver disease. Serum paracetamol levels are often falsely reassuring, particularly in those who have taken a staggered overdose. Intracranial hypertension is a complication of ALF.

2. Correct answer: 3

Hepatitis C usually proceeds to chronic liver failure.

3. Correct answer: 1

With the improvement in critical care services medical therapy for ALF in particular paracetamol-induced acute liver failure has good prognosis/ outcomes.

4. Correct Answer: 3

The investigation of choice to r/o hepatitis A is IgM anti-HAV.

5. Correct answer: C

The King's college criteria for paracetamol related acute liver failure suggests a combination of INR > 6.5/PT > 100 secs , > Grade 3 encephalopathy and serum creatinine > 300 micromol/L.

ACUTE LIVER FAILURE (ALF): WHAT DO THE FOUNDATION YEAR DOCTORS NEED TO KNOW?

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References

1. Hoofnagle JH, Carithers RL Jr, Shapiro C, et al. Fulminant hepatic failure: Summary of a workshop. Hepatology. 1995; 21:240-252
2. Bernal W, Hyyrylainen A, Gera A, et al. Lessons from look-back in acute liver failure. A single centre experience of 3300 patients. J Hepatol 2013:59:74-80
3. EASL Clinical practical guidelines on the management of acute (fulminant) liver failure. Journal of Hepatology 2017 vol.66, 1047-1081
4. Vaquero J, Polson J, Chung C, Helenowski I, Schiodt FV, Reisch J, et al, Infection and the progression of hepatic encephalopathy in acute liver failure. Gastroenterology 2003;125:755-764
5. Craig DGN, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol- induced hepatotoxicity. Br J Clin Pharmacol 2012;73:285-94
6. Fontana RJ. Acute liver failure including acetaminophen overdose. Med Clin North Am 2008; 92(4): 761-94, viii
7. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT,. Larson AM, Davern TJ, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009; 137(3): 856-64, 864 e1
8. Ellis A, Wendon J. Circulatory, respiratory, cerebral, and renal derangements in acute liver failure: Pathophysiology and management. Semin Liver Disease 1996;16:379-387
9. Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N Engl J Med 1991;324:1852–1857
10. Heard KJ. Acetylcysteine for acetaminophen poisoning. N Engl J Med 2008;359: 285-92
11. Carrascosa MF, Salcines-Caviedes JR, Lucena MI, Andrade RJ. Acute liver failure following atorvastatin dose escalation: is there a threshold dose for idiosyncratic hepatotoxicity? J Hepatol 2015;62:751–752
12. Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010;52:2065–2076
13. Wai CT, Tan BH, Chan CL, Sutedja DS, Lee YM, Khor C, et al. Drug-induced liver injury at an Asian center: a prospective study. Liver Int 2007;27:465–474
14. Pande C, Sarin SK, Patra S, Bhutia K, Mishra SK, Pahuja S, et al. Prevalence, risk factors and virological profile of chronic hepatitis B virus infection in pregnant women in India. J Med Virol 2011;83:962–967
15. Manka P, Bechmann LP, Coombes JD, Thodou V, Schlattjan M, Kahraman A, et al. Hepatitis E virus infection as a possible cause of acute liver failure in europe. Clin Gastroenterol Hepatol 2015;13:1836–1842
16. Heneghan MA, Yeoman AD, Verma S, Smith AD, Longhi MS. Autoimmune hepatitis. Lancet 2013;382:1433–1444
17. Ichai P, Duclos-Vallee JC, Guettier C, Hamida SB, Antonini T, Delvart V, et al. Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl 2007;13:996–1003
18. Shalimar, Acharya SK. Hepatitis E and acute liver failure in pregnancy. J Clin Exp Hepatol 2013;3:213–224
19. Westbrook RH, Yeoman AD, Joshi D, Heaton ND, Quaglia A, O'Grady JG, et al. Outcomes of severe pregnancy-related liver disease: refining the role of transplantation. Am J Transplant 2010;10:2520–2526
20. Lambert G, Brichant JF, Hartstein G, Bonhomme V, Dewandre PY. Preeclampsia: an update. Acta Anaesthesiol Belg 2014;65:137–149
21. Kisloff B, Schaffer G. Fulminant hepatic failure secondary to congestive heart failure. Dig Dis Sci 1976;21:895-900
22. Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. Gut 1998;42: 576-580
23. Polson J, Lee WM. AASLD Position Paper: The Management of Acute Liver Failure. Hepatology, 2005 vol. 41, 1180-1197
24. O'Brien CJ, Wise RJS, O'Grady JG, Williams R. Neurological sequelae in patients recovered from fulminant hepatic failure. Gut 1987;28:93-95.
25. Lisman T, Bakhtiari K, Adelmeijer J, Meijers JC, Porte RJ, Stravitz RT. Intact thrombin generation and decreased fibrinolytic capacity in patients with acute liver injury or acute liver failure. J Thromb Haemost 2012;10:1312–1319
26. O'Riordan A, Brummell Z, Sizer E, Auzinger G, Heaton N, O'Grady JG, et al. Acute kidney injury in patients admitted to a liver intensive therapy unit with paracetamol-induced hepatotoxicity. Nephrol Dial Transplant 2011;26:3501–3508.
27. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation: Cana- dian Critical Care Trials Group. N Engl J Med 1998;338:791-797.)
28. O'Grady J. Acute liver failure. In: O'Grady J, Lake J, Howdle P, eds. Comprehensive clinical hepatology, 1st ed. London: Mosby, 2000:30.1–20.
29. Ostapowicz GA, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947-954.

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CHRONIC LIVER DISEASE - COMPLICATIONS & MANAGEMENT REVIEW

V Galanakis, KS Kok, AH Mohsen

Abstract

Cirrhosis is the end result of progressive fibrosis of the liver. It is an increasing cause of morbidity and mortality, being the 4th most common cause of death in central Europe. Cirrhosis is a dynamic process and can be broadly divided into compensated and decompensated phase, based on the presence of cirrhosis related complications in the latter phase.

The importance of correct and timely intervention in decompensated liver disease cannot be underestimated. This is evident by deficiencies in care highlighted in a recent NCEPOD report (1). In this article, we aim to describe these complications, with focus on their management and components of a recent care bundle to aid management published by the British Society Gastroenterology (BSG) and British Association for the Study of the Liver (BASL).

This review is to educate junior doctors to recognize, assess and initiate prompt and appropriate management of decompensated liver disease with common specific conditions including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, variceal bleeding and hepatorenal syndrome.

Case

A 60 year old man with background of obesity (body mass index of 28), hypertension and diabetes type 2 was admitted with haematemesis. On examination, he did not have peripheral stigmata of chronic liver disease (Table 1). He used to drink 12 units of alcohol per week. He became haemodynamically unstable and was resuscitated under the local massive haemorrhage protocol.

An urgent gastroscopy showed oesophageal variceal bleeding, which was controlled by band ligation. An abdominal ultrasound revealed liver cirrhosis and portal hypertension and his non-invasive liver screen was negative. The most likely cause of liver cirrhosis was non-alcoholic steatohepatitis (NASH). This case highlights the importance of being vigilant of the patient with no peripheral stigmata of chronic liver disease, presenting with their first episode of decompensated liver disease.

System	Clinical Findings
Hands - Arms	Clubbing, palmar erythema, dupuytrens contracture, asterixis, bruising, excoriation marks
Face – Mouth	Pallor, jaundice, spider naevi, fetor hepaticus, parotid enlargement, Kayser Fleischer eye rings
Chest	Spider naevi, gynaecomastia in males
Abdomen	Ascites (shifting dullness), skin striae, hepatomegaly, splenomegaly
Legs	Peripheral pitting oedema, bruising, excoriation marks
Other	Cachexia (malnourishment), obesity

Table 1: Clinical findings in chronic liver disease.

Introduction

Depending on the underlying cause of liver disease, cirrhosis can take 10-35 years to develop. Once this occurs, the patients can remain in the compensated phase for another 10-15 years before developing complications from decompensated cirrhosis (2,3). Decompensation is usually caused by a precipitating event (Table 2).

Precipitating event	Complications
Excess of alcohol Drug induced Acute viral hepatitis	Variceal bleeding Hepatic encephalopathy Hepatorenal syndrome
Ischaemic hepatitis	Ascites
Surgery	Spontaneous bacterial peritonitis
Infection Constipation Hepatocellular carcinoma	Jaundice
Non-identifiable event	

Table 2: Liver decompensation precipitating events and complications.

A decompensation event can be divided into acute decompensation (AD) or acute on chronic liver failure (ACLF), based on the presence of organ failure in the latter. Mortality predictor scores that are commonly used in patients with chronic liver disease are the Model for End-Stage Liver Disease (MELD) score and Child-Pugh (CP) score (table 3 a/b). ACLF has a significant impact on mortality rates (table 3c). (4).

Parameter	1 point	2 points	3 points
Serum Bilirubin (mol/L)	<34	34-51	>51
Serum Albumin (g/L)	>35	30-35	<30
INR	<1.7	1.7-2.3	>2.3
Ascites	none	Mild	Severe
Hepatic encephalopathy	none	Grade 1-2	Grade 3-4
Points	**Class**	**1 year survival**	**2 years survival**
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Table 3a: Child-Turcotte-Pugh score.

MELD score	≤9	10-19	20-29	30-39	≥40
3 Months mortality rate in hospitalized patients	4%	27%	76%	83%	100%

Table 3b: MELD score - calculated by MELD formula.

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Organ/System	0	1	2	3	4
Liver Bilirubin (mg/dl)	<1.2	≥ 1.2- <1.9	≥ 2 – <5.9	≥ 6 - <12	≥ 12
Kidney Creatinine (mg/dl)	< 1.2	≥ 1.2- <1.9	≥ 2 - <3.5	≥3.5 - <5	≥5
Cerebral HE grade	No HE	1	2	3	4
Coagulation INR (or platelet)	<1.1	1.1 – 1.25	1.26 – 1.5	1.5 – 2.5	>2.5 or Platelet ≤ $20x10^3$/µl
Circulation MAP (mmHg) or vasopressor support	≥ 70	< 70	Dopamine Dobutamine Terlipressin	Dopamine Epinephrine norepinephrine	Dopamine Epinephrine norepinephrine
Lungs PaO_2/FiO_2 Or SpO_2/FiO_2	> 400 > 512	≤ 400 >357 - ≤ 512	≤ 300 >214 - ≤ 357	≤ 200 >89 - ≤ 214	≤ 100 ≤ 89

ACLF Grade	Definition
No	- No organ failure - Single organ failure (liver, coagulation, circulation, lungs) + creatinine <1.5 mg/dl + no hepatic encephalopathy - Single cerebral failure + creatinine < 1.5 mg/dl
1	- Single kidney Failure - Single organ failure (liver, coagulation, circulation, lungs) + creatinine <1.5 - ≤ 1.9 mg/dl and/or hepatic encephalopathy grade 1-2 - Single cerebral failure + creatinine < 1.5 - ≤ 1.9 mg/dl
2	- 2 organ failures
3	- 3 organ failures

Days 3-7	No ACLF	ACLF grade 1	ACLF grade 2	ACLF grade 3
Mortality Day 28	10%	21%	57%	87%
Mortality Day 90	24%	42%	74%	95%
Mortality Day 180	38%	47%	79%	96%

Table 3c: ACLF grade and associated mortality. Areas in yellow indicate system/organ failure.

On admission doctors are advised to use the decompensated cirrhosis care bundle which has been introduced as a result of a negative NCEPOD mortality outcome on patients admitted with decompensated liver disease (1). The bundle can be found on the BSG website.

1. Ascites

Ascites is the pathological accumulation of fluid in the peritoneal cavity. Over 60% of patients with liver cirrhosis develop ascites within 10 years of diagnosis, with 50% mortality within 3 years of development (5). A key factor of ascites development is portal hypertension, which leads to sodium retention and fluid accumulation.

Ascites can be diagnosed either clinically or with abdominal ultrasonography. National (6) and international (7) guidelines highlight the importance of performing a prompt diagnostic aspiration of ascites as part of delivering optimal care for patients hospitalised with decompensated liver disease, leading to reduced in-hospital mortality (8,9).

A diagnostic tap (aspiration of 10–20mls of ascitic fluid) to rule out spontaneous bacterial peritonitis, should be done irrespective of clotting parameters. Risk such as bowel perforation is rare, and a relative contraindication would be ileus with bowel distension.

Ascitic fluid samples:

1. Cultures. *Use aerobic and anaerobic blood culture bottles. Should be taken before commencing antibiotics.*
2. Neutrophil and white cell count: Use EDTA tube.
3. Albumin: *Use serum biochemistry tube.*
4. Cytology: *Use sterile pot.*

Calculating the serum-ascites albumin gradient can help delineate the cause of ascites (10).

- SAAG > 11g/L

  Portal hypertension
  Right sided heart failure
  Cirrhosis
  Nephrotic syndrome

- SAAG < 11g/L

  Malignancy
  Tuberculosis
  Pancreatitis

Management of uncomplicated ascites (6,7):

This is defined as ascites secondary to liver cirrhosis that is not infected and not associated with the development of HRS.

- Grade 1 ascites (mild):

  No treatment is indicated.

- Grade 2 ascites (moderate):

  a. Dietary sodium restriction to 90mmol/day.
  b. Diuretic therapy. Aldosterone antagonist (spironolactone) has been shown to be superior to loop diuretics (11).

Spironolactone: *Starting dose 100mg/day, increasing up to a maximum dose of 400mg/day. Weight loss should not exceed 0.5kg/day in patients without edema and 1kg/day in patients with oedema. Spironolactone should be stopped if patients develop serum potassium >6mmol/L.*

Furosemide: *Used as an adjunct, starting at 40mg/day, increasing to a maximum dose of 160mg/day. This should be stopped if patients develop serum potassium<3mmol/L.*

Diuretics should be stopped temporarily at a serum sodium level of 120-125 mmol/L. Other indications to stop diuretic therapy are progressive renal failure or hepatic encephalopathy.

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- Grade 3 ascites (large):

a. Therapeutic paracentesis.

Paracentesis can also be done for ascites refractory to diuretic therapy.

Liaise with hematologist for advice on correcting coagulation deficiencies.

Drain to dryness in a single session or remove the drain after 6 hours, whichever is first.

Paracentesis of < 5 litres: Synthetic plasma expander such as Gelofusin can be used for plasma expansion.

Paracentesis >5 litres: Use 100mls of 20% human albumin solution for every 2.5 litres of ascitic fluid drained.

Hold diuretics for 48-72 hours post paracentesis.

b. Diuretic therapy should be used as maintenance for Grade 3 ascites, once ascites is controlled.

