

bidā

Journal

Asthma in Adolescents
A Case Study

**Polycystic
Ovary Syndrome**

**Diagnosis, Metabolic Effects
and Management**

Oral Anticoagulants
A Report

**Cytoreductive
Surgery and
Heated Intra-Peritoneal
Chemotherapy**

An Overview

Penile Cancer
A Case Report

**Independent review into
Gross Negligence Manslaughter
and culpable Homicide**



The Journal of
The British International
Doctors' Association

Issue No.2, Volume 25. June 2019



www.bidaonline.co.uk

How a little change can make a big difference¹⁻⁸

Sereflo is therapeutically equivalent with the same dosing as Seretide. It's also the least expensive salmeterol/fluticasone propionate pMDI combination available, offering significant savings when compared to the market leader Seretide Evohaler.¹⁻⁸

Sereflo is part of Cipla's UK respiratory portfolio.



Sereflo[®]

(salmeterol/fluticasone propionate)

Sereflo is indicated in the regular treatment of adult patients (18 years and older) with moderate to severe asthma where use of a combination product (long-acting β_2 agonist and inhaled corticosteroid) is appropriate.^{1,2}

pMDI = pressurised metered dose inhaler.

Sereflo[®] Metered Dose Inhaler (salmeterol xinafoate/fluticasone propionate) Prescribing Information

Please consult the full Summary of Product Characteristics (SmPC) before prescribing Sereflo 25 microgram (μg) salmeterol xinafoate /125 μg or 250 μg fluticasone propionate per actuation pressurised inhalation, suspension. For both dose strengths the equivalent delivered dose per actuation is 21 μg of salmeterol and the delivered fluticasone propionate is 110 μg , for 125 μg dose strength and 220 μg , for 250 μg dose strength.

INDICATIONS: For use in adults with asthma 18 years of age and older only. Sereflo is indicated in the regular treatment of patients with moderate to severe asthma where use of a combination product (long-acting β_2 agonist and inhaled corticosteroid) is appropriate:
- patients not adequately controlled on a lower strength corticosteroid combination product or
- patients already adequately controlled on an inhaled corticosteroid in a mid or high strength and a long-acting β_2 agonist.

POSOLGY AND ADMINISTRATION: Patients should be instructed in the proper use of their inhaler (see SmPC and patient information leaflet). Recommended doses in adults 18 years and older - Two inhalations of 25 μg salmeterol and 125 μg or 250 μg fluticasone propionate twice daily. A short-term trial of salmeterol and fluticasone propionate may be considered as initial maintenance therapy in adults with moderate persistent asthma for whom rapid control of asthma is essential. In these cases, the recommended initial dose is two inhalations of 25 μg salmeterol and 50 μg fluticasone propionate twice daily. **Note:** Sereflo is not available in a lower strength product containing salmeterol 25 μg and fluticasone propionate 50 μg . Therefore, when initiating therapy, or when it is appropriate to titrate down to a dose below 125 μg , an alternative fixed-dose combination of salmeterol and fluticasone propionate containing a lower dose of the inhaled corticosteroid is required. **Use of a spacer device;** where required in those with difficulties in coordinating actuation of the inhaler with inspiration of breath, it is recommended ONLY for higher strength Sereflo containing salmeterol 25 μg and fluticasone propionate 250 μg . Patients should continue to use the same make of spacer device (Volumatic or the AeroChamber Plus) as switching between spacer devices can result in changes in the dose delivered to the lungs. See the SmPC for further information on initiation, titration down and spacer use.

CONTRAINDICATIONS: Hypersensitivity to either of the active substances or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS: Sereflo should not be used to treat acute asthma symptoms for which a fast- and short-acting bronchodilator is required. Patients should be advised to have their inhaler for relief in an acute asthma attack available at all times. Patients should not be initiated on Sereflo during an exacerbation, or significantly worsening or acutely deteriorating asthma. Serious asthma-related adverse events and exacerbations may occur with Sereflo. Patients should continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation. Treatment should not be stopped abruptly due to risk of exacerbation. Therapy should be down-titrated under physician supervision. All inhaled

medication containing corticosteroids should be administered with caution in patients with active or quiescent pulmonary tuberculosis and fungal, viral or other infections of the airway. Salmeterol and fluticasone propionate should be used with caution in patients with severe cardiovascular disorders or heart rhythm abnormalities and in patients with diabetes mellitus, thyrotoxicosis, uncorrected hypokalaemia or predisposition to low levels of serum potassium. Prescribers should also be aware of risk of adrenal suppression and acute adrenal crisis which may occur in patients on prolonged treatment with high doses of inhaled corticosteroids. Systemic effects may occur with any inhaled corticosteroid and it is important therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of asthma is maintained. **Drug Interactions:** Concomitant use should be avoided with; non-selective and selective β blockers, ritonavir and other potent/moderate CYP3A inhibitors, unless potential benefit outweighs the risk. Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics. See the SmPC for further information on contraindications and precautions.

PREGNANCY AND LACTATION: Balance risks against benefits.

UNDESIRABLE EFFECTS: Adverse events which have been associated with salmeterol/fluticasone propionate include: *very common*: nasopharyngitis and headache; *common*: candidiasis of the mouth and throat, pneumonia, bronchitis, hypokalaemia, throat irritation, hoarseness/dysphonia, sinusitis, contusions, muscle cramps, traumatic fractures, arthralgia and myalgia.

For other adverse events please consult the full SmPC.

MARKETING AUTHORISATION HOLDER & PL NUMBERS: Cipla (EU) Ltd, Dixcart House, Addlestone Road, Bourne Business Park, Addlestone, Surrey KT15 2LE. PL 36390/0237 and PL 36390/0238. **Legal category:** POM. **NHS Cost** 25 μg /125 μg 1x 120 dose MDI £14.99 and 25 μg /250 μg 1x 120 doses MDI £19.99. **Date of last revision:** December 2018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellowcard in the Google Play or Apple App Store. Adverse events should also be reported to Cipla (EU) Ltd on 0203 684 7710, drugsafety@cipla.com

References.

- Sereflo 25 microgram/125 microgram. Summary of Product Characteristics.
- Sereflo 25 microgram/250 microgram. Summary of Product Characteristics.
- Malhotra G et al. *Eur Respir J*. 2014; **44**(58): P940.
- Garg M et al. *J Bioequiv Availab*. 2017; **9**(6): 536-46.
- ePACT2 Data August 2018, available at <https://www.nhsbsa.nhs.uk/epact2> (accessed April 2019).
- MIMS.co.uk (accessed April 2019).
- Dictionary of medicines and devices (dm+d), available at <https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/dictionary-medicines-and-devices-dmd> (accessed April 2019).
- Seretide Evohaler. Summary of Product Characteristics, available at www.medicines.org.uk/emc/product/3825/smpc (accessed April 2019).



bida Journal Editorial

It is time for all of us to reflect on the Hamilton report the "Independent review into gross negligence manslaughter and culpable homicide".

Did you know that over the years, there have been an increasing number of criminal cases against doctors? How do we aim for a "just culture"? How do we protect our "reflections"? Hopefully the recommendations of this report will go a long way to allay the widespread concerns about the GMC's handling of such cases.

Bullying in the NHS remains an essential issue. We had highlighted this in our previous edition. I am pleased to say that there have been two recent conferences which have kept on highlighting the problem that affects doctors at all stages of their careers. The GMC is piloting a training scheme to help doctors call out colleagues' unprofessional behaviour. The training will initially be delivered at about 14 UK sites, identified by the GMC as organisations that may benefit from the training. The concept being promoted and suggested is that doctors can challenge unprofessional behaviour through "cup of coffee" conversations.

Have you seen the rosy picture, which the NHS long term plans have set out for the next 10 years? These milestones are incredibly positive steps. Dr. Preeti Shukla, GP Forum Chair has reported recent changes in the GP Contract, which seem positive for the Primary Care. BIDA would continue to participate in an optimistic way and closely monitor these changes.

Dr G C Sinha has highlighted a case, which demonstrates a fact of life that "men are reluctant to contact their GPs and seek medical advice. This is deeply rooted in their biological and psychological factors as well as their work conditions accepting risks acquired through social role and behaviour". Penile cancer can be a silent killer. There should be more awareness of this condition. GPs and other relevant health professionals need to be vigilant and ensure they think of this condition in any elderly male, which presents with vague symptoms of tiredness, loss of weight or a low HB. We are aware that HPV causes cancer in men including penile cancer. Are you aware that in the UK only girls and women are routinely offered vaccination? Since last year, men younger than 45 who have sex with men have been eligible for HPV



Mr. Amit Sinha
FRCS (Trauma & Ortho)
Co-Editor, BIDA Journal.
Consultant Orthopaedic Surgeon.



Dr. Ashish Dhawan
MD, MRCP
Co-Editor, BIDA Journal.
Consultant Cardiologist &
Cardiac Electro Physiologist,
Wigan Royal Infirmary

vaccination. Routine vaccination of boys aged 12 or 13 is expected to start soon in England.

We have some very interesting articles with a detailed one on "Cough in adolescents" by Aditi Sinha. This gives an up-to-date management plan of the condition. The article on "Polycystic Ovary Syndrome" raises an important issue that this condition is not only a gynaecological disorder but also has significant psychological and metabolic effects on women's health.

I must acknowledge approval and permission of the Editor of the Welsh Pharmacy Review for reproducing the article on oral anticoagulants by Mr Uttam Chouhan. This is an excellent article. Indeed, the entry of oral anticoagulants is a stroke of genius. This is a safer alternative to Warfarin and has already replaced it in the relevant medical conditions and replaced subcut- low molecular heparin for use as prophylaxis in joint replacement surgery. We await further trials for cancer patients.

The article on Cytoreductive surgery in cases of primary cancers with peritoneal metastases by Mr Selvasekar and his team is quite complex and specialised. The aim of cytoreduction is to ensure complete macroscopic removal of all peritoneal disease, which includes a combination of appropriate surgical procedures.

We are sure the Liverpool fans are still celebrating their victory. It's time to enjoy the World Cup cricket season. The BIDA sports events have commenced as well. Our best wishes to all the players, who participate in these events.

On behalf of the Editorial team we would like to thank our readers and members. Please put in the dates of the BIDA AGM/ARM, which is scheduled for the 20 - 22nd of September this year at The Samlesbury Park Hotel, Preston.

Best wishes

Ashish Dhawan & Amit Sinha

Co-Editors, BIDA Journal.

Contents

BIDA National Chairman's Report.....	4
BIDA G.P Forum Chairperson's Report.....	4
BIDA welcomes the High Commissioner of India on her maiden visit to Manchester.....	5
BIDA National Treasurer's Report.....	6
BIDA Subscriptions.....	6
BIDA Fellowship Awards 2019.....	6
Independent review into gross negligence manslaughter and culpable homicide: A long-awaited Hamilton Report published by the GMC.....	7 - 8
Asthma in Adolescents.....	9 - 11
Polycystic Ovary Syndrome.....	12 - 14
A Review of Oral Anticoagulants.....	15 - 17
An overview of Cytoreductive Surgery and heated intra-peritoneal chemotherapy in the management of peritoneal surface malignancies.....	18 - 20
Penile Cancer - A Case Report.....	21 - 22
Medical Quiz.....	23
Welcome to New BIDA Members.....	23
BIDA ARM / AGM 2019 Announcement.....	23
Congratulations: Dr Shikha Pitalia and Prof. Nirmal Kumar.....	24
Medical Quiz Answer.....	25
Why I joined BIDA.....	25
Divisional News: Bolton Division.....	26
BIDA Sports Events 2019.....	26

bida Journal

Editorial Committee:

Co-Editors

Mr A. Sinha
Dr Ashish Dhawan

Members:

Dr Sanjay Arya
Prof. D. Brigden
Dr B. Das
Dr C. Kanneganti
Dr P. Sarkar
Mr C. Selvasekar
Prof. S. Senapati
Dr B K Sinha
Mrs K. Upadhyay

Secretary: Mrs Margaret Barron

Any photographs offered for publication become the property of BIDA Journal and unfortunately cannot be returned.

Editorial Address:

The Co-Editors, BIDA Journal,
ODA House, 316A Buxton Rd.
Great Moor, Stockport, Cheshire SK2 7DD
E-mail: amitani2000@yahoo.co.in
bida@btconnect.com
Website: www.bidaonline.co.uk

Produced on behalf of the British International Doctors' Association by:

Graphic Design & Digital Artwork:

Nick Sample D&AD INFP

8 Fairways, Appleton, Cheshire WA4 5HA

Phone: 07950 332 645

E-mail: njcsample1@me.com

Website: www.nicksample.com

Printed by:

Minerva Print

King William House, 202 Manchester Road,
Bolton, Lancashire BL3 2QS

Phone: 01204 397522

E-mail: info@minervaprint.com

Website: www.minervaprint.com



Any views or opinions that may be expressed in articles or letters appearing in BIDA Journal are those of the contributor and are not to be construed as an expression of opinion in behalf of the Editorial Committee or BIDA. Members are asked to ensure that all enquiries and correspondence relating to membership or other matters are sent directly to ODA House, 316A Buxton Road, Great Moor, Stockport SK2 7DD. (T: 0161 456 7828 F: 0161 482 4535) and not to BIDA Journal.

BIDA National Chairman's Report



Dr Chandra Kanneganti
National Chairman, BIDA

Dear Colleagues,

We have been busy working for you in the last few weeks. BIDA represented our views on Gross Negligence Manslaughter to the independent review led by Leslie Hamilton. He has engaged with BIDA by speaking at our last conference, and has considered all the evidence submitted by us. The report is published now, and we will work for these recommendations implemented.

BIDA Executive Officers attended a dinner hosted for Mrs. Ruchi Ghanashyam, High Commissioner of India to UK, in Manchester in May 2019. We represented international doctors issues to her.

One of the major campaigns which we had been liaising with other organisations – DAUK, BMA – to include doctors into shortage occupation list, has been successful. The Migration Advisory Committee has accepted and recommended this. We now wait for the home office to accept the recommendation to implement it.

The BIDA Badminton and Table Tennis tournaments went very well. They were organised by Wolverhampton Division. Congratulations to the winners of this tournament.

The annual BIDA President's Cup cricket tournament is also under way, and I wish good luck to all of the teams.

I would like to take this opportunity to remind you all about our next ARM, on 20th-22nd September 2019, at The Samlesbury Park Hotel, Preston PR5 0UL.

This year's ARM is being hosted by Blackburn Division. As per the last 3 years, we have organised workshops and panel discussions for Saturday afternoon. Confirmed guests and speakers include Claire Light, Head of Equality, Diversity and Inclusion, GMC; Professor Iqbal Singh, Member, Honours Committee Health, CESOP Chair; Dr. Cicely Cunningham, Doctors Association UK and Manda Coppage from NHS resolutions. We are awaiting confirmation from Dr. Nikkin Kanani and Simon Stevenson from NHSE.

Topics to be discussed include support for international doctors in fitness to panel referrals, 'The Role of NHS Resolutions in supporting doctors', and DAUK and BIDA - working together.

Please register your attendance for our ARM as soon as possible.

Dr Chandra Kanneganti
National Chairman, BIDA

BIDA GP Forum Chairperson's Report



Dr Preeti Shukla
G.P. Forum Chairperson, BIDA

Dear Members,

This year saw the biggest change in history of general practice perhaps since 2004 with introduction of Network DES contract. This contract offers us an opportunity to shape services and our future. It's not a definitive blueprint but it's a good first stab at a roadmap that we can use to add meat onto the bones. Primary care network is being introduced as a Direct Enhanced service and gives a 5-year framework and ensures general practice takes a lead role in every PCN. It requires practices to group together within a coherent geographical area covering a population of 30,000 to 50,000 to deliver services.

Year 1 will include 100% recurrent funding for social prescribers and 70% for pharmacists. From 2020/2021 there will be 70% funding for physician associates and physiotherapists & 70% funding for paramedics from 2021/2022. There will be a shared saving scheme so that GP's benefit from work to reduce avoidable A&E attendances, admissions and delayed discharges.

There is going to be a recurrent network administration payment of £1.50 per patient and a clinical director for each PCN funded at £0.25 WTE per 50,000 patients. Funding will be paid to a nominated provider as agreed by network agreement. Extended access DES will be transferred to network DES.

State indemnity scheme was introduced in April 2019 for all practice staff including out of hours. By 2024 a typical network would have 5 clinical pharmacists, 3 social prescribers, 3 first contact physiotherapists, 2 physician associates and one community paramedic.

From 2020 network specification would be based on national processes and specification. It will include structured medication reviews, enhanced health in care homes, anticipatory care in partnership with community services, personalised care and supporting early cancer diagnosis.

I am cautiously optimistic about the future and think it's really important that we engage with PCNs. On a different note, it has opened a lot of leadership opportunities and if you are interested in being a PCN lead put your name forward. It's your chance to make a difference.

If you need any further information, support or guidance please feel to get in touch and thanks once again for your ongoing support.

Thanks

Dr Preeti Shukla
G.P. Forum Chairperson, BIDA

BIDA welcomes the High Commissioner of India on her maiden visit to Manchester



Recently the High Commissioner of India, **Mrs. Ruchi Ghanashyam** was in Manchester. She was accompanied by a high profile delegation of counsellors and ministers from the Indian High Commission, UK. This was her maiden visit. The High Commissioner of India, London and The Consulate General of India, Birmingham hosted an Interactive Evening with the Indian Diaspora at the Hilton Hotel, Manchester.

Several doctors, businessmen, academicians, religious leaders, social workers and other people of Indian origin who have made significant contributions to society attended this event.

BIDA office bearers were invited, and attended this evening. Our office bearers presented Mrs. Ganshyam with a bouquet of flowers. She showed a keen interest and appreciation for the cause of BIDA. BIDA representatives also interacted with various ministers and counselors highlighting to them the BIDA's ethos.

Overall, this was a very productive evening and BIDA looks forward to working closely with the High Commissioner of India for any health care related partnerships.

Dr Ashish Dhawan

National Secretary, BIDA



BIDA National Treasurer's Report



Mr Pranab K Sarkar
National Treasurer, BIDA

Dear Members,

Financially we are going through a difficult time. In recent years our annual income from members' subscriptions has continued to show a downward trend while our annual expenditures have continued to go up considerably outweighing our income.

A careful assessment of our current financial circumstances, makes me to think that we should rationalise our spending by prioritising our activities that are essential and that are not. It would be demanding on us that we should carefully plan for all our expenditures in order to remain financially stable. Now, financially we are faced with a challenging situation when we will have to make some difficult decisions. This may be one of the reasons why at last year's AGM, I proposed to increase our annual membership subscriptions. As this proposal was supported by the delegates, this increase which is expected to generate much needed additional income, will be effective from 1st October 2019.

Despite our current financial status, you will be pleased to know the NEC remains committed to support the publications of BIDA

Journal, sponsor various educational meetings, and annual sporting activities e.g. BIDA President's Cup Cricket Tournament and Annual Badminton / TT Competition. Our commitment to Divisional refunding and reimbursing delegates attending AGM/ARM will remain unchanged for the present time.

As the National Treasurer, I feel that, in the interest of our organisation, we should have a financial management strategy that should be in tune with the reality of our financial state. My financial goal is quite straightforward is to keep our finances in good health.

I am grateful to the NEC Members for supporting my financial strategy. I am thankful to Alison and Mandy, at our central office, for their support in doing my 'job' as effectively as possible.

Mr Pranab Kumar Sarkar
National Treasurer, BIDA

BIDA Subscriptions

Dear BIDA Member,

I am writing to inform you that at the last BIDA ARM/AGM in October 2018 the representative body unanimously voted and agreed that the membership fees should be increased with effect from the 1st of October 2019.

You may be aware that here has been no increase since October 2013 and with inflation rising constantly we believe that the increase is necessary in order to run our business.

We propose to increase the membership (per annum) as follows:

Standard Membership (Staff grade & above) from £99 to £110 - which is a 10% rise

Membership for couples to go from £145 to £160

Training Grades (all training & trainee GP's) to go from £45 to £50.00

Retired membership rate to go from £50 to £55.00

Life Membership £1100.00

Life membership for couples £1600.00

We would like to thank you for your continued support.