2. Spontaneous bacteria peritonitis (SBP)

Infection is the most common cause of decompensated liver disease, with SBP being the most frequent bacterial infection in cirrhosis (12). This can be a life-threatening condition and carries 20% mortality (13). SBP can be present in the absence of clinical signs of sepsis, such as fever or abdominal pain. The diagnosis of SBP is based on an ascitic neutrophil count >250 cells/mm3. Commonest organisms implicated include *Escherichia* coli, and Gram positive cocci such as *Streptococci.*

Treatment of SBP:

Promptly start empirical treatment with beta lactams, quinolones, or third generation cephalosporin without waiting for culture results.

Use albumin infusion: 1.5g/kg in the first 6 hours and 1g/kg on day 3 of admission. This has been shown to improve survival outcomes and incidence of hepatorenal syndrome (14).

A decrease of less than 25% in neutrophil count in a repeat ascitic tap after 48 hours of therapy indicates treatment failure.

Consider secondary bacterial peritonitis, caused by inflammation of intra-abdominal organs or a perforated viscus in the presence of multiple organisms in the ascitic fluid.

In patients with bacterascites, that is, ascitic fluid with a neutrophil count < 250 cells/mm3 but culture positive, empirical treatment for SBP should be initiated if symptomatic. If not, the ascitic tap and culture should be repeated.

Prophylaxis of SBP:

Start after first episode of SBP or if the ascitic fluid protein is less than 15g/L (2)

Prescribe Norfloxacin 400mg/day or ciprofloxacin 500mg once a day, long term.

3. Hepatic encephalopathy (HE)

Hepatic encephalopathy is a reversible brain dysfunction secondary to liver impairment and/or portosystemic shunt (15). The pathophysiology of this condition is poorly understood, but ammonia, neurotransmitters and circulating amino-acids seems to play important role.

Patients with liver cirrhosis have an up to 40% lifetime risk of developing overt HE (OHE) (16). HE can present with behavioral changes, pyramidal signs, extra-pyramidal signs, asterixis or myelopathy (17). HE can be graded using the West Haven criteria.

West Haven Criteria for grading HE:

Grade 1: *Trivial lack of awareness, euphoria or anxiety, Impairment of calculations, altered sleep rhythm, shortened attention span.*

Grade 2: *Lethargy or apathy, disorientation for time, obvious personality change, inappropriate behavior, dyspraxia, asterixis.*

Grade 3: *Somnolence to semi-stupor, responsive to stimuli, confusion, gross disorientation, bizarre behavior.*

Grade 4: *Coma.*

Precipitants of HE:

- *Infections*
- *GI bleeding*
- *Diuretics*
- *Electrolyte disturbance (hyponatremia, hypokaelemia) and acute kidney injury*
- *Constipation*
- *Unidentified causes.*

The diagnosis of HE is clinical, although several diagnostic tests exist, mainly utilized in clinical studies (17). Ammonia is a useful test in HE and normal values should question the HE diagnosis. On the other hand hyperammonaemia doesn't always suggest the presence of HE (18).

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Differential Diagnosis of HE (17):

- *Metabolic abnormalities (ketoacidosis, hypoglycemia, uremia)*
- *Alcohol related encephalopathy*
- *Drug related (opioids, neuroleptics)*
- *Central nervous system infection*
- *Electrolytes imbalance (hyponatraemia, hypercalcaemia)*
- *Epilepsy*
- *Psychiatric disorders*
- *Brain haemorrhage, infarct or mass*
- *Dementia*

Treatment of overt hepatic encephalopathy:

1. ABCDE approach. *If the patient's GCS is <8, please sought advice from anaesthetics with regards to airway support.*

2. Establish whether there is new cognitive impairment.

3. Address any precipitating causes.

4. Send initial baseline bloods, including ammonia l*evels (sample in ice). If the ammonia is normal then consider other* differential diagnoses.

5. If any clinical doubt, consider CT head *to rule out subdural haematoma, as patients with alcohol excess have an increased risk of developing this.*

6. Once diagnosis of HE is established, initiate treatment with lactulose *50-60 ml per day in divided doses. Stool chart should be started, aiming for >3 bowel motions per day. Lactulose is catabolized to short-chain fatty acids which acidifies the lumen, favoring the formation of non-absorbable ammonium rather than ammonia. Other contributory effects include reducing the gut bacterial load and promoting healthy flora growth (19).*

7. Rifaximin *is an oral antibiotic that can be used for re-current HE as an add-on therapy to lactulose (20). The usual dose is 550 mg twice a day.*

8. General supportive care: *Nutritional support (consider nasogastric feeding in OHE), falls prevention.*

9. Other treatments: *A rectal enema is commonly used in clinical practice although more studies are needed to establish its use. Neomycin, metronidazole, vancomycin, ornithine-aspartate (LOLA), branched-chain amino acids (BCAA), probiotics, albumin infusion have all been suggested as treatment of HE, although more studies are needed to establish their efficacy (17,20).*

In terms of prevention of HE, lactulose and Rifaximin are the mainstay of treatment to date. Liver transplant remains a treatment for intractable HE associated with poor liver function (17).

4. Variceal Haemorrhage in Cirrhotic patients

Varices develop as a result of increased venous pressure following distorted micro-architecture of liver parenchyma in cirrhosis. Retrograde venous pressure causes the development of shunts within the systemic circulation, including the gastro-oesophageal, rectal, para-umbilical, retroperitoneal and left renal veins. The strongest predictor of varices development is a hepatic venous pressure of >10mmHg (21).

4a. Acute variceal bleeding:

This is a medical emergency. The in-hospital mortality can reach 15-20% (22). Management steps include (21,23).

1. ABCDE *approach with a focus on ''C'' and calculate risk* scores *used in upper gastrointestinal track (UGI) bleeding (see table 4).*

2. Establish 2 wide-bore cannulas (green) and initiate fluid resuscitation *until blood products become available. Aim for a systolic blood pressure of 100 mmHg.*

3. Consider activating the Massive Haemorrhage *protocol after consulting your local trust's guideline.*

4. Send baseline blood tests *(Haemoglobin (Hb), urea, liver function tests, coagulation) and a venous blood gas for immediate haemoglobulin result.*

5. Cross match 4 *units of Red blood cells and transfuse to a target Hb of 7-8g/dL.*

6. Correct clotting deficiencies – *Liaise with Hematologist.*

- *Fresh Frozen Plasma: if Fibrinogen< 1*
or Prothrombin time >1.5 times of normal limit

- *Prothrombin complex (Beriplex): When on warfarin and actively bleeding*

- *Platelet transfusion: PLT< 50 and active bleeding*

7. Consider Terlipressin 2 *mg 4-6 hourly. This reduces risk of variceal bleeding by causing splanchnic vasoconstriction and reduction of the variceal pressure. Contraindications of Terlipressin are ischaemic heart disease (look at past medical history and electrocardiogram) and peripheral vascular disease.*

8. Give Antibiotics *according to Trust policy. Antibiotics have been shown to reduce mortality in variceal bleed.*

9. Ask for advice from a senior colleague *(Medical Registrar or Medical consultant).*

10. Inform endoscopy *department and request urgent gastroscopy. Ideal time of endoscopy is within 24 hours of variceal bleeding after adequate resuscitation. During gastroscopy variceal banding is aimed for oesophageal varices and cyanoacrylate injection for gastric varices. There is no need for intravenous proton pump inhibitors use before the endoscopy.*

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11. Failure *of the above treatment reflects the severity of the condition. Other measures include insertion of a Sengstaken-Blakemore tube, transjugular intrahepatic portosystemic shunt (TIPSS) procedure or surgical intervention.*

12. Hand over *to the on call team to ensure continuity of care.*

BLATCHFORD Score
Score = 0 Can be managed as Outpatient
Score>0 Needs medical intervention

Parameters on admission	Score
Serum Urea (mmol/l)	
6.5-7.9	2
8-9.9	3
10-24.9	4
>25	6
Haemoglobulin (g/dl)	
Men:	
12-13	1
10-11.9	3
<10	6
Women	
10-12	1
<10	6
Systolic BP (mmHg)	
100-109	1
90-99	2
<90	3
Other markers	
Pulse >100	1
Melaena	1
Syncope	2
Liver disease	2
Cardia failure	2

ROCKALL SCORE Score< 3 = good prognosis / Score > 8 = poor prognosis

Parameter	0	1	2	3
Age	<60	60-79	>80	
Shock	Systolic BP> and HR < 100	Systolic BP>100 and HR >100	Systolic BP<100 And HR > 100	
Co-morbidity	No major comorbidity		Cardiac failure, ischemic heart disease, other major co-morbidity	Renal failure or disseminated malignancy
Endoscopic source of diagnosis	Mallory Weiss tear or no lesion	All other diagnoses	Malignancy of upper GI tract	
Evidence of bleeding	none		Evidence or recent bleed	

Table 4: Upper GL bleeding scores.

4b. Primary prophylaxis for oesophageal varices (21)

Patients with a new diagnosis of liver cirrhosis need an outpatient endoscopy to assess for possible varices.

No varices:

- *Repeat endoscopy in 2-3 years' time.*

Grade 1 varices (can be flatten easily with air):

- *Repeat endoscopy after 1 year, no pharmacological treatment is required*

Grade 1 varices with high risk stigmata of bleeding or Grade 2 and 3:

- *1st line treatment is non-cardioselective b-blockers. Propranolol 20 mg twice a day or three times a day and if tolerated increase to 80 mg once a day (long-acting tablet). Carvedilol 6.25 mg once or twice a day is an alternative option.*

- *2nd line is variceal band ligation*

4c. Secondary prophylaxis (21):

Once variceal bleeding occurred, the risk of re-bleeding is high and secondary prophylaxis is recommended.

Oesophageal varices:

- *1st line: Beta-blockers and band ligation or monotherapy as alternative option.*

- *2nd line: TIPS or shunt surgery.*

Gastric varices:

- *Band ligation or cyanoacrylate injection, depending on varices location.*

5. Hepatorenal Syndrome (HRS)

Hepatorenal syndrome is a diagnosis of exclusion in a patient with liver disease and renal failure, with no identifiable cause for the renal failure. Recently, the diagnosis of acute kidney injury (AKI) has been re-defined in cirrhotic patients as the previous definition was thought to be less representative in this cohort of patients (24).

AKI definition:

Stage 1: *Increase in serum creatinine (sCr) ≥0.3 mg/dl (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline*

Stage 2: *Increase in sCr >2-fold to 3-fold from baseline*

Stage 3: *Increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 µmol/L) with an acute increase ≥0.3 mg/dl (26.5 µmol/L) or initiation of renal replacement therapy.*

Diagnostic criteria of HRS – ALL required (7)

1. Cirrhosis with ascites.

2. AKI diagnosis (above criteria).

3. No renal function improvement after withdrawal of diuretics and volume expansion with albumin infusion (1 gr/kg) for 2 consecutive days.

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4. No current or recent use of nephrotoxic drugs (contrast media, Non steroidal anti-inflammatory drugs).

5. Absence of shock.

6. No parenchymal or structural renal disease (no hematuria, proteinuria or obstruction on renal ultrasonography).

Hepatorenal syndrome can be divided into two types (7).

- Type 1 HRS (HRS-1): *Increase of serum creatinine ≥ 100% compared to baseline to a final level greater than 221 µmol/L in less than 2 weeks. It most commonly occurs in severe alcoholic hepatitis or in advanced liver failure complicated by an infection, especially spontaneous bacterial peritonitis.*

- Type 2 HRS (HRS-2): *It is characterized by a less progressive renal impairment. HRS carries a poor prognosis, with an average median survival time of three months (25).*

Pathophysiology of HRS

HRS occurs due to hypoperfusion of kidneys following renal artery vasoconstriction caused by activation of the sympathetic nervous system and the renal-angiotensin–aldosterone axis, as a response to splanchnic vasodilatation due to impaired liver metabolism in cirrhosis. It is important to realize that HRS is not a primary renal disease, but can lead to ischaemic renal changes (25).

Management of HRS (7)

1. Make the correct diagnosis *using the above criteria and set a ceiling of patient's care after consultation with a senior colleague.*

2. Start Terlipressin and Albumin infusion.

- Albumin: Dose 1 g/kg on day 1 and 2, followed by 40 g/day. The above treatment has showed survival benefit in HRS-1, and it is also efficacious in HRS-2 (26).

- Terlipressin: Dose 1 mg every 4 to 6 hours. The dose can be doubled if creatinine has not shown reduction of at least 25% at day 3. The duration of treatment can be prolonged for about 14 days or until a creatinine has return to less than 133 µmol/L. Once again ensure that there are no any contraindications to its use.

3. Ensure diuretics *have been* stopped. *Furosemide could be used to maintain urine output and treat fluid overload, although this is not evidence based. Also review the drug chart and omit any nephrotoxic drugs.*

4. Monitor parameters *such as urine output, fluid balance and blood pressure to assist volume expansion treatment. Aim for a mean arterial pressure of >80mmHg. Crystalloids are not contraindicated, but better avoided as could lead to fluid overload and dilutional hyponaetremia. Volume expansion should be aimed with albumin infusion.*

5. Screen for precipitating factors, *especially sepsis.*

6. Large volume paracentesis is best avoided as post-paracentesis circulatory dysfunction by fluid shifting may further hypoperfuse the kidneys. It can be used to drain small volumes for patient's comfort.

7. Liver transplantation *is the best treatment for hepatorenal syndrome, with survival rates of around 65% in HRS-1.*

6. Hepatorenal Syndrome

Patients with liver cirrhosis are at higher risk of developing HCC. In clinical practice, surveillance of high risk population is recommended every six months with alpha-fetoprotein levels and a liver ultrasound to detect any focal lesions.

7. Hepatopulmonary Syndrome

Hepatopulmonary syndrome needs to be suspected in cirrhotic patients who desaturate and no other cause has been found (27).

8. Nutrition in Cirrhotics

Malnutrition in liver disease is common, varying from 20% in compensated cirrhosis to 60% in decompensated cirrhosis. It is associated with higher rates of mortality and morbidity. Malnourished patients require 35–40 kcal/kg/day with a protein intake of at least 1.2–1.5 g/kg/day. Glucose should provide 50–60% of non-protein energy and lipid about 40–50%.

Nutrition needs to be introduced gradually while monitoring for refeeding syndrome. Folate, thiamine and Vitamin C deficiencies are the most common deficiencies in alcoholic liver disease. Pabrinex (thiamine) and multivitamins are prescribed when malnutrition is suspected. A dietician review is crucial to guide nutritional support. Oral or enteral (via nasogastric tube) feed are commonly the preferred feeding routes (28).

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Summary

- Use the liver care bundle as an aid in the management of decompensated liver disease.

- Suspect new diagnosis of decompensated liver disease in patients with risk factors, stigmata of liver disease, deranged LFTs, low platelets or abnormal clotting profile.

- Liaise with a senior colleague early when there is evidence of septic shock, acute kidney injury, hyponaetremia, hypovolemic shock (suspicion of variceal bleed), hepatic encephalopathy or jaundice.

- Ensure handover to the on-call team to chase pending results or further monitor response to initial treatment.

- Seek specialist advice within 24 hours.

Questions - Choose One Answer

1. A 46 year old male with known alcoholic liver disease is admitted with increased ascites.

What is/are the important initial tests to perform?

a. Full blood count and Prothrombin time
b. Diagnostic ascitic tap
c. Liver function tests
d. USS of the abdomen
e. All the above

2. A 39 year old female with known alcoholic liver disease and ongoing alcohol consumption is admitted to the ward with decreased conscious level (GCS=12).

Initial blood tests showed ammonia of 20 (normal), WCC 16, Hb 122, PLT 45, CRP 7, urea 6, creatinine 99 and INR 1.6. What action should you take?

a. Start lactulose
b. Start lactulose and Rifaximin
c. Perform an urgent abdominal USS
d. Perform an urgent CT head
e. Start neuro observation

3. A 56 year old man with non-alcoholic steatohepatitis was admitted with haematemesis. He is haemodynamically stable, awaiting a gastroscopy. The ward nurse asks you to review his drug chart. Which one of the options is incorrect?

a. Stop prophylactic enoxaparin
b. Give further Vitamin K even if he already had a STAT dose and his INR is 1.4
c. Stop the Antibiotics prescribed as there is no evidence of sepsis
d. Continue Terlipressin at 2 mg QDS even if urine output is good
e. Stop intravenous pantoprazole, which has been prescribed by the admission doctor

4. A 64 year old man with refractory ascites secondary to liver cirrhosis underwent a large volume paracentesis of 13 litres as an inpatient and 3 days later he developed AKI. Which of these statements is correct?

a. The patient needs HAS 20% 100 ml for every 5 litres of ascites drained
b. The AKI represents HRS type 1
c. The AKI represents pre-renal failure
d. Terlipressin is contraindicated
e. Spironolactone should be started immediately

5. A 68 year old male with liver cirrhosis is admitted with abdominal pain, ascites and diarrhoea. He has a background of ulcerative colitis and primary sclerosing cholangitis. His CRP is 45. His WCC is 20. An urgent tap was performed and the patient was started on Co-amoxiclav for possible SBP. Despite this, his pain worsens and cultures from a repeat ascitic tap showed the presence of E.coli and Enterococcus. What is the next best step in his management?

a. Seek microbiologist advice
b. Escalate empirical treatment to Piperacillin/Tazobactam
c. Continue current antibiotics
d. Request urgent computed tomography (CT) abdomen
e. Request urgent USS abdomen

Answers

Q1: E

Use the Liver care bundle for every patient with decompensated liver disease admitted in the hospital.

Q2: D

An urgent CT head is indicated as ammonia level is normal and other differential diagnosis apart from HE must be considered. Remember that patients with alcohol excess are at high risk of subdural haematoma. Her INR is 1.6 and platelets <50 which makes an intracranial bleed a likely cause.

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Q3: C

The incorrect step would be to stop antibiotics as this has a proven role in reducing mortality in variceal bleeding even if there is no clinical evidence of infection. Intravenous proton pump inhibitors are not indicated in variceal bleeding. Give Vitamin K 10 mg for 3 days to replenish stores, irrespective of INR.

Q4: C

The most likely cause of his AKI is secondary to hypovolaemia post-large volume paracentesis. He needs HAS 20% 100 ml for every 2.5 liters drained. Spironolactone, a potassium sparing diuretic, is contraindicated as his ascites is refractory and in AKI there is risk of hyperkalemia.

Q5: D

If multiple pathogens are identified in the ascitic fluid, secondary bacterial peritonitis must be excluded. In this case he has UC and a perforation needs to be excluded.

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References

1. McPherson S, Dyson J, Austin A, et al, Response to the NCEPOD report: development of a care bundle for patients admitted with decompensated cirrhosis—the first 24 h. Frontline Gastroenterology 2016;7:16-23
2. National Institute for Health and Care Excellence. Cirrhosis in over 16s. Assessment and management. London; NICE; 2016
3. Detlef Schuppan and Nezam H. Afdhal, Liver cirrhosis, Lancet. 2008 Mar 8; 371(9615): 838–851. doi: 10.1016/S0140-6736(08)60383-9
4. Moreau R, Jalan R, Gines P et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013 Jun;144(7):1426-37, 1437.e1-9. doi: 10.1053/j.gastro.2013.02.042
5. Pedersen J, Bendtsen F, Moller S. Management of cirrhotic ascites. Therapeutic Advances in Chronic Disease. 2015;6(3):124-137
6. Moore K. Guidelines on the management of ascites in cirrhosis. Gut. 2006;55(suppl_6):vi1-vi12
7. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and Hepatorenal syndrome in cirrhosis. European Association for the Study of the Liver. J Hepatol 2010 vol. 53 j 397–417
8. Orman E, Hayashi P, Bataller R, Barritt A. Paracentesis Is Associated With Reduced Mortality in Patients Hospitalized With Cirrhosis and Ascites. Clinical Gastroenterology and Hepatology. 2014;12(3):496-503.e1
9. Kim J, Tsukamoto M, Mathur A, Ghomri Y, Hou L, Sheibani S et al. Delayed Paracentesis Is Associated With Increased In-Hospital Mortality in Patients With Spontaneous Bacterial Peritonitis. The American Journal of Gastroenterology. 2014;109(9):1436-1442
10. Lenz K, Buder R, Kapun L, Voglmayr M. Treatment and management of ascites and hepatorenal syndrome: an update. Therapeutic Advances in Gastroenterology. 2014;8(2):83-100
11. Pérez-Ayuso RM, Arroyo V, Planas R, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Gastroenterology. 1984;84:961–968
12. Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. Gut. 2011;61(2):297-310
13. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis 2008;28:26–42.
14. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L et al. Effect of Intravenous Albumin on Renal Impairment and Mortality in Patients with Cirrhosis and Spontaneous Bacterial Peritonitis. New England Journal of Medicine. 1999;341(6):403-409
15. Cordoba J. New assessment of hepatic encephalopathy. J Hepatol 2011;54:1030–1040
16. Amodio P, Del Piccolo F, Pettenò E et al. Prevalence and prognostic value of quantified electroencephalogram (EEG) alterations in cirrhotic patients. J Hepatol 2001;35:37–45
17. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol (2014), http://dx.doi.org/10.1016/j.jhep.2014.05.042
18. Lockwood AH. Blood ammonia levels and hepatic encephalopathy. Metab Brain Dis 2004;19:345–349
19. Peter Ferenci. Hepatic encephalopathy in adults: Treatment. Up-To-Date May 2017
20. Sharma BC, Sharma P, Lunia MK et al. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. Am J Gastroenterol. 2013 Sep;108(9):1458-63
21. Tripathi D, Adrian J Stanley, Peter C Hayes et al. UK guidelines on the management of variceal haemorrhage in cirrhotic patients Gut 2015;0:1–25. doi:10.1136/gutjnl-2015-309262
22. Jairath V, Rehal S, Logan R, et al. Acute variceal haemorrhage in the United Kingdom: patient characteristics, management and outcomes in a nationwide audit. Dig Liver Dis 2014;46:419–26
23. Jennifer Clough, Elizabeth Sweeney, Philip J Smith. BSG GASTROENTEROLOGY HANDBOOK A Guide for Junior Doctors Based On The Ward
24. Paolo Angeli Pere Ginès, Florence Wong et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. J Hepatol. 2015
25. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009;361:1279–1290
26. Gluud LL, Christensen K, Christensen E, Krag. A Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. Hepatology. 2010 Feb;51(2):576-84. doi: 10.1002/hep.23286
27. Grace JA, Hepatopulmonary syndrome: update on recent advances in pathophysiology, investigation, and treatment. J Gastroenterol Hepatol. 2013 Feb;28(2):213-9. doi: 10.1111/jgh.12061
28. John Saunders, Anna Brian, Mark Wright, Mike Stroud. Malnutrition and nutrition support in patients with liver disease Frontline Gastroenterology 2010;1:105–111. doi:10.1136/fg.2009.000414

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CHRONIC PANCREATITIS

K Gordon, A C Li

Abstract

Chronic Pancreatitis is a progressive inflammatory disease of the pancreas that leads to fibrosis of the gland. It is often underestimated in both its prevalence and the effect it has on a patient. Whilst there are clear guidelines on acute pancreatitis and easy to follow acronyms, chronic pancreatitis can often induce the heart sink sensation in the physician.

However it is important to note that chronic pancreatitis is a chronic condition that results in significant morbidity for the patient. There are a number of complications associated with the condition, most commonly those of chronic pain and the loss of the endocrine and exocrine function of the pancreas. There are also more rare complications that carry a high mortality rate.

Foundation year trainees may meet patients with chronic pancreatitis in A&E, during acute takes (both medical and surgical) and in primary care. We discuss a rare presentation of Pancreatitis, and the appropriate management that follows.

Case History

A 72year old female was admitted with haematemesis. She reported a history of epigastric pain of over 4weeks duration that was not relieved by Proton Pump inhibitor therapy. Past medical history revealed only hypertension, she was a non-smoker and only drank minimal alcohol.

She did not report having a similar pain previously. On examination there was a palpable mass in the epigastrium and initial investigations showed a normocytic anaemia, Hb 78 and a raised INR of 1.6. Amylase was normal at 45, blood sugar was not raised. She was treated with an ABC approach, and fluid resuscitated initially with saline, then with cross matched blood.

ABCDE approach

IV access and take bloods –inc Hb, urea, clotting, G&S

Fluid resuscitate if systolic BP <90

Consider investigation & discuss with senior - ?endoscopy, CT angiography, surgery

Figure 1: Initial approach to a patient with Gastrointestinal Haemorrhage.

As the patient presented out of hours, in a hospital without gastroenterology cover, the initial investigation performed was a CT scan of the abdomen. This showed a mass in the region of the Pancreas, that was likely inflammatory in nature, with a haematoma and an aneurysmal Splenic artery (shown in figure 2).

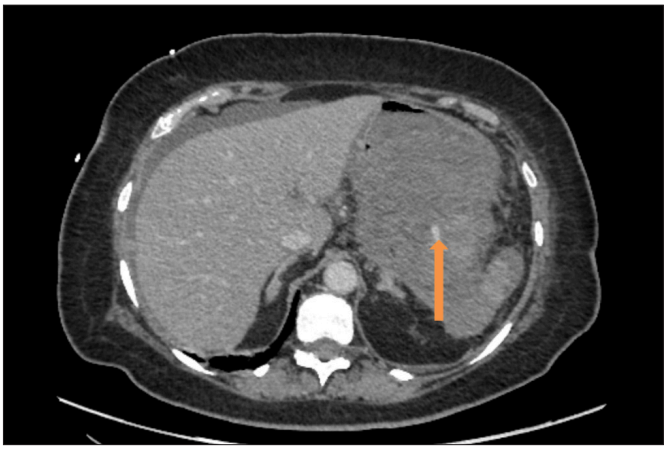

Figure 2: CT scan showing large haematoma and inflammatory mass with active bleeding (indicated by arrow).

The following morning, a Gastroscopy was performed that showed a bleeding ulcer in the stomach, which could not be treated endoscopically. The patient underwent embolization of the splenic artery via interventional radiology, after which she remained stable and had no further bleeding.

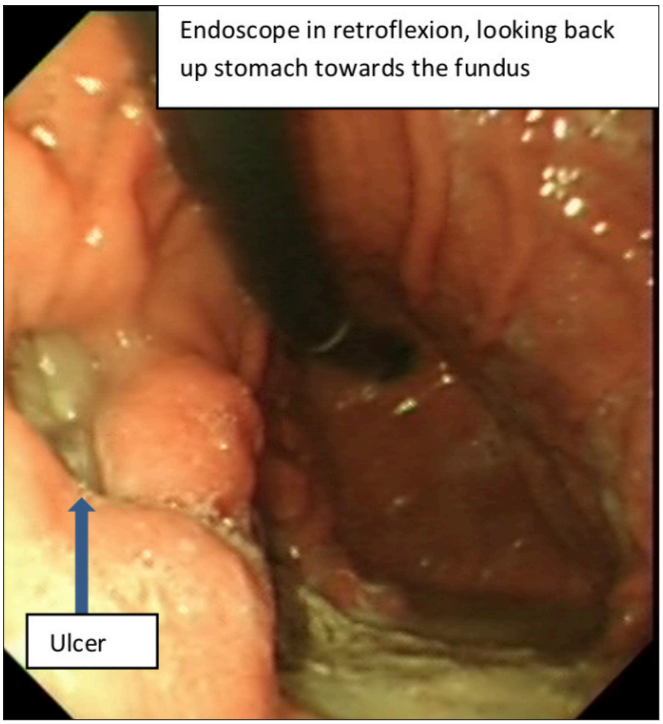

Figure 3: Repeat OGD image of ulcer.

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Repeat CT scan 4weeks later showed significant reduction in the inflammatory mass, the pancreas slightly shrunken but otherwise normal. Gastroscopy was repeated (shown in figure 3) and showed the ulcer healing.

The final diagnosis was that of Chronic Pancreatitis (given a history of longer than 4weeks), that led to a splenic artery aneurysm, which ruptured and caused a haematoma that eroded into the gastric wall, resulting in haemetemesis.

Discussion

What is chronic pancreatitis?

Chronic pancreatitis is, as the name suggests, chronic inflammation of the Pancreas, causing epigastric pain that may be difficult to control. Estimated annual incidence is 5-12/100,000 and a prevalence of 50/100,000 people (1). It is more common in men and in those aged between 30-40. The chronic inflammation leads to fibrosis of the pancreas, replacing the original parenchyma of the gland that can ultimately lead to the loss of the endocrine and exocrine function.

Causes are similar to those for Acute Pancreatitis: excess alcohol intake, biliary obstruction (for example by Gallstones or strictures), Cystic Fibrosis, Familial Pancreatitis and Autoimmune Pancreatitis.

Presentation is usually with chronic epigastric pain that may radiate through to the back. There may be associated nausea and vomiting, weight loss, steatorrhea and signs of malabsorption.

Differential diagnoses:
Acute pancreatitis
Peptic Ulcer
Gastroenteritis
Reflux disease
Non-GI cause – consider atypical cardiac pain, spinal problems

Figure 4: Differential diagnoses of severe epigastric pain.

How is it diagnosed?

Unlike Acute Pancreatitis, amylase levels are usually normal or only moderately raised in Chronic Pancreatitis, as it was in this clinical case. Lipase level may also be raised. The best way to diagnose Chronic Pancreatitis is with imaging. A CT scan may show calcification of the pancreas, inflammation or atrophy.

A biopsy may be performed, usually via an endoscopic ultrasound. Other tests to identify the cause should also be performed – this includes MRCP looking for obstructive gallstone disease or biliary obstruction; IgG4, ANA and ANCA looking for autoimmune pancreatitis; triglyceride levels.