Mr Pranab Kumar Sarkar
National Treasurer, BIDA

BIDA Fellowship Awards 2019

**TO ALL DIVISIONAL CHAIRMEN
& SECRETARIES**

Dear Colleague,

As you know BIDA awards 'Fellowships' to some members who have made an outstanding contribution to the Association. These awards are made at the ARM/AGM in the Autumn and if you would like to nominate a member from your division, please do so, but kindly note that nominations are to be received no later than Friday 28th June 2019.

It would be of assistance, if the nomination could be supported by a brief CV of the nominee.

I look forward to receiving your nominations.

Yours Sincerely,

Dr Birendra Sinha
National President, BIDA

"ODA House" 316A Buxton Road,
Great Moor, Stockport,
Cheshire SK2 7DD

Telephone: 0161 456 7828

Fax: 0161 482 4535

Email: bida@btconnect.com

Website: www.bidaonline.co.uk



Independent review into gross negligence manslaughter and culpable homicide:

A long-awaited Hamilton Report published by the GMC.



Dr Buddhdev Pandya MBE

The long-awaited report of the 'Independent review into gross negligence manslaughter and culpable homicide' is now published. The recommendations in the independent review chaired by consultant cardiac surgeon, Sir Leslie Hamilton is generally well received within the medical fraternity. The most important and practical recommendations are that no doctor should find themselves subject to a criminal investigation, without their workplace environment also being carefully examined by national inspecting bodies, such as the Care Quality Commission. The emphasis on hospitals getting their local processes right, and involving appropriately trained individuals, is an important and a key to reducing the blame culture, as well as reducing the risk of recurrent adverse events.

In my initial consultation response-outlines last year, I advocated for "more focus on triggering well developed processes for considering 'corporate manslaughter' aspects for tackling 'systemic failures', desperately requiring redress. Equally, the role of the licensing and regulatory bodies like GMC as well the CQC in developing formal and meaningful mechanism to collate evidences for enforcement of legitimate actions to procure safer environment for the professionals and patient care. More so, it would be prudent to review their powers to enforce changes, triggering stringent sanctions by the DoH for those service providing institution repeatedly failing to improve situation".

The long-awaited report of the 'Independent review into gross negligence manslaughter and culpable homicide' by Sir Leslie Hamilton is now published on 6th June 2019 the GMC.

The general reaction from the medical fraternity has been favourable since it shows how a number of changes need to be made to the current system to ensure greater fairness and consistency for those working in healthcare and also emphasising, the importance of ensuring families and relatives get the answers they need. More so, the review reflects on the whole system, from the local investigation stage through to the coroner's inquest and the role of the police and prosecuting authorities, as well as the GMC. However, in the context of the need to remove any potential 'triggers', including any focus on the importance of 'corporate manslaughter', has been downplayed. As well as the areas where the crucial role of DoH in monitoring and applying sections to deter the failing Trusts and providers of survives is not elaborated.

The opportunity is missed to specify areas of improvements with more clarifications to make progress, rather than highlighting what is already known to the doctors.

Its most welcoming indications is the emphasis on hospitals getting their local processes right, and involving appropriately trained individuals, is an important and a key to reducing the blame culture, as well as reducing the risk of recurrent adverse events. Recognising the importance of the 'Culture Shift' in the NHS and associated functions of various agencies for regaining confidence in the service provision can be considered a tipping point. The 'reflective' learning process is a two-edge sword often feared and eventually not guarantee that it will not be used against them! The report provides little relief in this context.

While touching the subject of groups of doctors particularly from Black, Asian and Minorities, despite having research evidence

pointing clearly to the increased risks doctors being referred into regulatory proceedings and the dangers of professional isolation and lack of support, the reports falls short of making more detailed remarks of significant nature. It is merely recommending that this is left for healthcare services and regulators alike to address.

Although it has acknowledged what is already known that all four countries of the UK have developed robust frameworks to enable good quality, fair and just investigation of incidents, they are inconsistently applied, poorly understood and inadequately resourced.

The report has acknowledged and reemphasized many issues already raised by individuals and national and local voluntary bodies representing doctors and other frontline personnel. The report, I hope marks beginning of new era for adopting a positive change of culture' to improve the health care environment. What remains to be seen is how much these are interpreted into definable and measurable actions!

There are 29 Recommendations listed in the report. In brief;

Recommendations 1-2: The GMC must take urgent steps to repair that relationship so that it is better able to work with and support doctors in delivering a high standard of care for their patients.

Recommendations 3-4: This refers to close adherence to the professional and statutory duty of candour when death or serious injuries occur. Also expects all healthcare service to provide clear policies and ensure consistency in the implementation in line with the relevant national frameworks.

Recommendations 5-9: the report confirms that some groups of doctors feel particularly at risk. Yet, it argues that the statistical data is limited but recognizes that research evidence points clearly to

Independent review into gross negligence manslaughter and culpable homicide'

the increased risk for Black, Asian and Minority Ethnic (BAME) doctors being referred into regulatory proceedings and the dangers of professional isolation and lack of support. This is an issue for healthcare services and regulators alike to address

Recommendation 10: The need for appropriate external authorities to scrutinise the systems within the department where the doctor worked. This is particularly relevant where the doctor involved is a trainee.

Recommendations 11-14: Reliability of expert opinions and how they are chosen once an investigation is underway. Also how their opinions are calibrated and how their work is quality assured. The weight of concern points to a widespread lack of confidence in a system which relies on the confidence placed in experts.

Recommendation 15: Improvements in patient safety are most likely to come through local investigations into patient safety incidents which are focused on learning not blame. Emphasise on the need for the investigation team to have the time and the appropriate experience, skills and competence (including understanding of human factors) to undertake investigations, and the necessary degree of externality to command confidence in the process. We also stress the need to involve and support families and staff. Framework implementation at the local level is patchy. We therefore recommend that the appropriate authorities in each of the four UK. Recommends authorities take responsibility for ensuring they are consistently and effectively applied.

Recommendation 16: The appropriate authorities in the four UK countries should quality assure the effective application of local investigation frameworks for patient safety incidents. This external scrutiny should include a specific focus on how healthcare service providers address human factors issues within their investigation processes.

Recommendation 17: Difficulties for individual coroners to develop experience in handling such cases and knowing when the police should be notified. The Chief Coroner and his Deputies have a role in supporting greater consistency of decision making.

Recommendation 18: Doctors appearing at coroners' courts also need better support. Healthcare service providers have a responsibility to provide support and guidance for doctors involved in these processes so that they are better prepared.

Recommendation 19: Investigating officers should have early access to independent medical advice to inform their understanding of what is alleged to have taken place. Responsible Officers are well placed to co-ordinate the provision of suitable independent advice for the police in the initial stages of an investigation

Recommendation 20: Lack of confidence in organisations and processes based on perception. Suspicion that the CPS recruits experts who will support the case for prosecution rather than provide a balanced view on the doctor's conduct. Whether or not perceptions are well-founded in fact, they are powerful in influencing behaviours. Greater transparency is needed to aid

understanding about how decisions are made and improve confidence in the integrity of key processes.

Recommendation 21: Doctors' loss of confidence in the GMC was at the heart of this review. The recommendations are aimed at helping the GMC to tackle this issue so as to support better and fairer regulation. It is recommended that the GMC examine the processes which contributed to doctors' loss of confidence. The report also supports the UK Government's plan to remove the GMC's power to appeal decisions of the Medical Practitioners Tribunal Service.

Recommendations 22-23: The GMC regulates doctors on behalf of society and has a statutory duty to regulate so as to promote and maintain public confidence in the medical profession. Commissioned independent research: The results of that research are complex and nuanced, and point both to an understanding of the pressures under which doctors work, but also an expectation of accountability when patients are harmed. There is work for the GMC to do to improve understanding of its role and its responsibility not to punish doctors for past mistakes but to ensure their ongoing fitness to practice. The GMC and Medical Practitioners Tribunal Service must consider how this is reflected in their guidance to tribunals

Recommendations 24-25: There is also work for the UK Government in bringing forward planned legislative reform that will enable the GMC to take a more proportionate approach to its handling of concerns about doctors' fitness to practice.

Recommendation 26: But even with legislation that is fit for purpose, some of the changes that are needed cannot be delivered by the GMC alone. There is much that doctors can do to help themselves. This includes using the tools that have been developed to help them engage in reflective practice in a way which will support their learning and limit their perceived vulnerability to the misuse of their reflective notes in other proceedings

Recommendation 27: Doctors' professional bodies, medical defense organisations, healthcare service providers and others should work with the GMC to explore how doctors under investigation can be better supported.

Recommendation 28: Healthcare service providers can do more to provide induction and support for those doctors who are new to medical practice or returning to clinical practice after a significant absence.

Recommendation 29: The recommendations contained in this report are directed at a number of different organisations. Although these are independent bodies, we hope they will recognise the need for change to enhance public and professional confidence in the processes over which they preside.

Finally, the report hopes that the GMC which has commissioned the review, the GMC eventually will monitor the adoption and implementation of the proposals.

Dr Buddhdev Pandya MBE

Asthma in Adolescents



Dr. Aditi Sinha
MRCPCMBChBSc (Hons)
ST5 Paediatric Trainee

Case Study

A.Y. was diagnosed with asthma at the age of 2 due to persistent wheezy episodes. Under general paediatric follow up, she was eventually commenced on regular inhaled corticosteroids. As a pre-school infant she had infrequent hospital admissions and exacerbations only with respiratory tract infections. During her early teenage years, her asthma symptoms accelerated with persistent cough and wheeze requiring the addition of Montelukast as well as preventer therapy with Symbicort (Budesonide/formoterol). Further investigation revealed high IgE levels, eosinophilia and an obstructive picture on spirometry (FEV1 86% FVC 95%). To try and alleviate her symptoms the family dog was removed, carpets were replaced with laminate flooring and strategies to reduce house dust mites were undertaken. There were no smokers in the family.

Despite this, by the age of 15 she was frequently admitted to hospital, missing extensive amounts of school and was significantly limited in her activities. She was eventually referred to the child and adolescent mental health services due to emotional bullying and self-inflicted injury. She was also referred to Dermatology for severe eczema and was attending Allergy Clinic for multiple allergies to pet dander, house dust mites, tree/grass pollen as well as allergic rhinitis. As she was now requiring continuous oral corticosteroids so a synacthen test was undertaken which revealed adrenal suppression. She was commenced on hydrocortisone replacement and referred to Endocrinology. She was reported to be significantly Cushingoid at this point.