When Chronic Pancreatitis is suspected, it may also be necessary to investigate for associated complications, following a thorough history. If there are symptoms suggestive of steatorrhoea, Faecal Elastase would indicate if there is Pancreatic insufficiency and malabsorption. It is important to identify if the patient has developed diabetes with glucose level, HbA1C and glucose tolerance test if necessary.

Test	Reason
Amylase & lipase	Is there evidence for acute inflammation of the pancreas?
LFTs inc. clotting	Is there evidence of biliary tract involvement?
Glucose	Hypoglycaemia is associated with chronic pancreatitis
Triglycerides	Hyperlipidaemia can be a cause for pancreatitis
IgG4, ANA, ANCA	Testing for autoimmune pancreatitis
CT abdomen	Looking for evidence of calcification, atrophy of the pancreas
MRCP	Looks more closely at the biliary tree
EUS	Allows directed biopsy sampling
Faecal elastase	Low result indicates pancreatic insufficiency

Figure 5: Tests to request when considering chronic pancreatitis.

CHRONIC PANCREATITIS

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Complications

The most common complications are those of pain and the loss of Pancreatic function leading to malabsorption and Diabetes, treatment of which is discussed below.

Rarer complications include

Pseudocyst – a well circumscribed sack containing fluid, Pancreatic enzymes, blood and necrotic tissue, typically located in the lesser sac. Often Pseudocysts do not require a specific treatment, other than observation. However, if they progress in size rapidly, they may require drainage, which is performed either radiologically or endoscopically with Ultrasound guidance.

Splenic vein thrombosis – this can result in Portal hypertension with subsequent Oesophageal or Gastric varices.

Splenic artery aneurysm – such as in this case, pseudo-aneurysms can develop, which are at high risk of rupture. They are a very rare complication however they almost always present with catastrophic effects (2) that carry a very high mortality rate of up to 90% (3). Treatment is either radiological by embolization or surgical.

Treatment

Pancreatic enzyme replacement is necessary to replace those not being produced by the Pancreas. This helps to reduce the experience of steatorrhea and improves intestinal absorption. Dietitians should also be involved to ensure that patients are receiving adequate nutrition- some may require fat soluble vitamin replacement.

Diabetes can be particularly difficult to control and patients often experience hypoglycaemic attacks (4). Particular caution must be paid to those started on insulin.

Pain is often long standing, and difficult to overcome. Patients often require large amounts of analgesia including opiates. There has been some evidence for the use of octreatide. Analgesic block of the coeliac axis and surgery may be required.

Screening for osteoporosis is advised in those who have malabsorption, with a DEXA scan.

It is important to consider a holistic approach, and if the patient has Chronic Pancreatitis secondary to alcohol excess, it is an opportunity to discuss alcohol intake and whether the patient may require further help and support in reducing their alcohol intake.

MCQs

1. A patient presents with severe epigastric pain – what is the first investigation, after observations, history and examination?

a. Bloods inc. amylase, ABG

b. CXR

c. USS

d. CT

2. A patient presents with severe epigastric pain, radiating through to the back. They have reported coffee-ground vomiting, with a history of alcohol excess. What is the most likely diagnosis?

a. Acute pancreatitis

b. Chronic pancreatitis

c. Peptic ulcer

d. Gastroenteritis

3. What would be appropriate tests to establish the cause of Pancreatitis?

a. Salt sweat test

b. IgG4

c. Lipid profile

d. MRCP

e. All of the above

4. A patient diagnosed with chronic pancreatitis secondary to alcohol is found unresponsive on the ward. What is the first investigation you would perform?

a. CT head

b. Vitamin levels

c. Bedside blood sugar

d. ABG

CHRONIC PANCREATITIS

K Gordon, A C Li

5. Chronic pancreatitis increases risk of pancreatic cancer?

a. True
b. False

Answers

1A

Whilst imaging is likely required and a CT scan is gold standard, it is important not to forget baseline investigations, initially with bloods.

2C

All of these options are differential diagnoses for the patient described, however peptic ulceration is the most common cause of upper gastrointestinal bleed.

3E

Salt sweat test would aid the diagnosis of cystic fibrosis; IgG4 is the most common immunomarker of Autoimmune Pancreatitis; and Hypercholesterolaemia is a recognised cause of chronic pancreatitis, which is often familial.

4C

Whilst all of these investigations may be necessary, the most immediate and close to hand is that of a BM and patients with chronic pancreatitis are at higher risk of developing hypoglycaemia.

5A

Chronic inflammation of the pancreatitis increases the chance of developing pancreatic cancer, particularly in those with a history of alcohol excess

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References

1. https://pancreasfoundation.org/patient-information/chronic-pancreatitis
2. Shah, S., Dani, S. & Shah, R. V. (2002) Pseudoaneurysm from splenic artery associated with Chronic Pancreatitis. Indian Journal of Radiology and Imaging, 12(4): 505-506.
3. Agrawal, G., Johnson. & Fishman, E. (2007) Splenic artery and Pseudoaneurysms: clinical distinctions and CT appearances. American Journal of Roentgenology 188(4):992-997.
4. https://cks.nice.org.uk/pancreatitis-chronic

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OBESITY

S Ahmed

Mechanisms of appetite control including the physiological and psychological aspects that influence food intake & strategies to prevent and treat weight gain in susceptible individuals.

Introduction

Venus of Willendrof, a limestone statue, represents prehistoric description of an obese woman about 20,000-25,000 BCE in early Stone Age (1). But historic description of obesity as a disease and a gateway for other diseases by Hippocrates (2) showed that ancient Greeks were aware of its potential consequences on health about 2300 years ago.

In modern era of current civilization, a robust drive to recognize, prevent and treat excessive weight gain came from its profound impact not only on morbidity and mortality in cardiovascular diseases and diabetes but also its recent recognition in Cancer pathogenesis (3).

Mechanism of appetite control

Appetite is derived from a Latin word 'Appetitus' which means strong desire to strive (8). Various biological, neuronal and psychological mechanisms are involved in increased appetite and weight gain.

1 - Central control of appetite.

Hypothalamus contains centres to control appetite and energy generation. Many different hormones, peptides and neurotransmitters integrate with neuronal circuits in Arcuate nucleus of Hypothalamus to control appetite. Arcuate nucleus can further interact with Lateral hypothalamus which increases appetite and ventromedial hypothalamus which is a satiety centre and can decrease appetite (12).

There are 2 distinct groups of neurons in Arcuate nucleus one group expresses AgRP/NPY (agouti-related protein/neuropeptide Y) and other group expresses CART/POMC (Cocaine and amphetamine-related transcript/pro-opiomelanocortin). (Figure 1)

1 - AgPR/NPY

It stimulates appetite by stimulating lateral hypothalamus (LH) and inhibiting ventromedial hypothalamus (VMH)

2 - CART/POMC

This group Inhibits appetite by inhibiting LH and stimulating VMH (9).

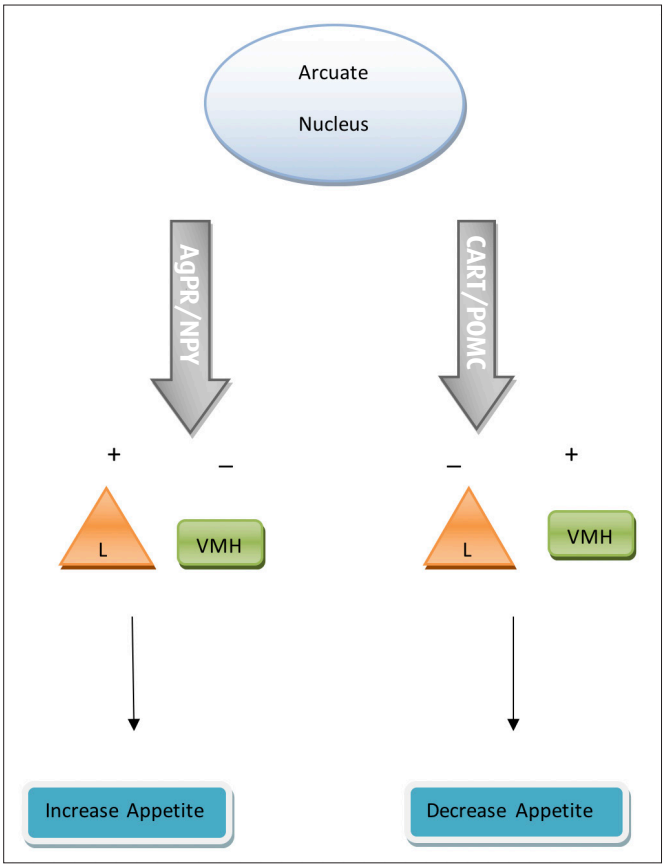

Figure 1: AgRP-Agouti related peptide, CART-cocaine and amphetamine related transcript, POMC-pro-opiomelanocartin, NPY-neuropeptide Y, LH- lateral hypothalamus, VMH-ventromedial hypothalamus.

Furthermore it is interesting to note that these neuronal circuits are affected by hypothalamic peptides including neuropeptide Y (NPY), melanin concentrating hormone (MCH), agouti related peptide (AgRP), Orexin and endocannabinoid which can increase appetite and melanocyte stimulating hormone (a-MSH), cocaine and amphetamine related transcript(CART), glucagon related peptide (1) (GLP-1) and serotonin which can decrease appetite. These hypothalamic peptides in turn are influenced by various hormones and gut peptides which I will discuss.

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2 - Hormones

i) Leptin

Adipose tissue is an endocrine organ (10) releasing different hormones of which leptin has profound impact on controlling hunger and food intake.

Its discovery in 1994 revels its negative feedback to hypothalamus regarding energy reserves and adipose tissue (11). NPY/AgRP neurons in Arcuate nucleus of hypothalamus stimulate food intake and they are inhibited by leptin as evidenced by low Leptin levels in state of hunger and vice versa. But obese individuals develop Leptin resistance and despite high circulating levels of leptin there food intake isn't inhibited (12).

ii) Insulin

Insulin has a negative feedback effect on appetite similar to leptin (12). In type II diabetes and insulin resistance, hypothalamus also develop resistance to insulin effect. Bruning J.c.et al (13) did an interesting study using neuronal insulin receptor knockout mice (NIRKO) and found that they developed hyperphagia, weight gain and reproductive abnormalities.

iii) Cortisol

High cortisol levels are related to increased appetite. Epel E and colleagues found that stress related increased cortisol secretion in women caused increased appetite and they consumed more sweet foods (14).

3 - Gut peptides

i) CCK

Cholecystokinin is a gut peptide secreted in response to fat entering duodenum and can cause contraction of gallbladder, releasing bile and pancreatic enzymes for digestion of fat and protein.

It can also decrease appetite through different proposed mechanisms such as inhibiting stomach emptying, stimulating vagal afferents signals for satiety and through its central action via CCK receptors in brain.

In this regard an interesting study showed how Proglumide (CCK antagonist) can increase stomach emptying and resultant increase appetite in rats (17).

ii) Ghrelin

Ghrelin is a neuropeptide also called ''Hunger Hormone'' (15). It secreted by stomach and act on NPY pathway in Arcuate nucleus to stimulate appetite through its receptor ghrelin/growth hormone secretaguage receptor (GHSR) (12,15). A.M.Waren and colleagues demonstrated that intra cerebral and intraperitoneal administration of Ghrelin can stimulate appetite in rats (16).

Furthermore it is also involved in reward perception and can inhibit vagal signals from stomach stretch to prevent inhibiting appetite.

iii) PYY

Peptide YY is a gut peptide hormone which is released from ileum and colon in response to food. Apart from water and electrolyte absorption it has a profound effect on appetite suppression. It activates NPY pathway in arcuate nucleus by acting on Y2R receptors causing appetite supression (18, 19).

In one study it was demonstrated that intravenous infusion of PYY can cause appetite suppression in rats and this effect is dose dependent (20).

In randomized control trial it was demonstrated how administration of PYY can cause appetite suppression in humans and post prandial rise in PYY cause satiety (18).

Another study demonstrated that after PYY infusion, appetite decreased to one third during a buffet in obese and lean individuals (21).

4 - Metabolites

i) Glucose

Though glucose isn't a major factor in regulating appetite but it can increase hunger as evidence in individuals with hypoglycaemia. Also T Shiiya and colleagues demonstrated that oral or intravenous infusion of glucose can decrease ghrelin level in body which can further decrease hunger and appetite (22).

ii) Ketosis

Ketosis decrease hunger and appetite. Alexander M Johnson and colleagues compared effect of high protein low carbs ketogenic diet with high protein medium carbs non ketogenic diet on obese men and found that ketogenic diet significantly reduced hunger, appetite and weight in those subjects (23).

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5 - Vagal afferent

Vagal afferent from stomach stretch give negative feedback to suppress appetite (25). A study in mini-pigs demonstrated that continuous vagal nerve stimulation can decrease appetite and weight (24).

6 - Genetic Factors

Genetics also plays its role in obesity as several monogenic and polygenic patterns are involved in its pathogenesis (27).

Mutation in ob gene can lead to defect in production of leptin and can cause hyperphagia and obesity in rodents and humans. Lep R (db) gene mutation can cause leptin resistance by affecting its receptor causing obesity.

Furthermore mutation in MSH receptor gene (MC4R) can inhibit satiety. Also production of melanocyte-stimulating hormone is decreased due to mutation in POMC gene which leads to inhibition of satiety signals to the brain. 0ther genes including PC-1, TrkB, GAD2, ENPP1 and Insig (2) are also involved in pathogenesis of obesity (26, 27).

7 - Cultural and social factors

Several social and cultural factors affect appetite. Wealthy women in developed countries are usually slim but in developing country there is trend towards obesity. Most of the content of main meal in south East Asia is carbohydrate and fat based. Also availability of fast food and sedentary lifestyle in developed counties contributes to obesity.

In children time spending on TV is found to have impact on obesity (32).

8 - Psychological factors affecting appetite;

Food derives pleasure through its sight, smell and taste and this pleasure can cause excessive eating by disrupting homeostatic mechanism to suppress appetite through hormonal and neuronal signals leading to weight gain (13, 7).

Furthermore appearance, smell, composition and quantity of food are also important. Its glucose, fat, protein and fibre contents help in achieving satiety (4, 5, 6).

De Graaf et al noticed that portion size can effect satiety. Mostly people finish their portions also size of the portion terminate apatite.

Furthermore cognition, timing between meals, reward perception and texture of food also affect appetite.

Management of excessive weight gain

NICE and public health emphasis on its management has many dimensions. Here I would like to discuss two fold approaches.

Community awareness

Through various strategies including media, commercials, education of school children, parents, patients and children visiting primary care and through community awareness programs, awareness should be given to prevent weight gain, its consequences on health and to promote weight loss.

Recommendations for physicians

Patient evaluation

It involves...

i) Assessment of BMI as weight loss strategies, pharmacological and surgical treatment depend upon BMI (28).

ii) Focused history, including dietary habits, daily exercise, co morbidities due to obesity including cardiovascular disease and diabetes and other health issue to rule out secondary causes of obesity (endocrine causes and syndromes).

iii) Focused examination measuring waist circumference, body fat distribution and blood pressure.

iv) Investigations including glucose and lipid.

v) Patient expectations and commitment.

Treatment

European clinical practice guidelines recommend treating obesity as a chronic disease for which treatment should be life-long. Aim of treatment should be weight loss and prevention of weight gain. Here I would discuss different modalities to accomplish this aim.

1 - Non pharmacological treatment

A - Diet therapy

A general dietary advice to patient includes keeping food diary, avoid energy dense foods and carbohydrate based drinks and include fruits and vegetables in diet.

There are three different types of dietary regimen suggested for weight loss and it should be in consultation with a dietician.

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i - Energy deficient diet

In this dietary regimen a diet is recommended which is deficient of about 600 Kcal/day than patient normally take and it can predict a weight loss of 0.5kg daily (29).

ii - Hypocaloric diets

These diets provide about 1200kcal/day and require dietician advice and monitoring.

iii - Very low caloric diets

These diets provide very low energy less than 800kcal/day and can further leads to micronutrient deficiency. This diet isn't recommended for children, elderly patients and pregnant women.

B - Physical activity

Diet along with exercise has a profound impact on weight loss. Its aim includes promotion of active healthy lifestyle and reducing sedentary behaviour. European guidelines recommend 30 to 60min of moderate intensity exercise for most of the days of a week but American public health department suggest 30min moderate intensity exercise all days in a week to maintain weight loss. Depending upon patient physical fitness, motivation and expectation this physical activity can be increased in terms of duration and intensity for which personnel trainer advice is helpful.

C - Cognitive behavioural therapy

To improve patient compliance to weight loss regimen and address patient beliefs and myths regarding weight loss CDT proves to be helpful. This includes self-monitoring, control of impulsive eating and relaxation techniques.

2 - Pharmacological treatment

Pharmacological treatment should be considered for patients with BMI greater or equal to 30 or those patients with BMI of 27 with hypertension, diabetes or other obesity related co morbidities.

In this regard there are many drugs in use for weight loss and prevention of weight gain. Scottish Intercollegiate guideline network (SIGN) only recommends Orlistat (30).

FDA has approved Sibutramine and Orlistat for obesity and European Clinical Practice Guidelines recommend Rimonabant along with Orlistat and Sibutramine.

Orlistat

Orlistat reduce fat absorption from diet by inhibiting pancreatic lipase. Its side effects include bloating, abdominal pain and malabsorption. It is contraindicated in patient with cholestasis or previously having bowel problems or malabsorption

Sibutramine

Sibutramine is a norepnephrine and serotonin reuptake inhibitor act centrally on Hypothalamus to suppress appetite. Its side effect includes insomnia and headache. It is contraindicated in patient with ischemic heart disease or psychiatric illness.

Rimonabant

It acts on cannabinoid receptors CB-1 and inhibits intake of sweet and fat based food. It is also contraindicated in psychiatric illness and renal/hepatic dysfunction (31).

Other drugs in Clinical trial studies

These include Leptin agonist, NPY antagonist, peptide YY, and Ghrelin antagonist (31).

3 - Surgical treatment

Surgical treatment improves morbidity and mortality. It is also very effective in weight loss and its maintenance. Surgical treatment is recommended for patient with BMI greater or equal to 40 or BMI of 35 with obesity related co morbidities.

Following surgical procedures are used

i - Gastric banding

ii - Gastric bypass surgery

iii - Biliopancreatic diversion

Conclusion

Management of obesity requires a multidisciplinary team approach and community as well as health care professionals have to play their active role in its prevention and treatment. There is no easy quick fix approach so patient need psychological and community support to accomplish goal of weight loss and then to sustain it.

Also as obesity is now an epidemic, obesity treatment centres are not enough to support its management. It should be supported by primary care as well as physicians and surgeons in all specialties in secondary and tertiary care which require revised setup, open door policy and structure & framework to support it.

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MCQs

1 - Central control of appetite is governed by;

A - Caudate Nucleus

B - Hypothalamus

C - Basal ganglia

D - Nucleus Ambigus

E - Midbrain

2 - Which of the following hormone increase appetite;

A - Cholecyctokinin

B - Gherlin

C - Peptide Y

D - Insulin

E - Leptin

3 - Daily energy expenditure is calculated by all of the following except;

A - Basal metabolic rate

B - Thermic effect of food

C - Occupational activities

D - Non occupational activities

E - Carbohydrate content of food

4 - What will be the next best step to manage a 34 year old male with BMI >30 who has failed dietary and lifestyle modification;

A - Gastric bypass surgery

B - Liposuction

C - Metformin

D - Orlistat

E - Biliopancreatic diversion

5 - Which of the following hormone is released by adipose tissue;

A - Peptide Y

B - Leptin

C - Colecystokinin

D - Somatostatin

E - Melatonin

Answers

1. Correct Answer; B

Hypothalamus contain Arcuate nucleus, VML and LH which regulate appetite and are influenced by various hormones and neuropeptides.

2. Correct answer; B

Gherlin is a gut hormone It secreted by stomach and act on NPY pathway in Arcuate nucleus to stimulate appetite.

3. Correct Answer; E

Total daily enery expenditure is sum of basal metabolic rate, thermic effect of food, occupational and non occupational activities.

4. Correct answer; D

Orlistat is next best step for management of obesity in people with BMI greater or equal to 30 or BMI>27 and obesity related complications e-g diabetes or hypertension.

5. Correct Answer; B

Leptin is secreted by adipose tissue and inhibit appetite.

OBESITY

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References

1. Antl-Weiser, Walpurga. "The anthropomorphic figurines from Willendorf" (PDF). Niederösterreichischen Landesmuseum.

2. Haslam DW, James WP (2005). "Obesity". Lancet (Review) 366 (9492): 1197–209.

3. Andrew G, 'Obesity and cancer: Pathophysiological and biological mechanisms'. Archive of physiology and biochemistry. Volume 114, Issue 1, 2008.

4. Blundell J' Appetite control: methodological aspects of the evaluation of foods.' Obesity Reviews, Volume pages 251–270, March 2010.

5. Slavin JL. Dietary Fibre and Body Weight. Nutrition. 2005; 21:411–418. [PubMed: 15797686].

6. Lawton CL, Delargy HJ, Brockman J, Smith FC, Blundell JE. The degree of saturation of fatty acids influences post-ingestive satiety. Br J Nutr. 2000; 83:473–482. [PubMed: 10953671].

7. David J. Mela,' Eating for pleasure or just wanting to eat? Reconsidering sensory hedonic responses as a driver of obesity.' Appetite; Volume 47, Issue 1, July 2006.

8. American Heritage dictionary.

9. Wynne K 'Appetite control'; journal of Endocrinology, 2005, vol. 184.

10. Erin E. Kershaw, Jeffrey S. Flier,' Addipose tissue as an endocrine organ,'JCEM; 89(6):2548–2556.

11. J. P. H. Wilding,' Neuropeptides and appetite control,' Diabetic Medicine, Volume 19, Issue 8, pages 619–627, August 2002.

12. Morton, G.J.et al.Central nervous system control of food intake and body weight. Nature, 443, 289-295 (21 September 2006).

13. Bruning JC et al, Role of brain insulin receptor in control of body weight and reproduction. Science 289, 2122-2125(2000).

14. Epel.E.et al.Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behaviour. Psychoneuroendocrinology, Vol 26(1), Jan 2001, 37-49.

15. WREN.A.M.et al. Gut hormones and appetite control. Gastroenterology 2007; 132:2116-2130.

16. Wren.A.M.et.al.The Novel Hypothalamic Peptide Ghrelin Stimulates Food Intake and Growth Hormone Secretion. Endocrinology [2000, 141(11):4325-4328].

17. Shillabeer.G.et.al. Proglumide, a cholecystokinin antagonist, increases gastric emptying in rats. Am J Physiol. 1987 Feb; 252(2 Pt 2):R353-60.

18. Degen.et.al.Effect of Peptide YY3–36 on Food Intake in Humans. Gastroenterology. Volume 129, Issue 5, Pages 1430–1436, Nov 2005.

19. Rachel.L.et al. Gut hormone PYY3-36 physiologically inhibits food intake. Nature 418, 650-654 (8 August 2002).

20. Chelikani .P.K .et.al.Intravenous Infusion of Peptide YY (3–36) Potently Inhibits Food Intake in Rats. Endocrinology. 2005 Feb; 146(2):879-88.

21. Batterham.R.L.et.al. Inhibition of Food Intake in Obese Subjects by Peptide YY3–36 . The New England Journal of Medicine, Vol 349(10), Sep 2003, 941-948.

22. Shiiya. T.et.al.Plasma Ghrelin Levels in Lean and Obese Humans and the Effect of Glucose on Ghrelin Secretion. J Clin Endocrinol Metab 87, 240-244, 2002.

23. Johnston.A.M.et.alEffects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum.The American Journal of Clinical Nutrition [2008, 87(1):44-55].

24. Val-Laillet.D.et.al.Chronic vagus nerve stimulation decreased weight gain, food consumption and sweet craving in adult obese minipigs. Appetite 2010 Vol. 55 No. 2 pp. 245-252.

25. Cummings.D.E.et.al.Gastrointestinal regulation of food intake. The Journal of Clinical Investigation [2007, 117(1):13-23.

26. Farooqi.I.S.et.al.Genetic factors in human obesity. Obes Rev. 2007 Mar;8 Suppl 1:37-40.

27. Harrison's Principles of internal medicine 2012.Chapter: Nutrition; Topic: obesity management.

28. Tsigos.C.et.al.European guidelines for management of obesity. Obes Facts. 2008; 1(2):106-16.

29. Ayyad.C.et.al.long term efficacy of dietary treatment of obesity. Obes Rev. 2000 Oct;1(2):113-9.

30. Logue.J.et.al.Management of obesity 115. Scottish Intercollegiate guideline network. BMJ. Vol. 340, No. 7744 (27 February 2010), pp. 474-477.

31. Barry.G.A.et.al.Pharmacological treatment of overweight patient. Pharmacological Reviews [2007, 59(2):151-184].

32. Gortmaker SL, et.al.Television viewing as a cause of increasing obesity among children in the United States, 1986–1990". Arch Pediatr Adolesc Med (Review) 150 (4).

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GASTROPARESIS

M Mallet, N Vincent, AF Muller

Abstract

Gastroparesis is a condition most commonly seen with diabetes. It typically presents with persistent nausea and vomiting, and is diagnosed with gastric scintigraphy. In this article, the difficulties in managing patients with this condition are highlighted and multiple possible therapies are described. There are some novel agents being trialled that it is hoped will help relieve symptoms of gastroparesis in the future.

Case history

A 30 year-old male with type 1 diabetes since childhood presented to the emergency department with nausea and vomiting. He had had over 30 admissions in the preceding year with a similar presentation and was diagnosed in 2015 with diabetes related gastroparesis.

Introduction

Gastroparesis is a syndrome of significantly delayed gastric emptying, without mechanical obstruction. Normal gastric emptying relies on the complex coordination of the enteric and central nervous system; parasympathetic efferent nerves from the vagus terminate in the myenteric plexus, whilst sympathetic fibres extend to the coeliac ganglia (1). When a meal is digested, the antrum distends, which in turn causes the fundus to relax and store the food. Contractions of the stomach ensure the breakdown of food which then passes into the duodenum via the pylorus (2).

Impaired gastric accommodation can occur in gastroparesis due to disruption of the cholinergic pathway, which in turn can increase sensory afferent signals to the chemoreceptor trigger zone which causes nausea and vomiting (2).

Furthermore, the antrum, responsible for emptying of food from the stomach, is known to have a reduced motor function in patients with gastroparesis (3). In particular, acute hyperglycaemia is associated with antral hypomotility, as is seen in hyperglycaemic patients (2).

Studies have shown that, when looking at the time taken to empty solids from the stomach, patients with acute hyperglycaemia take on average 15 minutes longer that euglycaemic patients (4). Patients with diabetes have been seen to have increased pyloric tone which is further related to gastroparesis (5). Further pathophysiology of gastroparesis includes duodenal dysmotility, autonomic dysfunction, and visceral hypersensitivity (2).

Non-specific symptoms such as upper abdominal pain or discomfort, abdominal distension, bloating, nausea, early satiety, and postprandial fullness are further characteristics of this condition (6). There are multiple causes of gastroparesis, see table 1, and often no identifiable cause can be found (2). In this article, there will be a focus on diabetes related gastroparesis. It is widely thought that autonomic neuropathy is the mechanism of action by which diabetes related gastroparesis occurs, however there is conflicting evidence in the literature about whether this is the sole cause (7).

Aetiology	Examples
Autonomic nervous system	Diabetes
Post surgical	Pancreaticoduodenectomy, bariatric surgery, oesophagectomy (8,9)
Post Viral	Rotavirus (10,11), cytomegalovirus, Epstein-Barr virus, varicella zoster (12)
Neurological diseases	Parkinsons disease, multiple sclerosis, brainstem stroke or tumour (12)
Medications	Opioids, tricyclic antidepressants, calcium channel blockers, dopamine agonists (12)

Table 1: Aetiology of the commoner causes of gastroparesis.

Epidemiology

The prevalence of diabetes related gastroparesis is difficult to determine due to the non-specific symptoms. Evidence from the literature is inconsistent. In a study based in Denmark the prevalence of symptoms of diabetes related gastroparesis was investigated in a large cohort (7). This study estimated that 9.8% of type 1 diabetes patients had clinical symptoms of gastroparesis but that only 1 in 10 of those patients had an existing diagnosis.

Having diabetes related complications, such as retinopathy, polyneuropathy, and nephropathy (7), can be risk factors for diabetes-related gastroparesis. Patients with diabetes who have higher glycated haemoglobin (HbA1c) levels have a higher incidence of diabetes related complications (7). Gastroparesis is also more likely to be found in those patients with longstanding diabetes (2).

Diagnosis

A firm diagnosis of gastroparesis can be made in a patient with nausea and vomiting when delayed gastric emptying is demonstrated using appropriate studies, and there is no structural obstruction in the stomach (13 - 16). When a patient presents, a thorough history must be taken in order to exclude other recognised causes of nausea and vomiting as seen in table 2.

Differential diagnoses of nausea and vomiting
Gastro-oesophageal reflux disease
Gastroenteritis
Diabetic ketoacidosis
Pregnancy
Migraine
Thyroid disease
Hypercalcaemia
Small bowel obstruction
Myocardial infarction

Table 2: The differential diagnoses to be considered in a patient presenting to the emergency department with nausea and vomiting (14) (15).