Despite good compliance, her asthma control remained poor. Her management was escalated to step 4 of the stepwise approach (Seretide 250 twice a day plus Montelukast) and she was referred to the tertiary paediatric respiratory team. Further investigations showed peak expiratory flow variability (30% over 1 week) and a positive exercise test (FEV1 dropped by 38%). Her chest x-ray showed perihilar bronchial wall thickening but her high resolution CT thorax was normal. A pH study indicated mild gastro-oesophageal reflux so she was

commenced on a proton pump inhibitor. She was started on a 6-8 week weaning regime of oral steroids and Slo-phyllin. A trial of Omalizumab (a subcutaneous monoclonal antibody to IgE used for severe allergic asthma) was initiated.

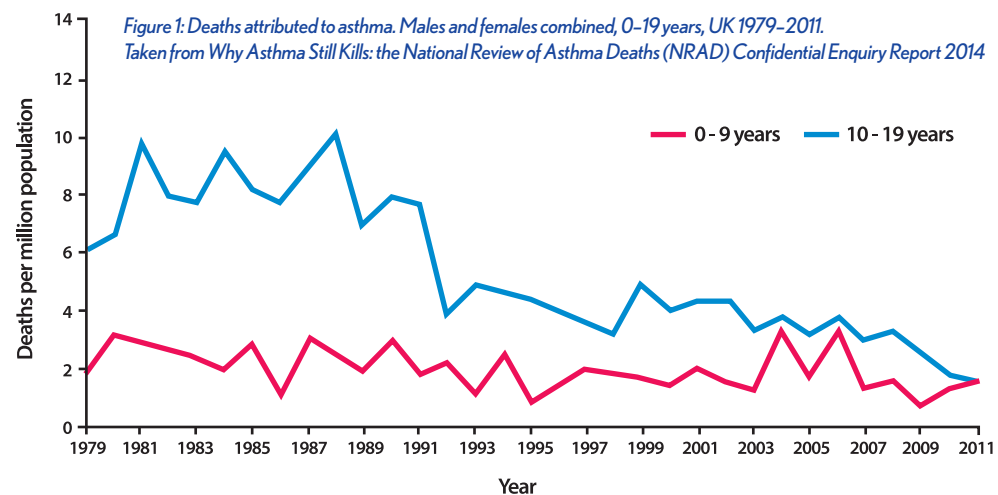
By the age of 17 she was established on Omalizumab injections, which resulted in a dramatic improvement in her quality of life and reduced hospital admissions. Her lung function normalised (FEV1 99% & FVC 101%) and she was no longer on persistent oral steroids. The transition process to adult services was undertaken successfully so that the adult respiratory physicians now regularly follow her up for her severe allergic eosinophilic asthma. She is currently stable on her ongoing treatment with Omalizumab, Seretide, Montelukast and Slo-phyllin.

Introduction:

Asthma is common in adolescence. Frequent or severe episodes of wheezing in childhood

age. The key elements of working effectively with adolescents in this transition to adulthood include, seeing them on their own, separate from their parents for part of the consultation as well as discussing confidentiality and its limitations. It is also important to address issues of adherence to treatment (unintentional and intentional) and encouraging them to see good control of their asthma as a sign of adult capability and responsibility. Discussing lifestyle choices such as smoking, diet and exercise and asking about symptoms of anxiety or depression can also identify further co-morbidities.

The consequences of not being diagnosed with asthma and not receiving adequate healthcare are substantial. The National Review of Asthma Deaths (NRAD): Why asthma still kills was published in May 2014 and reported that most of the deaths that are still occurring in children with asthma are those who are adolescents between 10-19 years of age (see Figure 1)².



are associated with recurrent wheeze that persists into adolescence. Data from 2016 has shown that in 13-14 year olds prevalence of asthma is around 14.3% and in those with more severe asthma the prevalence is 6.2%¹. Due to significant under reporting of symptoms, there is also a proportion of under diagnoses in approximately 20-30% of the adolescent population.

Adolescence is the transitional period of growth and development between puberty and adulthood, between 10 and 19 years of

Diagnosis and Assessment:

Signs and symptoms of asthma in adolescents are no different from those of other age groups. Exercise-related wheezing and breathlessness are common, therefore in any adolescent presenting with cardio-respiratory symptoms, a diagnosis of asthma should be considered.

Assessment of asthma in adolescents can be undertaken via a variety of methods (see Figure 2). Tests of airflow obstruction/airway responsiveness may provide support but the

Questionnaires	<ul style="list-style-type: none"> The asthma control questionnaire (ACQ) and the asthma control test (ACT) have been validated in adolescents with asthma
Quality of Life Measures	<ul style="list-style-type: none"> QoL scales (such as AQLQ12+) can be used.
Lung function	<ul style="list-style-type: none"> Tests of airflow obstruction and airway responsiveness may provide support for diagnosis of asthma but most adolescents with asthma will have normal lung function.
Bronchial hyper-activity	<ul style="list-style-type: none"> A negative response to an exercise test is helpful in excluding asthma in children with exercise-related breathlessness.

Figure 2: Assessments used in adolescents with asthma. Taken from BTS/SIGN British guideline on the management of asthma 2016.

chance of a false negative result is high. Additionally, only a minority of adolescents referred for assessment of exercise-induced symptoms show objective evidence of exercise-induced bronchospasm.

Risk factors & Co-morbidities

Risk factors associated with difficult asthma control in adolescents include:

- Female gender
- Frequent or severe episodes of wheezing in childhood
- Atopic dermatitis/rhinitis
- Low birth weight due to prematurity
- Smoking (current/passive)
- Low socioeconomic status
- Family problems
- Low physical activity and high BMI (evidence conflicting and not fully established in adolescents)
- Chlorinated swimming pools

The risk of hospital admission in females is double that observed in males¹. However frequent symptoms, airway hyper-responsiveness, atopy and low lung function identify those adolescents at highest risk of multiple hospital admissions.

Co-morbidities such as gastro-oesophageal reflux disease (GORD) are common in adolescents with asthma but there is no evidence that GORD treatment improves asthma symptoms. There is also an increased likelihood of major depression, panic attacks and anxiety disorders. In fact depressive symptoms were identified as a risk factor in adolescents who died of asthma¹. Clinical conditions associated with anxiety may be mistaken for asthma. These include dysfunctional breathing (hyperventilation syndrome and sighing dyspnoea), vocal cord dysfunction, and psychogenic cough. Therefore screening questionnaires suitable for use in adolescents should be used to help identify those with significant anxiety and depression.

Studies have showed that adolescents and young adults with relatively mild asthma had slightly more limitations in vocational and professional careers than those without asthma and also had a small increase risk in limitations

of daily activity. Careful future planning regarding career choices to mitigate against high risk occupations that might exacerbate symptoms is therefore essential.

Management

1. Inhaler devices: Specific evidence about inhaler device use and choice in adolescents is limited. Although they may be competent at using certain inhaler devices, actual adherence to treatment may be affected by preference. For example, there are many adolescents who do not use spacers as they are too inconvenient. It is also important to enquire about factors that may affect inhaler device use in real life settings, such as school and extra-curricular activities. It may be worth considering prescribing more portable devices for when away from home. With the development of wireless technology and cloud data, devices, which connect to a phone or tablet via an app are being used to change the way we manage adolescent patients with asthma (see Figure 3).

Smart Touch

Clips around a standard meter dose inhaler to record the date and time of inhaler activation.



Smart Turbo

Small sensor device attaches on the top of an existing reliever/preventer inhaler to record the time and place the inhaler is used.



Inhaler Compliance Assessment (INCA) device

Records actuation and uses a digital audio recording to provide an objective assessment of both the time and the technique of inhaler use.



Table 1: Different types of Smart inhaler devices (4)

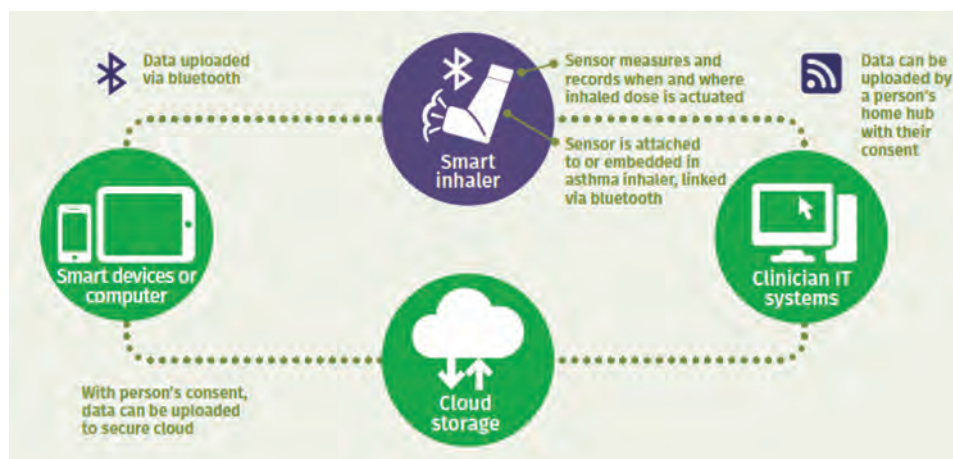


Figure 3: Schematic diagram taken from the report on connected devices by Asthma UK (4)

A large number of Smart inhalers have been developed which can be used to track, prompt and remotely monitor patient's use of medication (see Table 1). With increasing use of technology especially within the paediatric and adolescent population, these devices will allow empowerment so adolescent patients can self-manage their own asthma.

2. Patient education & self-management: It is essential that asthma education is provided by a trained professional who can engage with,

encourage and motivate adolescents. Education within schools has been found to be increasingly important. School-based, nurse-led asthma clinics increase the uptake of asthma reviews in adolescents from 51% to 91%¹. Peer led education in schools has also been shown to improve quality of life, asthma control and days off school. Web-based tailored management programmes found that after 12 months, students reported fewer symptoms, fewer school days missed,

reduced restricted-activity days and less frequent hospitalisations.