GASTROPARESIS

M Mallet, N Vincent, AF Muller

Due to the various differential diagnoses of nausea and vomiting (see table 2), there are multiple investigations that may be considered appropriate, as shown in table 3.

Investigations		Differential diagnoses
Bloods:	Full blood count, C reactive protein, urea and electrolytes (including calcium)	Electrolyte imbalances e.g. hypercalcaemia, infection
	Thyroid function tests	Hypo- or hyperthyroidism
	Blood glucose levels, HbA1c, blood ketones, venous blood gas	Hypo- or hyperglycaemia, diabetic ketoacidosis
Imaging:	Abdominal X-ray, Chest X-ray	Bowel obstruction
	Magnetic resonance imaging of the head, Computed tomography of the head.	Brain tumours, brainstem stroke
	Gastric scintigraphy	Gastroparesis
Other:	*Helicobacter pylori* faecal antigen testing	*H. pylori* infection
	Electrocardiogram (ECG)	Myocardial infarction
	Beta-human chorionic gonadotropin	Pregnancy

Table 3: Investigations to consider in patients presenting to the emergency department with nausea and vomiting.

The investigation of choice to confirm a diagnosis of gastroparesis is gastric scintigraphy. This is when a standardized radiolabelled meal is ingested and images are taken at 30, 60, 90 and 120 minutes in order to determine whether there has been any gastric retention of solids. Images are taken anteriorly and posteriorly. T 1/2 is the time taken for half the radioactive material to pass through the stomach. T 1/2 for a patient with normal gastric emptying is 100 + 25.

Examples of scintigraphy images of normal gastric emptying and gastroparesis are displayed in figures 1a and 1b, respectively (14).

Examples of images of gastric emptying

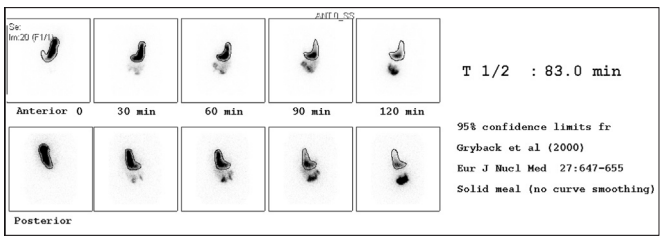

Figure 1a: Gastric scintigraphy of a patient with normal gastric emptying. The radioactive meal passes through the stomach into the small bowel, starting at 30 minutes and most of the meal has passed by 120 minutes. The T 1/ 2 is within normal ranges for this patient.

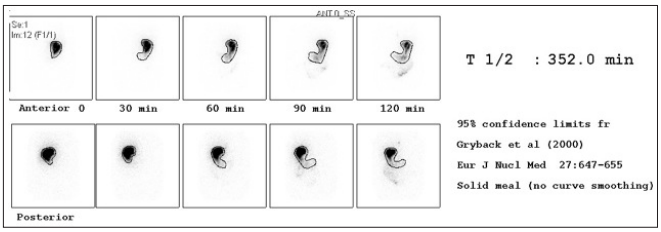

Figure 1b: Gastric scintigraphy of a patient with gastroparesis. The ingested meal is seen to clearly remain in the stomach at 120 minutes with a minor amount moving into the small bowel at this time.

The longer T 1/2 demonstrates delayed gastric emptying (the later images are not recorded in this figure).

Management

Once the diagnosis of gastroparesis is confirmed the following management strategy should be followed (table 4) :

- **Emphasise the importance of strict glycaemic control**
- **Involvement of the GP and community diabetes team**
- **Lifestyle advice including avoiding alcohol & smoking cessation (these prolong gastric emptying times)**
- **Care with carbonated drinks (which can cause gastric distention)**
- **Advise caution with foodstuffs that may slow gastric emptying such as foods that are spicy, acidic or high in fat / fibre.**
- **Arrange Dietetics referral (17)**
- **Trial of prokinetic agents (18)**
- **Possible use of pyloric botulinum toxin injection therapy**
- **Gastric stimulation devices**
- **New drug treatments that are on the horizon including Velusetrag and Relamorelin**

Table 4: Management strategy for patients with gastroparesis.

GASTROPARESIS

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Medical management

The National Institute of Clinical Excellence (NICE) guidelines for type 2 diabetes (18) suggested that agents that increased gastric motility should be trialled. Examples of agents that promote gastric emptying are domperidone, erythromycin and metoclopramide. However, they are associated with uncommon but significant and serious complications including cramps, diarrhoea and ventricular dysrhythmias and therefore limit their use (18-25).

Pyloric botulinum toxin therapy (Bo-Tox)

Injection of bo-tox into the pylorus to reduce pyloric tone has been used for patients with gastroparesis but debate exists about its efficacy (14). Some studies have observed short-term improvement of 2-6 weeks in symptoms due to the reduction of pylorospasm and improvement in gastric emptying (26). However randomised trials have failed to demonstrate an improvement compared with placebo (17).

Gastric stimulation

Gastric stimulation is a NICE recommended technique used in refractory gastroparesis. A gastric electrical stimulator is inserted into the abdominal wall and electrodes attached to the stomach. This sends impulses to the distal stomach via leads that aid gastric emptying. Meta-analysis studies have demonstrated that this treatment option improves the symptoms of gastroparesis. Complications of the procedure include small bowel infarction, heart failure, bowel perforation, and infection (27).

New oral medications

Novel oral medications are currently being trialled. Velusetrag, a serotonin agonist that increases gut motility is currently in a phase 2b trial. Early tests have documented velusetrag to be well tolerated and improved gut emptying time (28, 29). Relamorelin is a prokinetic, ghrelin agonist that is being investigated for its role in the treatment of diabetes related gastroparesis.

It appears to be well tolerated and has been shown to improve symptoms (30, 31, 32). The Food and Drug Administration in the United States are fast tracking these two promising agents (28, 32). It is hoped that they will provide additional treatment options for patients who have failed to respond to other therapies.

Case history

The 30 year-old patient with diabetes related gastroparesis has had trials of treatment with oral erythromycin that have not been beneficial at relieving symptoms. He has previously had botox injections, which have provided short-term relief for up to one month. He is currently on the waiting list for gastric stimulation.

Conclusion

Gastroparesis may occur in fewer than 10% of patients with type 1 diabetes, however the non-specific symptoms of gastroparesis often create difficulties with initial diagnosis. There are no studies currently on the cost to the National Health Service (NHS) and the number of admissions of patients with gastroparesis. The cost of diagnosing and treating a patient with gastroparesis is likely to be high due to the difficulties in initial diagnosis and multiple admissions related to treatment resistant symptoms.

Patients presenting with persistent vomiting secondary to gastroparesis should be managed using appropriate resuscitation and medical therapies. Management through lifestyle choices and tight glycaemic control are a key part of treatment of diabetes related gastroparesis. In the NHS, gastric stimulation techniques can aid severe, recurrent gastroparesis. It is hoped that more novel treatments currently being trialled may provide further options in the future.

MCQs

1. The investigation of choice for the diagnosis of gastroparesis is :

a) A plain abdominal X-RAY
b) An abdominal US examination
c) A barium meal and follow through
d) Gastric scintigraphy
e) Gastroscopy

2. The treatment options available for gastroparesis include:

a) Improvement of glycaemic control
b) Treatment with Relamorelin
c) A high fat diet
d) Vitamin supplementation
e) Oesophageal bo-tox treatment

3. Which of the following is not a potential cause of vomiting in a patient with longstanding type 1 diabetes and poor glycaemic control:

a) Gastro-oesophageal reflux
b) Terminal ileal Crohns
c) Necrobiosis lipoidica
d) Autonomic neuropathy
e) Migraine

4. Potential newer treatments for gastroparesis;

a) May inhibit the ghrelin receptor
b) May interrupt motilin production
c) May be available for use this year
d) Can be prescribed by General Practitioners
e) May have an effect on the vagus nerve

5. Gastric scintigraphy in a gastroparesis patient:

a) Will have a normal T ½
b) Can demonstrate dumping syndrome
c) Will have a prolonged T ½
d) Will have a shortened T ½
e) Is not useful in diagnosing gastroparesis

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Answers

1. D **2. A** **3. C** **4. A** **5. C**

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References

1. Wood JD, Alpers DH, Andrews PL. Fundamentals of neurogastroenterology. Gut [Internet]. 1999;45 Suppl 2:II6-II16. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1766686&tool=pmcentrez&rendertype=abstract
2. Nguyen LA, Snape WJ. Clinical presentation and pathophysiology of gastroparesis. Vol. 44, Gastroenterology Clinics of North America. 2015. p. 21–30.
3. Camilleri M, Brown ML, Malagelada JR. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. Gastroenterology [Internet]. 1986;91(1):94–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3710086
4. Camilleri M. Clinical practice. Diabetic gastroparesis. N Engl J Med. 2007 Feb;356(8):820–9.
5. Mearin F, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. Gastroenterology [Internet]. 1986;90(6):1919–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3699409
6. Camilleri M, Bharucha AE, Farrugia G. Epidemiology, Mechanisms, and Management of Diabetic Gastroparesis. Vol. 9, Clinical Gastroenterology and Hepatology. 2011. p. 5–12.
7. Kofod-Andersen K, Tarnow L. Prevalence of gastroparesis-related symptoms in an unselected cohort of patients with Type 1 diabetes. J Diabetes Complications. 2012;26(2):89–93.
8. Palmes D, Weilinghoff M, Colombo-Benkmann M, Senninger N, Bruewer M. Effect of pyloric drainage procedures on gastric passage and bile reflux after esophagectomy with gastric conduit reconstruction. Langenbeck's Arch Surg. 2007 Mar;392(2):135–41.
9. Parmar AD, Sheffield KM, Vargas GM, Pitt HA, Kilbane EM, Hall BL, et al. Factors associated with delayed gastric emptying after pancreaticoduodenectomy. HPB (Oxford) [Internet]. 2013;15(10):763–72. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3791115&tool=pmcentrez&rendertype=abstract
10. Meeroff JC, Schreiber DS, Trier JS, Blacklow NR. Abnormal gastric motor function in viral gastroenteritis. Ann Intern Med. 1980;92(3):370–3.
11. Bityutskiy LP, Soykan I, McCallum RW. Viral gastroparesis: a subgroup of idiopathic gastroparesis--clinical characteristics and long-term outcomes. Am J Gastroenterol [Internet]. 1997;92(9):1501–4. Available from: http://www.ncbi.nlm.nih.gov.ezp-prod1.hul.harvard.edu/pubmed/9317072%5Cnhttp://www.ncbi.nlm.nih.gov.ezp-prod1.hul.harvard.edu/pubmed/9317072?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum
12. Camilleri M. Gastroparesis: Etiology, clinical manifestations, and diagnosis. UpToDate. 2016.
13. Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association medical position statement: diagnosis and treatment of gastroparesis. Gastroenterology. 2004 Nov;127(5):1589–91.
14. Camilleri M, Parkman HP, Shafi M a, Abell TL, Gerson L. Clinical guideline: Management of gastroparesis. Am J Gastroenterol [Internet]. 2013;108(1):18–37. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84872013597&partnerID=40&md5=a4ed8e764e92ca3f6f244a4c7e776657
15. NHSChoices. Nausea and Vomiting in Adults [Internet]. 2016 [cited 2017 Jun 13]. Available from: http://www.nhs.uk/conditions/vomiting-adults/Pages/Introduction.aspx#causes
16. The ABCDE approach [Internet]. Resuscitation Council UK. 2017 [cited 2017 Jun 13]. Available from: https://www.resus.org.uk/resuscitation-guidelines/abcde-approach/
17. Camilleri M. Treatment of gastroparesis [Internet]. UpToDate. 2015 [cited 2017 May 3]. Available from: https://www.uptodate.com/contents/treatment-of-gastroparesis?source=search_result&search=treatment of gastroparesis&selectedTitle=1~132#H67864665
18. NICE. Type 2 diabetes in adults: management [Internet]. 2017 [cited 2017 May 10]. Available from: https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations#managing-complications
19. Catnach SM, Fairclough PD. Erythromycin and the gut. Gut. 1992 Mar;33(3):397–401.
20. Richards RD, Davenport K, McCallum RW. The treatment of idiopathic and diabetic gastroparesis with acute intravenous and chronic oral erythromycin. Am J Gastroenterol. 1993 Feb;88(2):203–7.
21. GMC. Prescribing guidance: Prescribing unlicensed medicines [Internet]. 2013 [cited 2017 May 10]. Available from: http://www.gmc-uk.org/guidance/ethical_guidance/14327.asp
22. NICE. Gastroparesis in adults: oral erythromycin [Internet]. 2013 [cited 2017 May 10]. Available from: https://www.nice.org.uk/advice/esuom13/chapter/Key-points-from-the-evidence
23. MHRA. Domperidone: risks of cardiac side effects. 2014.
24. Lee A, Kuo B. Metoclopramide in the treatment of diabetic gastroparesis. Expert Rev Endocrinol Metab [Internet]. 2010;5(5):653–62. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3027056/pdf/nihms263650.pdf%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/21278804%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3027056
25. MHRA. Metoclopramide: risk of neurological adverse effects [Internet]. 2013 [cited 2017 May 16]. Available from: https://www.gov.uk/drug-safety-update/metoclopramide-risk-of-neurological-adverse-effects
26. Ezzeddine D, Jit R, Katz N, Gopalswamy N, Bhutani MS. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. Gastrointest Endosc. 2002;55(7):920–3.
27. NICE. Gastroelectrical stimulation for gastroparesis [Internet]. 2014 [cited 2017 May 3]. Available from: https://www.nice.org.uk/guidance/ipg489/chapter/2-Indications-and-current-treatments
28. Ahn A Shaywitz D, Grimaldi M, Canafax DM BC. Velusetrag improves gastric emptying time in subjects with diabetic or idiopathic gastroparesis. [Internet]. Vol. 148, Gastroenterology. 2015. p. S507. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=cctr&NEWS=N&AN=CN-01089113
29. Gala R, Brons T. Theravance Biopharma Receives FDA Fast Track Designation for Velusetrag (TD-5108) for Idiopathic and Diabetic Gastroparesis. Theravance Biotherma. 2016.
30. Camilleri M, McCallum RW, Tack JF, Spence SC, Gottesdiener K, Fiedorek FT. Relamorelin in Patients with Diabetic Gastroparesis: Efficacy and Safety Results from a Phase 2B Randomized, Double-Blind, Placebo-Controlled, 12-Week Study (RM-131-009). Gastroenterology [Internet]. 2017 Jun 14;152(5):S139–40. Available from: http://dx.doi.org/10.1016/S0016-5085(17)30796-5
31. Camilleri M, Acosta A. Emerging treatments in Neurogastroenterology: Relamorelin: A novel gastrocolokinetic synthetic ghrelin agonist. Vol. 27, Neurogastroenterology and Motility. 2015. p. 324–32.
32. Nelson AD, Camilleri M, Acosta A, Busciglio I, Linker Nord S, Boldingh A, et al. Effects of ghrelin receptor agonist, relamorelin, on gastric motor functions and satiation in healthy volunteers. Neurogastroenterol Motil. 2016;28(11):1705–13.

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UNUSUAL CAUSE OF DYSPNOEA IN CIRRHOSIS

S K Gangadharan, HC Young, W Taj-Aldeen, B Vijayan

Abstract

We present two patients with a new diagnosis of Hepatopulmonary Syndrome (HPS). Hepatopulmonary syndrome is a syndrome of shortness of breath and hypoxemia caused by vasodilation in the lungs of patients with liver disease. Both patients had established liver cirrhosis and presented with dyspnoea and hypoxia. Even though HPS is a rare cause of hypoxia, clinical finding of clubbing on the background of cirrhosis should prompt one to elicit orthodeoxia, a bedside test to diagnose this complex and disabling disorder.

Case 1

65 year old gentleman was diagnosed with Hepatitis C virus Genotype 3 (HCV) related cirrhosis in 2014. He was treated with Daclatasvir, Sofosbuvir and Ribavarin and cleared the virus. On follow up at the Hepatoma surveillance clinic he was found to have multifocal Hepatocellular carcinoma (HCC not suitable for surgery or Liver Transplantation) He was offered Trans Arterial Chemo Embolisation (TACE) followed by a trial of Lenvatinib chemotherapy. He is an ex smoker, and drinks <14 units of alcohol per week.

He was admitted with gradually worsening shortness of breath of six months duration. His symptoms were pronounced on walking and relieved by lying flat. On examination, he was conscious, dyspnoeic at rest and required supplemental oxygen. Examination of his hands and legs revealed clubbing (grade 3), but no evidence of icterus or pedal edema. On Pulse oximetry Spo2 was 91% on sitting position and 81% on standing posture suggestive of orthodeoxia.

Examination of his chest revealed normal vesicular breath sounds but no added sounds. Abdomen was soft; there was no organomegaly or ascites. Laboratory examination revealed Haemoglobin of 130 g/l; Platelet counts – 100 x 10>9/l. His Prothrombin time was 14 (INR- 1.3). The Liver function tests: (Bilirubin -12 umol/L; Albumin-31 g/L; ALT -23U/L; Alkaline phosphatase -96U/L).

A CT Pulmonary Angiogram (CTPA) in October 2015 (as Lenvatinib theoretically can produce emboli) showed no evidence of Pulmonary Thromboembolism. Repeat CTPA during this current admission was also normal. CT scan of the Thorax did not reveal any major abnormality to account for his hypoxia. Abdominal imaging did not reveal any collaterals/shunts or Portal vein occlusion. Features of liver cirrhosis with portal hypertension and a stable HCC were seen.

In view of the orthodeoxia and underlying liver cirrhosis, a contrast bubble Echocardiogram was done which showed a delayed passage (>6 seconds) of significant amount of bubbles into the left heart. A diagnosis of Hepatopulmonary syndrome was made. He was instituted on home oxygen therapy and was discharged home. He continued to be symptomatic and oxygen dependent.

The dose of lenvatinib was decreased to half, but continued. Interestingly, his oxygenation and shortness of breath improved on Lenvatinib dose reduction. Since his HCC was stable, he was evaluated for liver transplantation. He underwent orthotopic liver transplanttion on April 29th 2017. Following the transplant, he was completely off supplemental oxygen. He was followed up after a month post transplant and is completely independent in his activities of daily routine with no Dyspnoea even on walking a mile.

Case 2

40 year gentleman with chronic alcohol dependence and poly substance misuse, currently on methadone was diagnosed to have cirrhosis when he presented with haemetemesis in 2008. Initially he underwent variceal band ligation and subsequently underwent an emergency (Transjugular Intrahepatic Porto Systemic Shunt) TIPSS procedure for refractory variceal bleeding in 2009. Following TIPSS insertion he remained stable with no futher Haematemesis and remained abstinent of alcohol.

He was admitted with abnormal behavior of 2 weeks duration. His partner found him confused intermittently along with memory disturbance over a 6 month period preceding this admission. He also complained of exertional dyspnoea, which was gradually worsening over a 2 year period. There was no cough, fever, chest pain, palpitations. He admitted to smoking 40 cigarettes a day and taking recreational drugs but remained abstinent of alcohol.

On clinical examination; he was obese, with bilateral grade 3 clubbing of hands and feet and numerous spider naevi were seen over his chest wall. Pulse oximetry SpO2 revealed orthodeoxia (91% - lying down) and 85% - standing). Normal vesicular breath sounds were heard with no added sounds on examination of the chest. Heart sounds were normal and there was no murmur. Abdominal examination revealed moderate splenomegaly but there was no ascites. Even though he had memory disturbances, no asterixes were demonstrated to suggest Hepatic Encephalopathy.

His laboratory reports showed hemoglobin of 137g/l, MCV of 81 and platelets: 72-100X10>9/l. The PT was 17.2seconds (INR1.5). Liver functions tests: (Bilirubin -14umol/L, Albumin -32g/L, ALT – 24U/L, ALP- 73U/L).

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The Ultrasound abdomen revealed features of cirrhosis, splenomegaly but no ascites and TIPSS stent was blocked. CT chest did not show evidence of pulmonary thromboembolism. Abdominal CT scan showed extensive splenic collaterals. His arterial ammonia was not elevated and the EEG showed no evidence of slow waves suggesting that there was no lab evidence of hepatic encephalopathy.

Mild obstructive picture was noted on spirometry but not severe enough to consider COPD. Sleep studies were not performed as his score was low in the Sleep Apnea questionnaire. Hence a pulmonary cause for dyspnoea was ruled out. Subsequently, he underwent a bubble echocardiogram which showed evidence of delayed shunting into the left atrium suggestive of HPS.

To summarize, both patients had cirrhosis, dyspnoea, clubbing and hypoxia with orthodeoxia. The second patient had extensive thoracic spider naevi irrespective of abstaining from alcohol for 7 years. The clinical picture was suspicious of intrapulmonary shunting and possible hepatopulmonary syndrome. Both of them underwent bubble echocardiogram after infusion of intravenous agitated saline which was diagnostic of HPS.

Approach to management of dyspnoea in cirrhosis

One of the common complaints in cirrhotic patients is dyspnoea which could be due to a variety of reasons. Arterial Blood Gas abnormalities have been demonstrated in 45% of cirrhotics while abnormal pulmonary function tests occur in 50%. (1, 2).Customarily, the various causes of dyspnoea in liver disease are classified as Diseases specific to liver disease and those unrelated to liver disease as given in the Table below.

Specific to liver disease:	
1	Mechanical effect - Ascites , Hepatic Hydrothorax
2	Pulmonary Vascular abnormalities –Hepatopulmonary Shunts /Syndrome , Porto pulmonary hypertension
3	Emphysema- Alpha1antitrypsin deficiency
4	Fibrosing alveolitis ,Pulmonary granulomas-Primary Biliary Cholangitis
5	Sarcopenia
Unrelated to Liver disease:	
1	Infections – Pneumonia
2	COPD, Asthma ,Atelectasis ,Interstitial lung disease
3	Cardiac-Congestive Cardiac Failure, Pulmonary Oedema
4	Pulmonary Vascular causes – Pulmonary Thromboembolism
5	Anaemia

Table 1: Causes of dyspnoea in liver disease.

Hepatopulmonary syndrome consists of a triad of cirrhosis with portal hypertension, intrapulmonary vasodilatation and arterial hypoxemia (oxygen saturation <80%). The incidence of HPS has been estimated to be 5-32 % in patients evaluated for transplantation (1). Around 40% of cirrhotics develop pulmonary vasodilatation but only about 10-15 % of them develops hypoxia. (1)

The pathogenesis of intrapulmonary vasodilatation in Cirrhosis is quite complex. Cirrhosis is a hyperdynamic state and several studies have documented high levels of Vasodilators in the Pulmonary as well as peripheral circulation such as Nitric oxide and Endothelins. This excess of vasodilators in the lungs results in pulmonary vasodilatation/pulmonary shunts, leading to deoxygenated blood bypassing the alveoli and reaching the left heart. It is essentially ventilation-perfusion mismatch.

The classic symptoms and signs are dyspnoea, platypnoea and orthodeoxia. In a Cirrhotic patient upright posture such as standing causes preferential vasodilatation in the lower part of the lungs leading to postural gas exchange abnormalities and thereby hypoxia. Long standing hypoxia leads to clubbing which is characteristic of patients with HPS. The presence of numerous Spider naevi, especially in nonalcoholics should raise the suspicion of HPS.

Diagnosis remains on demonstrating hypoxia and intrapulmonary shunting. Hence, any cirrhotic patient with hypoxia should have a standing pulse oximetry and Arterial Blood Gas measurement (ABG). An increased alveolar arterial oxygen gradient while breathing room air (widened A-a >15 mm Hg) suggests HPS.

Such patients should also undergo tests to rule out other causes of dyspnoea by chest Xray, PFT and if clinically indicated Pulmonary angiogram. When the above mentioned tests return normal, a contrast bubble Echocardiogram is done to demonstrate the pulmonary shunts. Tc-99 macro aggregated albumin scanning (TC MAA) is a useful adjunct to quantify the shunting.

Bubble contrast Echocardiogram is done by infusing agitated saline into the peripheral circulation and observing the arrival of the bubbles into the left side of heart. Under normal physiological circumstances, the bubbles which are >20 microns are trapped by the alveoli and hence do not appear in the left atrium. It appears immediately in the left atrium in the presence of right to left intracardiac shunts. However, in HPS, the bubbles can pass through the dilated capillaries causing delayed appearance after 6 cardiac cycles and is diagnostic.

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In Tc MAA scan, the amount of Tc is quantified in various capillary beds like brain, kidney or spleen. Normally, the Tc tracer is trapped by alveoli and absorbed so that it will not appear in the capillaries.

Dyspnoea can occur with interferon and Ribavirin which are used in the treatment for hepatitis C, however our first patient received newer Direct Acting Antiviral medications (DAAs) which are quite safe and do not cause dyspnoea. Other causes for dyspnoea described in HCC are pulmonary metastasis; lymphadenopathy, pulmonary embolism and intracardiac extension were ruled out in the first patient.

Lenvatinib is a multireceptor tyrosine kinase inhibitor which acts through inhibiting Vascular Endothelial Growth Factors (VEGF) thus inhibiting the tumor growth, angiogenesis and progression of cancer. Few cases of Pulmonary thromboembolism have been reported with lenvatinib treatment in the setting of thyroid cancer, however no such data exists with HCC till now.Theoretically ,Lenvatinib can improve HPS by inhibiting pulmonary angiogenesis and decreasing the intrapulmonary shunts.

In our second patient, even though the TIPSS stent was blocked, the extensive splenic collaterals can cause shunting of the blood resulting in HPS.

Treatment

The definitive treatment of HPS is liver transplantation. Severe hypoxemia (PaO_2 <50mm Hg) is associated with significant post transplant mortality. The role of TIPSS is controversial and there have been many case reports of TIPSS improving hypoxemia. Majority of the patients require lifelong supplemental oxygenation unless transplanted. The 5 year survival with HPS was 23% compared to 63 % in matched controls with liver disease and no HPS.

To conclude, HPS is a rare but disabling complication of Cirrhosis with significant morbidity and mortality. High index of clinical suspicion is the key to diagnosis. HPS should be suspected in any patient with liver disease who presents with clubbing and hypoxaemia. Liver Transplantation should be considered in suitable patients.

Questions

A. All the features are seen with HPS except

1. Cirrhosis

2. Hepatic Encephalopathy

3. Hypoxemia

4. Orthodeoxia

B. The best treatment for HPS

1. Supplemental Oxygen

2. Sildenafil

3. TIPSS

4. Liver transplantation

C. The diagnosis of HPS is confirmed by

1. Pulse Oximetry

2. Bubble Contrast ECHO

3. ECG

4. MRI

D. Orthodeoxia means

1. Hypoxia on Standing

2. Hypoxia on Lying down

3. Angina on exertion

4. Hypoxia on resting

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E. Dyspnoea in cirrhosis is caused by all except

1. Massive Ascites

2. Hepatic Hydrothorax

3. Portopulmonary Hypertension

4. None

5. All

Answers

A. Hepatic encephalopathy

B. Liver transplantation

C. Bubble Contrast ECHO

D. Hypoxia on standing

E. None

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References

1. Michael B. Fallon And Gary A. Abrams ; Pulmonary Dysfunction In Chronic Liver Disease , Hepatology Vol. 32, No. 4, 2000
2. Sood G, Fallon Mb, Niwas S, Tutton T, Van Leeuwen Dj, Bloomer Jr, Mcguire Bm, Et Al. Utility Of A Dyspnea-Fatigue Index For Creening Liver Transplant Candidates For Hepatopulmonary Syndrome [Abstract]. Hepatology 1998;28(Suppl):742a.
3. Lange Pa, Stoller Jk. The Hepatopulmonary Syndrome: Effect Of Liver Transplantation. Clin Chest Med 1996;17:115-123.
4. Kim YK1, Kim Y, Shim SS.Thoracic complications of liver cirrhosis: radiologic findings. Radiographics. 2009 May-Jun;29(3):825-37. doi: 10.1148/rg.293085093.
5. Loredana Lorusso,1 Letizia Pieruzzi,1 Agnese Biagini,1 Elena Sabini,1 Laura Valerio,1 Carlotta Giani,1 Paolo Passannanti,1 Benedetta Pontillo-Contillo,2 Valentina Battaglia,2 Salvatore Mazzeo,2 Eleonora Molinaro,1 and RossellaElisei . Lenvatinib and other tyrosine kinase inhibitors for the treatment of radioiodine refractory, advanced and progressive thyroid cancer. Onco Targets Ther.2016;9:6467-6477.

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VERRUCOUS CARCINOMA OF THE OESOPHAGUS: A DIAGNOSTIC DILEMMA & PHYSICIAN & ENDOSCOPIC MANAGEMENT OPTIONS

K Yip, S Mc Grath, G Armstrong, R George, YS Ang

Abstract

Verrucous carcinoma of the oesophagus is a rare variant of squamous cell carcinoma. This case report of a 62 year gentleman who initially presented with dysphagia and weight loss illustrate how diagnosis can be challenging due to difficulties in attaining adequate biopsies specimens. This can lead to delay in treatment. We discuss latest investigation and treatment modalities available to physicians in the management of such patients.