Qualitative data has provided insight about the concerns adolescents have about their asthma and its management. Adolescents frequently report:

- Embarrassment over using inhalers in front of others
- Sadness over not being able to take part in normal activities
- Frustration and anger at the way they are treated by their families
- Anxieties around fear of dying
- Feeling guilty over the effect their illness has on the family
- Concerns about needing to rely on someone else

As clinicians we need to engage, empower and motivate adolescents to take independent responsibility for their own management and recognise those that need emotional support for coping with their feelings. We must also support parents to hand over responsibility for management to their child and stress the importance of support from friends at school, especially those with asthma themselves. Furthermore, accompanying information, both written and oral, should be personalised rather than general and use non-medical language that adolescents can understand.

3. Adherence: One of the greatest barriers to improving the health of asthma patients is drug adherence. Most adolescents admit they do not always follow their treatment plans. These reasons include:

- Forgetfulness
- Inhalers being ineffective/hard to use
- Treatment plan too complicated or confusing
- Concern about adverse effects
- Denial and embarrassment about asthma diagnosis
- Intentional non-adherence - more important things to do, can't be bothered

Adherence is linked to other health risk behaviours such as smoking, alcohol and drug use, and also depression. Not only do these behaviours impact on adherence but they also have been highlighted as potential 'beacons of distress' in adolescents who are poorly controlled¹. Support from the parents,



physicians and nurses, and a positive attitude towards the disease and treatment were related to good reported adherence. Other strategies to improve adherence in adolescents includes focusing on the individual and their lifestyle, individualising asthma planning and personal goal setting as well as utilising the new technologies via telehealth solutions and mobile apps.

4. Transition of Care: The process of transition must be co-ordinated between adult and paediatric services, involving multidisciplinary and multiagency teams. Although there are no studies on transition of adolescents with asthma to adult services, it is recommended that the process should be planned early, and be both age and developmentally appropriate. Young people are encouraged to take part in their transition process and additional youth support programmes must be available for them to engage with if required. In the initial period after transition, adolescents are best seen by one consultant who will oversee their transition in order to build confidence and encourage attendance.

Conclusion

Adolescence is a confusing time for most young people, but especially for those who have a chronic disease such as asthma. It can impact on daily life and school attendance, cause night-time disturbances and in some cases restricted participation in everyday activities. Reduction of asthma symptoms and exacerbations via excellent disease control are the goals of asthma treatment and recognising co-morbidities or risk taking behaviour can identify those adolescents most vulnerable. Utilising resources within technology to adjust delivery devices and monitor inhaler techniques, involving multi-agency teams in the co-ordination of transition and commissioning school/college based asthma education are all key elements

required to successfully manage adolescent asthma. Ultimately, as clinicians we should seek to engage adolescent patients as partners in planning and implementing their own management, creating treatment goals that have been negotiated with them rather than dictated⁵.

Key learning points

- ✓ Frequent or severe episodes of wheeze in childhood is associated with recurrent wheeze persisting into adolescence
- ✓ Due to under reporting of symptoms approximately 20-30% of adolescents are under diagnosed
- ✓ Screening for common co-morbidities such as GORD, depression and anxiety disorders should be undertaken
- ✓ New technologies can be used to effect adherence to treatment, changing the way we manage adolescent patients
- ✓ School-based asthma education is a key element required to successfully manage adolescent asthma
- ✓ The process of transition should be planned early and be co-ordinated between adult and paediatric multidisciplinary teams

References:

- 1 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. A national clinical guideline 2016. Available online: <https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2016/>
- 2 Why Asthma Still Kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry Report. Royal College of Physicians, London 2014. Available online: www.rcplondon.ac.uk/sites/default/files/why-asthma-still-kills-full-report.pdf
- 3 McArthur R & Small I. Quick guide to asthma management - Primary Care Respiratory Society. Primary Care Respiratory Society UK Formerly known as General Practice Airways Group 2015. Available online: www.pcrs-uk.org/sites/pcrs-uk.org/files/AsthmaGuide_FINAL_2015.pdf
- 4 Asthma UK. Connected asthma: how technology will transform care 2016. Available online: <https://www.asthma.org.uk/1290191z/globalassets/get-involved/external-affairs-campaigns/publications/connected-asthma/connected-asthma--aug-2016.pdf>
- 5 MacDonald P. Managing asthma in adolescence. Nursing Times 2001; 97:38, 40

Polycystic Ovary Syndrome

Dr. Anuradhai Arunaganesekaran
MRCOG
Senior Clinical Fellow
(pictured right)

Dr Kalpana Upadhyay
MRCOG
Consultant in Obstetrics
and Gynaecology,
Wrexham Maelor Hospital,
BCUHB, North Wales

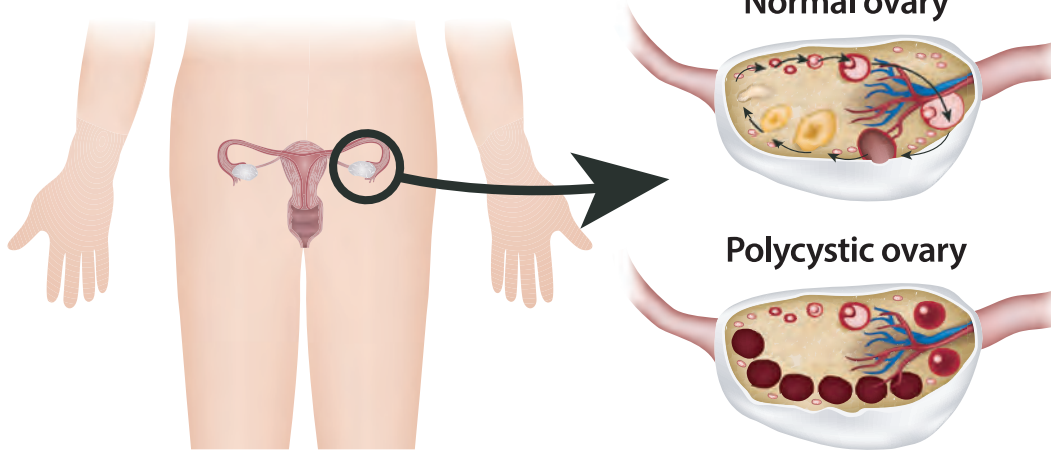


Polycystic Ovary Syndrome (PCOS) is one of the commonest endocrine disorders in women, with a prevalence of 2.2 - 26%.¹ It is difficult to estimate the prevalence due to the use of different diagnostic criteria and varied prevalence among ethnic groups. A recent meta-analysis showed lowest prevalence in Chinese women and highest in Black women¹.

Aetiopathogenesis

The etiology of PCOS is not clear; it is proposed to be multifactorial involving both genetic and environmental factors (Figure 2). Women with PCOS are found to have insulin resistance which can lead to hyperandrogenism and ovulatory dysfunction.²

Figure 1. Normal and Polycystic ovary



Diagnosis

PCOS should be diagnosed when women have two of the following three features, based on the revised Rotterdam 2003 consensus criteria³ and endorsed by ESHRE (European Society of Human Reproduction and Endocrinology in 2018).

Polycystic ovarian morphology on Ultrasound - Ovarian volume of ≥ 10 ml and / or presence of ≥ 20 follicles per ovary in either of the ovaries⁴. As per the new international guidelines, PCOS should not be diagnosed based on ultrasound morphology in young women < 8 years from menarche, due to higher incidence of multi follicular ovaries in this stage.

Irregular cycles and ovulatory dysfunction - It is important to note that girls have irregular cycles during pubertal transition. When diagnosis is in doubt, they can be re-assessed at 8 years from menarche or earlier if required⁴.

Clinical and / or biochemical signs of hyperandrogenism - Clinical signs of hyperandrogenism are acne, alopecia and hirsutism. Acne is common in adolescents; hence severe acne is used as diagnostic criteria⁴. Hirsutism is defined as presence of terminal hair in male pattern distribution in women. Women with features of virilisation (deep voice, clitoromegaly, reduced breast size, increased muscle bulk) or rapidly progressing hirsutism or high testosterone levels of more than 5 nmol/L are unlikely to have PCOS and should prompt a search for androgen secreting tumors and late onset congenital adrenal hyperplasia⁵. High quality assays are recommended to measure total or free testosterone.

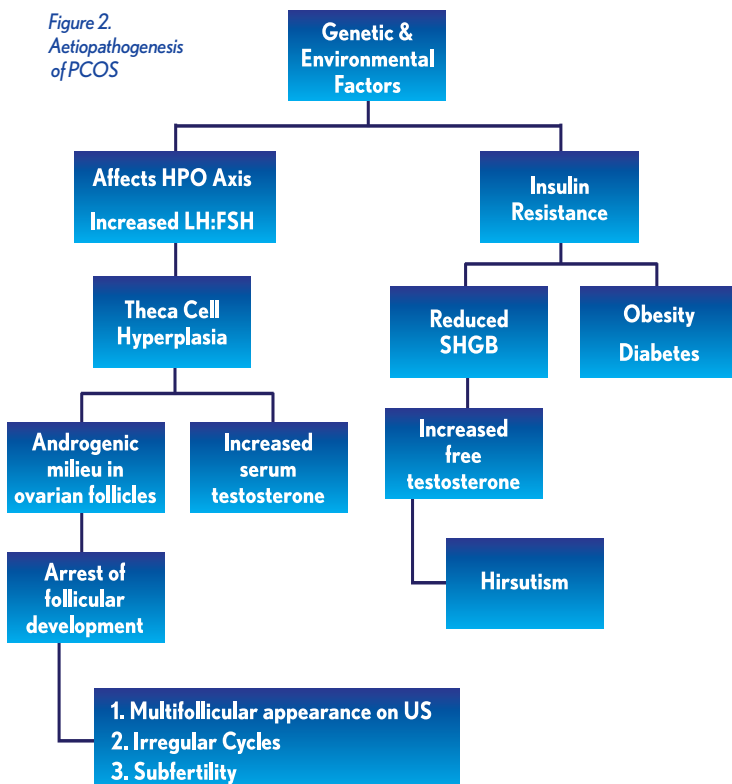
Free Androgen index = $100 \times (\text{total testosterone} / \text{SHBG})$
Normal values should be less than 5.

The diagnosis of PCOS should be made after excluding other causes of irregular cycles like thyroid dysfunctions, acromegaly, hyperprolactinemia if there is clinical suspicion⁵.