We present the case of a 62yo white Caucasian male who was referred to his local district general for symptoms of dysphagia and weight loss developing insidiously over the course of a few weeks. His past medical history consisted of ischaemic heart disease, previous myocardial infarction, diet controlled non-insulin dependent diabetes mellitus and osteoporosis. He took 75mg aspirin a day and was on no other regular medication. He had a significant smoking and alcohol history, smoking 20 cigarettes per day and drinking on average 60 units a week.

Oesophagealgastroduodeonscopy [OGD] demonstrated multiple polyp like lesions in the upper oesophagus; immediately after the pharynx, in the anterior middle oesophagus and the posterior middle oesophagus. Biopsies were taken and the patient was planned for discussion at a multidisciplinary team [MDT] meeting. CT demonstrated that the staging would be T2/3 N1 M0, if malignancy were to be proven.

However, the histology proved inconclusive and the outcome of the MDT meeting was that the patient required an endoscopic ultrasound with repeat biopsies.

The working diagnosis was that of possible verrucous carcinoma or fungal oesophagitis with squamous proliferation and the patient was started on high dose fluconazole.

A repeat OGD was performed 6 days after the MDT meeting by a consultant gastroenterologist. The macroscopic findings from the first OGD were confirmed and Lugol iodine spray gave staining patterns consistent with squamous cell carcinoma. Fungal stains were negative. EUS showed a hyper echoic lesion with no invasion and no dysplasia, staging the disease as T1 N0.

The biopsies from the second OGD showed appearances representing a reactive hyperplastic squamoproliferative process, however, well differentiated squamous neoplasia could not be excluded. This was now 6 weeks after the first OGD and the patient was yet to be given a clear diagnosis and management plan. The plan was then to proceed to general anaesthetic assisted endoscopic mucosal resection [EMR] of one of the lesions in order to provide a tissue sample for histological diagnosis.

EMR - an increasingly popular alternative to surgical resection

Endoscopic resection is an alternative to surgical resection of submucosal neoplastic lesions. It is both a therapeutic and diagnostic facility. Lesions that are limited to the mucosa or superficial layers of the submucosa appear to be most amenable to endoscopic curative treatment.

The criteria for cancers amenable to EMR technique are:

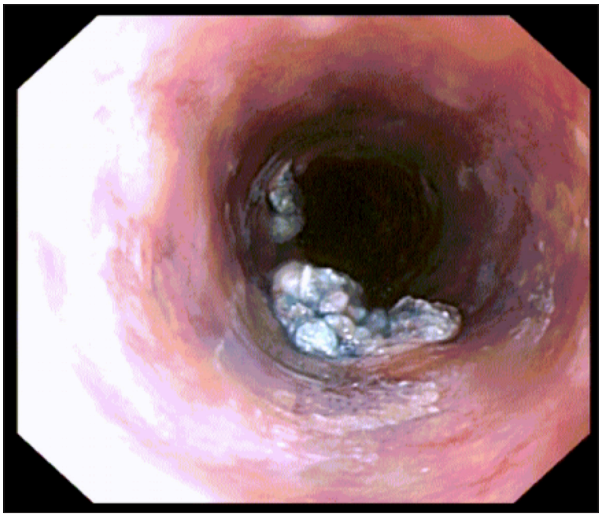
Diameter < 2cm

Involves < 1/3 of the circumference of the oesophageal wall

Are limited to the mucosa of the oesophagus [stage T1a)

Technique

Via an endoscope, the lesion to be excised is identified using Lugol iodine staining. A submucosal fluid cushion (SFC) is created by injecting a hypertonic solution into the submucosa deep to the lesion. This SFC decreases the rate of perforation during EMR and non-lifting of the lesion can inform the clinician early into the procedure that there may be invasion of the muscularis propria.



Endoscopic view of polyp lesions in oesophagus stained with Lugol iodine staining.

There are then two groups of techniques for removing the lesions. Cap-technique involves placing a cap over the lifted lesion and applying suction to draw the lesion away from the muscularis propria. The other technique involves the use of rubber band ligation (Duette multiband mucosectomy technique) to pull the lesion away from the muscularis propria, after which a snare is used to resect the specimen. EMR is technically more challenging, requiring a great deal of fine manual dexterity.

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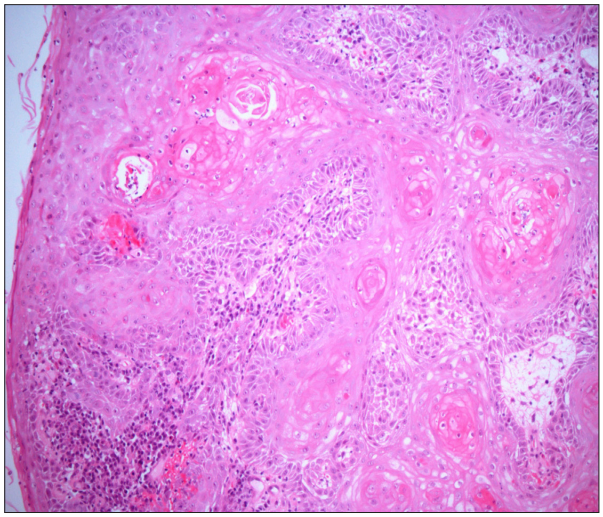
Increasingly, EMR, to remove larger superficial areas, is being followed by radiofrequency ablation [RFA]. This involves the the delivery of controlled pulses of radiofrequency energy, via a catheter, to cause thermal ablation of thin layers of epithelium.

As with all procedures, the patient must be made aware of possible complications when giving consent for EMR/ RFA. Complications are rare and procedures are usually performed as outpatient day cases. However, there are small [<1% of each] risks of bleeding, perforation, and stricture formation. A more significant proportion of patients will experience pain and dysphagia for a few days following the procedure and advice should be sought from dieticians regarding in feeding and nutritional supplements.

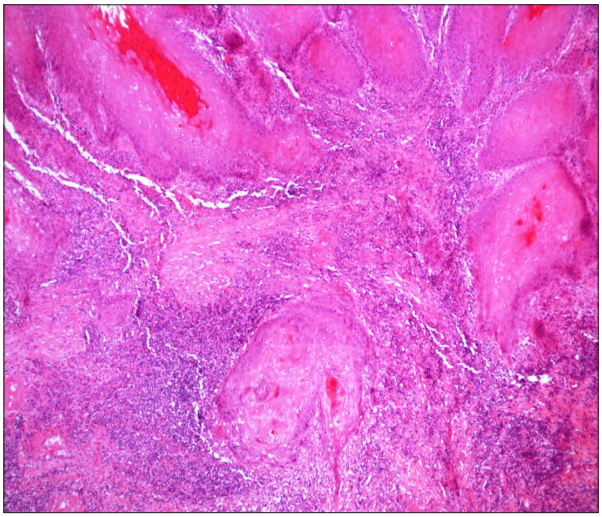
As a foundation doctor, it is vital to remember that GMC guidelines state that a consent can only be sought a doctor qualified to carry out the procedure themselves.

Case Outcome

The sample provided by EMR gave a diagnosis of very well differentiated squamous cell carcinoma. From the histology specimens it was not possible to rule out submucosal invasion [T1b]. The patient was therefore staged at T1a/T1b. Positron emission tomography [PET] scan was performed which showed increased fluorodeoxyglucose [FDG] uptake in the oesophagus but no clear evidence of any nodal disease or metastatic disease.



(1) Biopsies: benign squamo-proliferative lesion vs. well differentiated squamous cell carcinoma (H&E, x100)



(2) Well differentiated squamous cell carcinoma; invasive area shown (H&E, x50).

The patient met with a consultant UGI surgeon and UGI specialist nurse in clinic. He was advised of the results and on discussion opted for surveillance endoscopy over oesophagectomy. He was offered radical chemoradiotherapy as an alternative to surgery. He was then referred to a specialist oncology unit for consideration of chemoradiotherapy based on his performance status.

Discussion

Verrucous carcinomas are a type of squamous cell carcinoma. They are seen in the oropharynx, larynx, scrotum, glans of the penis, cervix, vulva, vagina, endometrium, bladder, anorectum, and soles of the feet.

The aetiology appears to be chronic inflammation or long term local disease process. Risk factors for oesophageal verrucous carcinoma are smoking, alcohol abuse, hiatal hernia, achalasia, oesophagitis. There is also a possible association with HPV infection though screening for HPV infection in this patient is not essential as it does not influence prognosis.

A verrucous carcinoma is slow growing rare form of squamous carcinoma. Since it is a squamous cell variant, it has an excellent response to chemoradiation. Unfortunately, despite being slow growing, and low propensity for lymph node involvement and metastasis, it carries a poor prognosis. There is often a delay between onset of symptoms and a definitive diagnosis and management plan.

As was demonstrated by this case, the delay is usually due to difficulties in arriving at a clear histological diagnosis. In, total 10 biopsies were taken which were found to be too superficial to arrive at a clear diagnosis of verrucous carcinoma. However, due to the exophytic appearance of the lesions on endoscopy, a high index of suspicion for the diagnosis was maintained and eventually the MDT opted for the relatively specialist technique of EMR to help acquire a sample sufficient for the pathologists to confirm verrucous carcinoma.

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Learning Points

EMR is a technique offered in a handful of specialist centres in the country which provide a diagnostic and therapeutic facility for superficial lesions.

Squamous cell carcinomas and its variants demonstrate a good response to chemoradiotherapy

One must only seek consent from patients for procedures for which the practitioner has had training in the practical techniques and the recognized complications. This is so that the patient can be necessary information to provide informed consent

The role of the multidisciplinary team in managing patients with cancer; this patient's case involved upper GI surgeons, gastroenterologists, upper GI specialist nurses, histopathlogists, dieticians, radiologists and clinical oncologists during the course of his management

MCQs

Q1. Which of these is the most common presenting sign/ symptom of oesophageal carcinoma

a. Weight loss

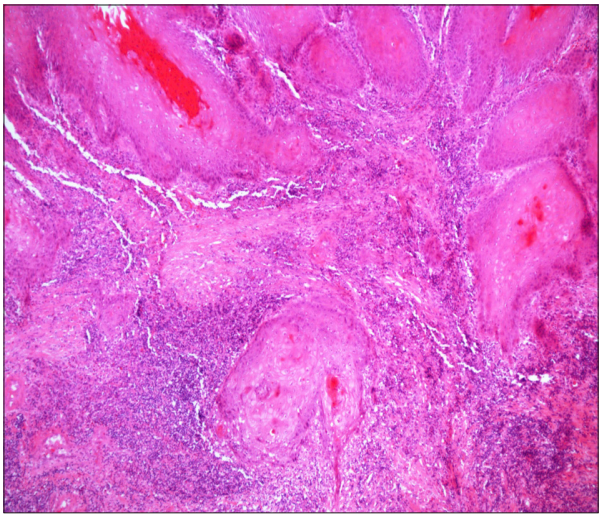
b. Dysphagia

c. Odynophagia

d. Respiratory symptoms

e. Haematemesis

Q2. What does this histopathology specimen show?



a. Normal tissue

b. Well differentiated squamous cell carcinoma

c. Adenocarcinoma

d. Barrett's oesophagus

e. Benign squamous-proliferative lesion

Q3. Which of these are not recognized risk factor for development of verrucous carcinoma of the oesophagus?

a. Betel nut chewing

b. HPV exposure

c. Obesity

d. Smoking

e. High Alcohol intake

Q4. Which of the following are not criteria that make a lesion amenable to EMR technique?

a. Stage T1a

b. Diameter <2cm

c. Involves < 1/3 of the circumference of the oesophageal wall

d. Only one lymph node region involved on PET

e. Are limited to the mucosa of the oesophagus

Q5. Which of the following statements regarding consent are correct?

a. Consent is not required if it is in the patient's best interest to perform an investigation or procedure

b. Only the clinician performing the procedure can gain consent

c. Consent has to be explicit in all circumstances

d. In cases that involve higher risk, it is important that you get the patient's written consent.

e. All of the above

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Answers

1. Dysphagia is the most common symptom at initial presentation, weight loss second most common.

2. The correct answer is b.

3. Obesity is not linked to squamous cell cancer of the oesophagus. All the others are.

4. Only lesions of stage T1a are suitable for EMR technique use as curative intent. Lesions of higher tumor staging will require consideration for surgical resection under UGI.

Lymph node involvement and distal metastasis would warrant referral to a clinical oncologist for consideration of chemoradiotherapy. The correct answer here is d).

5. Only d. is the correct statement regarding consent.

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References

1. Minielly JA, Harrison EG, Jr, Fontana RS, Payne WS. Verrucous squamous cell carcinoma of the esophagus. Cancer. 1967;20:2078–2087.

2. Malik AB, Bidani JA, Rich HG, McCully KS. Long-term survival in a patient with verrucous carcinoma of the esophagus. Am J Gastroenterol. 1996;91:1031–1033.

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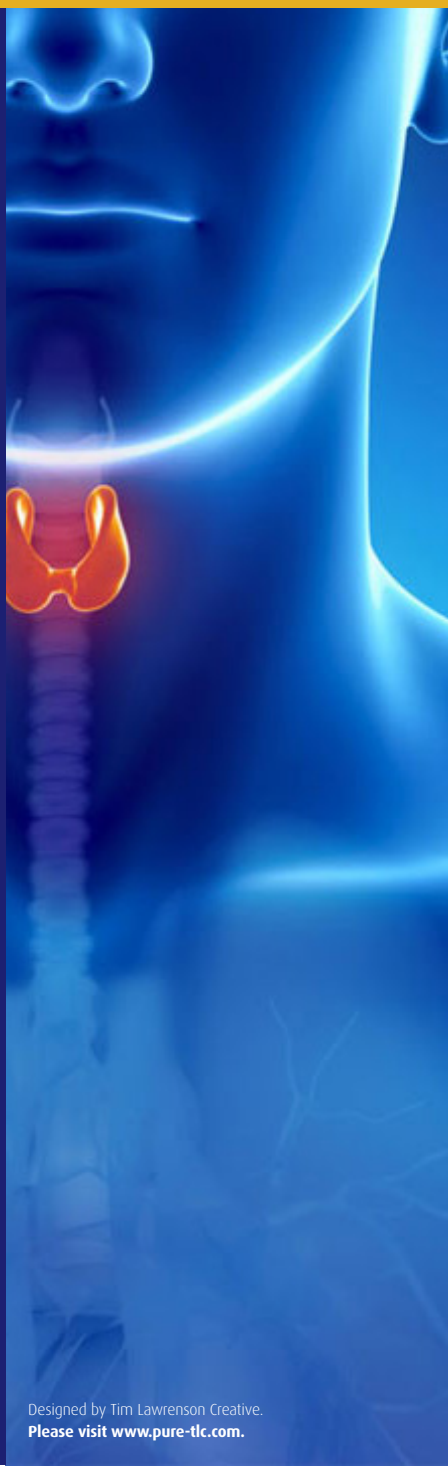

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