Metabolic effects of PCOS

Diabetes: Women with PCOS are at risk of developing gestational diabetes, impaired glucose tolerance and type II diabetes due to insulin resistance, independent of obesity. All women should be offered

Figure 2. Aetiopathogenesis of PCOS



screening for diabetes at diagnosis⁴ and for gestational diabetes mellitus in pregnancy with a 2hour 75g OGTT⁵. They should be offered regular screening for diabetes, frequency of which can be based on presence of other risk factors and ethnicity.

Cardiovascular disease (CVD): Insulin resistance has shown to contribute to the development of CVD⁷. Hence women should be assessed for the presence of other risk factors for CVD (obesity, lack of physical activity, cigarette smoking, family history of type II diabetes, dyslipidemia, hypertension, impaired glucose tolerance, type II diabetes) at diagnosis of PCOS.

Obesity: Studies have shown increased prevalence of central obesity in women with PCOS⁸. The systematic review also showed that Caucasian women with PCOS had a greater prevalence of obesity than Asian women. BMI and waist:hip ratio should be used to diagnose obesity as per WHO guidelines⁴.

Obstructive sleep apnoea: Studies have shown an increased prevalence of obstructive sleep apnoea in women with PCOS. Women should be screened for sleep apnoea if symptomatic⁵.

Psychological health: Health related Quality of life is found to be reduced in women with PCOS. This is commonly due to hirsutism, menstruation and infertility. There is increased prevalence of depression and anxiety in these women, warranting screening at diagnosis. They are at risk of eating disorders like binge eating or Bulimia nervosa⁹. Women can have body image dissatisfaction due to acne, hirsutism and obesity¹⁰. The recent international guidelines recommends the use of PCOS quality of life tool (PCOSQ) or the modified PCOSQ tool to identify features causing greatest distress and to evaluate treatment outcome.

Risk of cancer: Women are at increased risk of developing endometrial cancer due to endometrial hyperplasia from unopposed action of estrogen on endometrium. It is essential to induce withdrawal bleeds every 3-4 months at least to reduce this risk. Women with amenorrhea or irregular bleeding should be offered ultrasound and endometrial biopsy if required.

Management

Lifestyle intervention: A healthy lifestyle includes adopting healthy diet, regular exercise and achieving and maintaining a healthy weight. A Cochrane systematic review has shown that this improves body composition, hyperandrogenism and insulin resistance in women with PCOS⁶. This in turn helps in regularising periods, reduces hirsutism, improve fertility and also reduces risks of cardiovascular disease and diabetes. A small reduction of 5 % of weight has shown to improve reproductive, metabolic and psychological health. Women should be encouraged to follow healthy lifestyle even if they become asymptomatic later.

Irregular cycles: Women are diagnosed to have irregular cycles if their periods are more frequent (less than 21 days interval) or less frequent (more than 45 days). This can be managed with combined oral contraceptive pills (COCP), Progesterone only pills (POP) or Mirena coil. Any combination of low dose COCP, rings, patches, injectable hormones can be prescribed. COCP regularises cycle and also prevents worsening of hirsutism. The medical eligibility criteria should

Definition of irregular cycles:
Normal in first year post menarche
>1 to <3 years post menarche: <21 or >45 days
>3 years post menarche to peri-menopause: <21 or >35 days or less than 8 cycles per year
>1 year post menarche: >90 days for any one cycle
Primary amenorrhea by age 15 or > 3 years post thelarche (breast development)

Table 1: Definition of Irregular cycles

be checked as they can also have risk factors like hypertension and thromboembolism.

Sub fertility: Women need pre conception counselling to emphasise on weight loss, smoking cessation, omitting alcohol just like in general population. They should be offered screening for diabetes, hypertension and mental health risks and these should be managed appropriately to improve fertility and treatment outcomes. The woman and her partner should be evaluated for other causes of sub fertility. Some women with PCOS can have anovulation in spite of regular cycles. Luteal phase serum progesterone can be performed in these women to confirm ovulation. NICE recommends clomiphene citrate or metformin or combination of both for ovulation induction¹¹. Women resistant to clomiphene can be managed with either metformin or gonadotrophins or laparoscopic ovarian drilling. Some women may need artificial reproductive techniques like in vitro fertilisation. The most recent ESHRE guidelines⁴ however recommend use of aromatase inhibitors like "Letrozole" as first line drug for ovulation induction in PCOS with an increase in livebirth rates by 40-60% as compared to clomiphene citrate.

Hirsutism: A modified Ferriman Gallwey score of $\geq 4-6$ is used to identify women with hirsutism. It is essential to advise women to

Medical management of hirsutism:		
DRUG	MODE OF ACTION	SIDE EFFECTS
Combined Oral Contraceptives	Suppress ovarian androgens and free androgen levels.	Nausea, vomiting, migraine, VTE
Cyproterone acetate and Drospirenone	Peripheral anti-androgen	
Spirolactone	Androgen receptor antagonist	Postural hypotension, hyperkalemia
Flutamide	Androgen receptor antagonist	Liver toxicity
Finasteride	Inhibits peripheral conversion of testosterone to dihydrotestosterone	Feminisation of male fetus, liver toxicity
Metformin	Improves insulin resistance and reduces free androgens	Nausea, diarrhoea, hepatitis, lactic acidosis
Eflornithine hydrochloride	Reduces the rate of hair growth in face. Licensed for facial hirsutism.	Skin irritation, acne, rash, systemic toxicity

Table 2: Medical management of hirsutism

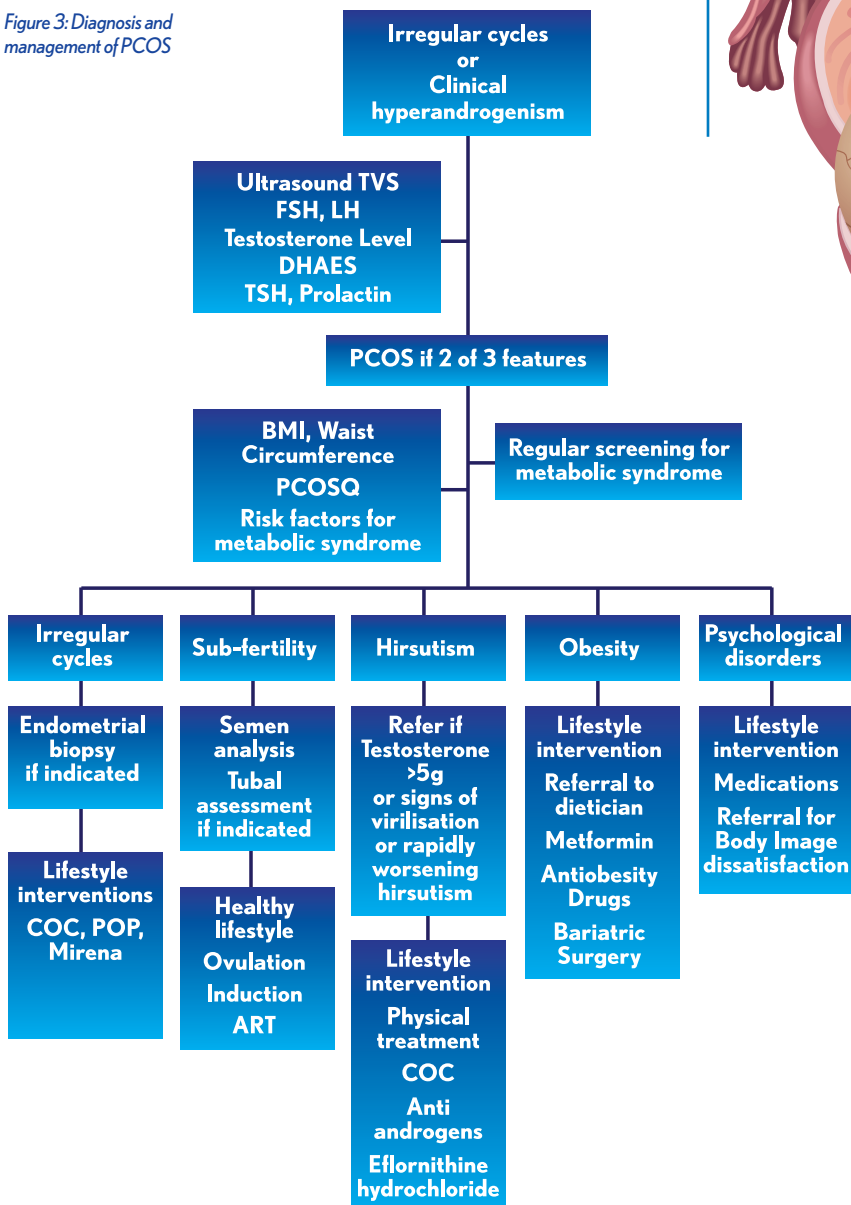
Polycystic Ovary Syndrome

describe the severity of hair growth as most of them would be using some method of hair removal. Cosmetic methods include plucking, waxing, shaving, depilatory creams and bleaching. Physical methods include electrolysis and laser to destroy the hair follicles. Low dose combined oral contraceptives are the first line of management. The progestogen component suppress the luteinizing hormone and thereby reduces ovarian androgen secretion. The estrogen component increases the hepatic sex hormone binding globulin (SHBG), thereby reducing the free androgen levels.

Metformin: It is an insulin sensitising agent, not licensed for use in PCOS in the UK. The recent international guidelines on PCOS states metformin (up to 1.7g/day in 2-3 divided doses) could be recommended for treatment of weight, hormonal and metabolic outcomes in adult women. The RCOG states there is insufficient evidence to recommend for metabolic outcome.

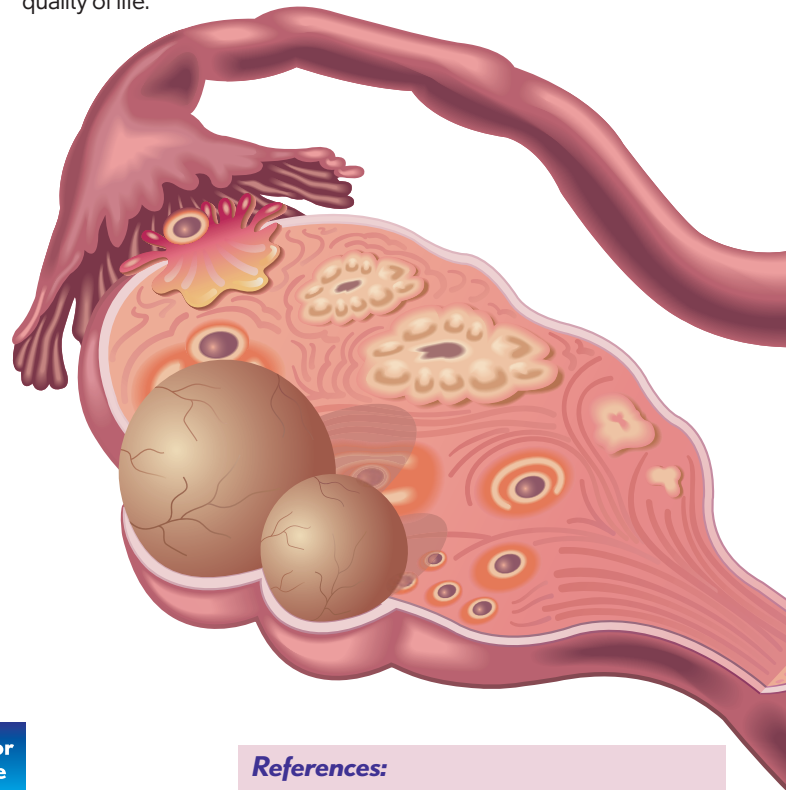
Anti-Obesity drugs: Orlistat and Sibutramine can be considered in women with PCOS for weight management as per general population guidelines.

Figure 3: Diagnosis and management of PCOS



Conclusion

PCOS is not only a gynaecological disorder but also has significant psychological and metabolic effects on women's health. As care providers we should screen for risk factors, educate them about its implications and provide them support to improve their health related quality of life.



References:

- 1 The prevalence of polycystic ovary syndrome in reproductive aged women of different ethnicity: a systematic review and meta-analysis. T.Ding et al, Oncotarget, v.8(56); Nov 2017
- 2 The Pathogenesis of Polycystic ovary syndrome: The Hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Rosenfield RL, Ehrmann DA, Endocrine review, Oct 2016; 37(5): 467-520
- 3 Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovary syndrome. Rotterdam ESHRE/ASRM sponsored PCOS consensus workshop group. Fertility sterility, 2004 Jan;81(1): 19-25
- 4 International evidence based guideline for the assessment and management of polycystic ovary syndrome 2018. CREPCOS, Monash University, ASRM, ESHRE.
- 5 Long term consequences of polycystic ovary syndrome. GTG No.33, November 2014, RCOG
- 6 The effect of a healthy lifestyle for women with polycystic ovary syndrome. Moran LJ et al, Cochrane library, July 2011.
- 7 Association between insulin resistance and the development of cardiovascular disease. V.Ormazabal et al, Cardiovascular Diabetology, 2018, 17:122
- 8 Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. S.S.Lim et al, Human Reproduction Update, Vol.18, Issue 1, November 2012: 618-637.
- 9 Polycystic ovary syndrome: Adverse mental health outcomes. Robert L Barbieri et al, UpToDate, October 2018.
- 10 Polycystic ovary syndrome and mental health; A review. Melissa J.himelein, Samuel S.Thatcher. Obstetrical and Gynecological survey, Vol.61, Number 11, 2006.
- 11 Fertility problems: assessment and treatment, Clinical guideline 156, NICE, Feb 2013.
- 12 NICE Clinical Knowledge Summaries, Hirsutism, December 2014(NICE)
- 13 Van Zuuren EJ, Fedorowicz Z, Carter B, Pandis N. Interventions for Hirsutism (excluding laser and photolysis therapy alone). Cochrane Database of Systematic Reviews 2015

A Review of Oral Anticoagulants



Uttam M Chouhan

Pharmacist, Glan Clwyd Hospital,
Rhyl, North Wales LL18 5UJ

Introduction

Although the gap in the underuse of anticoagulants is closing in, lack of information relating to the medication's role in preventable blood clots remains. To address this strand of therapy – from early beginnings, and the impact of drug interactions, the importance of clinical indication, and the standard of care required by the pharmacist, this article presents a comprehensive review of oral anticoagulants.

Warfarin

Introduction of warfarin into clinical practice was heralded in 1955 when it was prescribed to the then President of USA, Eisenhower, following his myocardial infarction (MI). Although warfarin has been shown to be effective in secondary prevention following MI, aspirin is the preferred agent due its safety (significantly lower bleeding incidence) in comparison to warfarin¹. The benefits of secondary prevention in MI patients include, prevention of another myocardial infarction, stroke, and death.

Currently warfarin is indicated for the treatment of acute thromboembolic (TE) events, pulmonary embolism and deep vein thrombosis and in patients who have mechanical heart valves. It is also used in patients with antiphospholipid syndrome which carries a high risk of TE events. However, its biggest use is for the prevention of thromboembolic events, primarily stroke in patients with atrial fibrillation (AF) who also have additional risk factors of age (≥ 65 years), heart failure, hypertension, diabetes, or vascular disease such as angina².

The name warfarin is derived from "WARF" – Wisconsin Alumni Research Foundation – and "arin" from coumarin. The credit for discovery of warfarin goes to Karl Link and the discovery of vitamin K in 1930s lead to Henrik Dam and Edward Dosty being awarded the Nobel prize for physiology in 1943.

Vitamin K is important in the synthesis of clotting factors and warfarin is a vitamin K antagonist. The onset of action of warfarin is dependent on how quickly the clotting factors are reduced. Furthermore, the enzyme that warfarin blocks (vitamin K epoxide reductase (VKORC1)) and the enzyme responsible for its metabolism are under the genetic influence. These genetic components along with variable dietary

intake of vitamin K necessitate that the anticoagulant effect of warfarin should be regularly monitored. This is achieved by monitoring prothrombin time and reported as international normalised ratio (INR).

The therapeutic INR range is between two to three. Drug interactions with warfarin are also very common due to its effects of the enzymes previously mentioned, and effect on the content of gut vitamin K.

For warfarin to be effective in preventing thromboembolic events in AF patients INR has to be maintained within the range 2 to 3 for at least 65% of the time over a six month period. This is called time in therapeutic range (TTR).

NICE clinical guidance released in 2014 on the management of atrial fibrillation specifies what constitutes poor INR control based on six months of INR values:

- TTR < 65%
- TWO INR values > 5
- ONE INR reading > 8
- TWO INR readings < 1.5

The two main issues when initiating warfarin are that it can exacerbate the thromboembolic condition and it has a slow onset of action. It is for these reasons that intravenous heparin infusion is employed in acute VTE and continued until INR is in therapeutic range. Except for certain clinical scenarios, intravenous heparin infusion has now been replaced by low molecular weight heparins.

Alternatives to Warfarin

It was not surprising that the search for alternatives to warfarin has been ongoing for several years, culminating initially with ximelagatran which was short-lived due to liver toxicity. However, the landmark RE-LY study³ was presented at the European Congress of Cardiology in Barcelona in August 2009 comparing two doses of dabigatran with warfarin in over 18,000 AF patients. Dabigatran received its EU marketing authorisation in August 2011.

The game changer was the NICE technology approval in March 2012 of dabigatran for stroke prevention in AF patients. Since then three other oral anticoagulants have been approved by NICE – rivaroxaban, apixaban and edoxaban. These agents are called direct acting oral anticoagulants (DOACs). The decision

to approve each agent was based on large clinical trials comparing new agent with warfarin in stroke prevention in AF. In acute venous thromboembolism (VTE) two of the DOACs, apixaban & rivaroxaban, were compared directly with enoxaparin/warfarin whilst dabigatran and edoxaban were initiated after at least five days of treatment with enoxaparin.



A Review of Oral Anticoagulants

...continued

A meta-analysis⁸ of all the four trials of DOACs in over 70,000 AF patients shows the following in comparison to warfarin:

Mortality reduction of	10%
Haemorrhagic stroke reduction of	51%
Intracranial haemorrhage reduction of	52%
GI bleeding increase of	25%
Major bleeding reduction of	14%

A similar meta-analysis⁹ of DOACs in acute VTE demonstrates that the DOACs cause significantly lower major bleeding incidence than enoxaparin / warfarin.

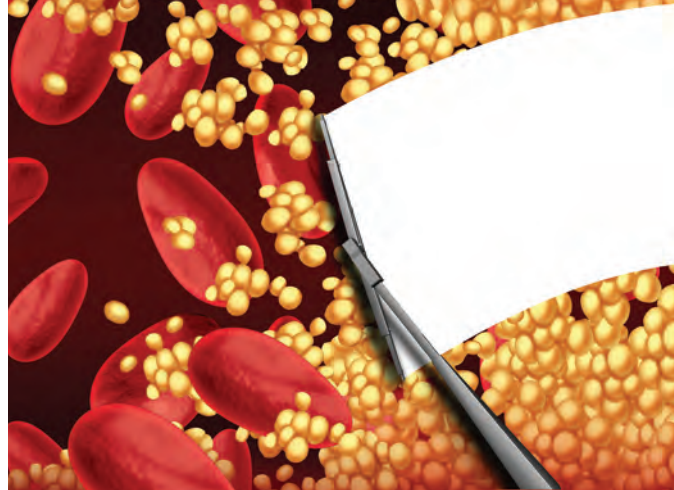
	WARFARIN	DOAC
Peak effect	Several days to achieve therapeutic INR	One to four hours
Half life	40 hours	Around 10 to 12 hours
Dose	Variable depending on INR	Fixed depending on indication
Number of drug-drug interactions ⁽⁴⁾	439	Up to 68
Availability of antidote ^(5,6,7)	Vitamin K (IV or oral) Prothrombin Complex Concentrate (4 factors), PCC	Idarucizumab for dabigatran For factor Xa inhibitors PCC has been used successfully however andexanet alfa has received approval for reversal of anti-coagulant effect of apixaban & rivaroxaban in America
Annual drug costs	Few pounds (excludes INR monitoring)	Several hundred pounds

Table 1: Summary of the major differences between DOAC agents versus warfarin

In cancer patients with acute VTE, low molecular weight heparin e.g. enoxaparin, dalteparin is recommended, but has to administered as subcutaneous injection on a daily basis for up to 6 months. Two DOACs, edoxaban and rivaroxaban have been studied in patients with active cancer and acute VTE and the results have recently been published.

Edoxaban was shown to be as effective as dalteparin (primary outcome was combination of recurrent VTE and bleeding) but caused a higher incidence of major bleeding¹⁰. On the other hand, rivaroxaban has been shown to be more effective (based on primary outcome of recurrent VTE) with higher bleeding incidence¹¹. At present none of DOAC is recommended by any society for acute VTE in active cancer.

All DOACs are contraindicated in patients with mechanical heart valves.



With the exception of edoxaban, DOACs are also indicated in the prevention of VTE following knee or hip replacement surgery.

Drug - Drug Interactions

As mentioned above there are several interactions reported between drugs and warfarin necessitating at least weekly monitoring of INR when an interacting agent is introduced or stopped. This degree of monitoring should continue until INR becomes stabilised. Although the scale of drug-drug interaction with DOAC is of lower magnitude compared to warfarin, it is important to bear in mind that commonly prescribed medicines do interact eg carbamazepine with rivaroxaban. The use of this combination is not recommended¹². So it is vital to check for drug-drug interaction when patient is taking a DOAC.

A patient with AF who also acquires coronary stent(s) presents a special challenge as the risk of bleeding with combination of oral anticoagulant (for stroke prevention) and dual antiplatelet therapy (for prevention of stent thrombosis) is considerable. Recent studies show that combination of DOAC (dabigatran¹³ or rivaroxaban¹⁴) with single antiplatelet agent (mainly clopidogrel) causes significantly lower bleeding than triple therapy (oral anticoagulant & dual antiplatelet therapy).

Bleeding

This is the most significant adverse event with any anticoagulant, ranging from nuisance bleeding eg nose bleeds to intracranial bleeds. In females, menorrhagia can be prolonged and severe when on oral anticoagulant therapy.

Guidance is available giving management strategies to deal with major bleeding event with DOAC¹⁵ and vitamin K antagonists⁵. However, of note an observational study¹⁶ demonstrated better survival outcomes in patients who had major bleeds with DOAC compared to warfarin, despite the lack of availability of specific antidote for DOAC.

Invasive Procedures

The majority of AF patients established on oral anticoagulant are elderly and have chronic condition(s). Recent studies show that around 25 to 33% of these patients require some form of invasive procedures e.g. dental extraction, biopsy or surgery. For the majority of patients, these invasive procedures will be planned so that it can be safely undertaken to minimise the risk of TE event or major bleeding. The BRIDGE study¹⁷ showed that bridging with LMWH was more harmful and has had a significant influence in how AF patients having invasive procedures should be managed¹⁸.

Since DOAC have a considerably shorter half-life compared to warfarin, management during planned procedures is much simpler. In short, DOAC can be stopped around 48 hours before provided renal function is satisfactory without the need for LMWH, procedure safely executed

and DOAC restarted 24 to 72 hours later depending on the risk of bleeding^{15,18}. Of note, there is growing body of evidence that oral anticoagulant therapy can be continued uninterrupted for specific surgical procedures without leading to increased incidence of bleeding.

The role of the Pharmacist

- For warfarin patients check INR records and assess as mentioned above. AF patients with INR values consistently below 2 are at higher risk of strokes.
- Discuss with the patient the clinical indication for the anti-coagulant, be it warfarin or a DOAC.
- For DOAC confirm the dose is correct for the indication.
- Check for drug-drug interaction even if the combination is initiated from a hospital. An example is aspirin with DOAC/warfarin and duration of this combination.
- Remind the patient to have full blood count & renal function at least six monthly.
- Reinforce the importance of regular compliance, especially with DOAC.

Prescribing of DOACs

Since the introduction of DOACs into clinical practice after NICE approval, the prescribing of DOAC have gradually increased primarily because of its ease of use without any anticoagulant monitoring (cf warfarin) and patient preference. However, there is accumulating evidence that up to 20% of patients on DOAC may not be prescribed the correct dose based on clinical indication, patient age and renal function determined by the crockcroft-gault equation¹⁹. The clinical consequence of incorrect dose is increased incidence of bleeding, TE event, hospitalisation and mortality.

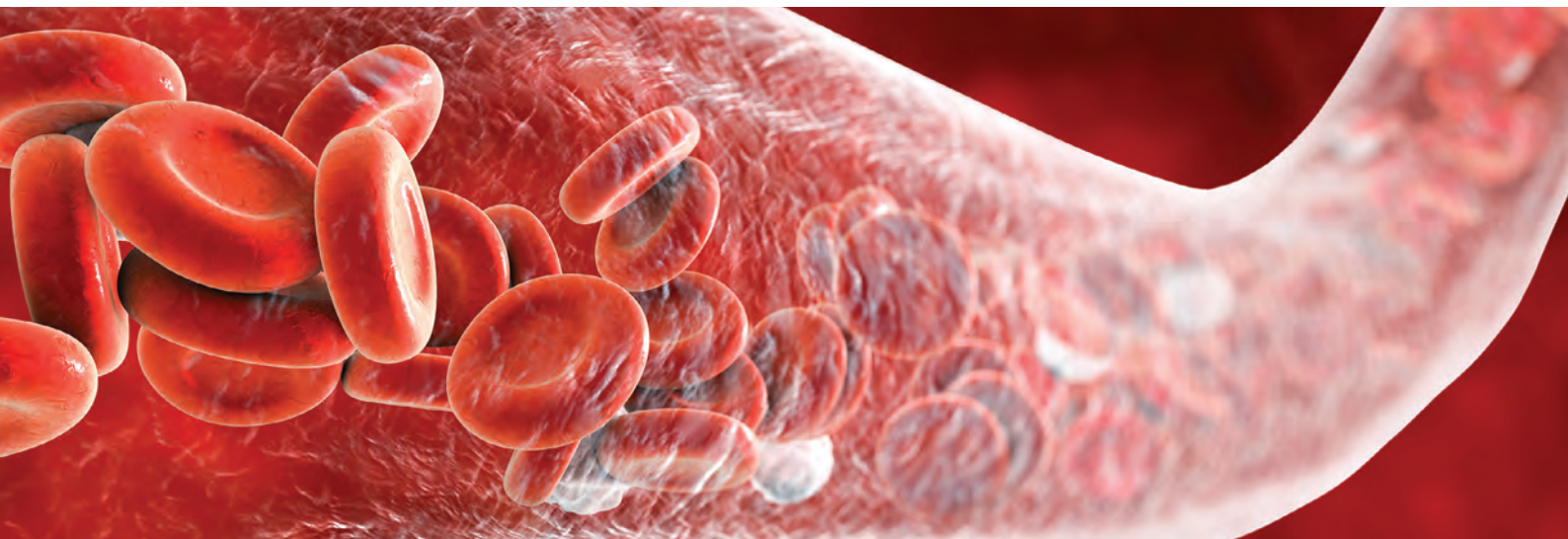
In conclusion, anticoagulants are a major group of medicines that are widely used in clinical practice for the prevention and treatment of thromboembolic condition. Warfarin continues to be widely prescribed but requires regular anticoagulant monitoring to maximise its efficacy and safety. It remains the anticoagulant of choice in patients with mechanical heart valves.

DOAC uptake has increased dramatically as they have clinical advantages, predictable half-life, easier to manage around the time of an invasive procedure, and with fewer drug-drug interactions. However, a substantial majority of patients are not prescribed the correct dose, which has to be challenged.

References:

1. Guidelines on oral anticoagulants: third edition. Br J Haem 1998; 101:374-378
2. 2016 ESC Guidelines for the management of atrial fibrillation. European Heart J 2016; 37: 2893-2962
3. Connolly S J, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009; 361: 1139-1151
4. MicroMedex accessed 7th August 2018
5. Hunt BJ and Levi M Urgent reversal of vitamin K antagonists. BMJ 2018; 360;5424
6. Majeed A, Agreen A, Holmstrom M, et al. Management of rivaroxaban- or apixaban- associated major bleeding with prothrombin complex concentrates: a cohort study. Blood 2017; 130:1706-1712
7. Andexxa- An Antidote for Apixaban and Rivaroxaban. JAMA 2018; 320:399-400
8. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383:955-962
9. van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014; 124:1968-1975
10. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. NEJM 2018; 378:615-624
11. Young AM, Marshall A, Thirlwall J, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomised Trial (Select D). J Clin Oncol 2018; 36: 2017-2023
12. UpToDate accessed 15th August 2018
13. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic therapy with dabigatran after PCI in Atrial Fibrillation. NEJM 2017; 377:1513-1524
14. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. NEJM 2016; 375:2423-2434
15. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. European Heart J 2018; 39:1330-1393
16. Xu Y, Schulman S, Dowlatshahi D, et al. Direct Oral Anticoagulant- or warfarin- related Major Bleeding. Chest 2017; 152:81-91
17. Douketis JD, Spyropoulos AL, Kaatz S, et al. Perioperative Bridging Anticoagulation in patients with Atrial Fibrillation. NEJM 2015; 373:823-833
18. 2017 ACC Expert Consensus Decision Pathway for periprocedural management of anticoagulation in patients with non-valvular atrial fibrillation. JACC 2017; 69:871- 898
19. Steinberg BA, Shrader P, Thomas L, et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes. JACC 2016; 68:2597-2604

*This article was originally published in the September 2018 issue of the **Welsh Pharmacy Review** and is reproduced by the permission of the Editor.*



An overview of cytoreductive surgery

and heated intra-peritoneal chemotherapy in the management of peritoneal surface malignancies

Dulantha de Silva,
Thanenthiran Antony
& Chelliah Selvasekar
Colorectal and Peritoneal Oncology Centre,
Christie Hospital, Manchester
General Sir John Kotelawala
Defence University, Sri Lanka

Abstract

Peritoneal metastasis has poor prognosis. In certain primary cancers with peritoneal metastasis, the prognosis is improved by cytoreductive surgery and heated intraperitoneal chemotherapy. The success of this treatment depends on careful patient selection, multidisciplinary decision-making process in high volume centres with high quality surgery and a system set up to deliver this procedure in a safe and effective way.

Introduction

Cancers affecting the peritoneal surface can arise primarily, as in the case of peritoneal mesothelioma. Most peritoneal surface tumours, however, arise from peritoneal metastases of major gastrointestinal and ovarian malignancies. These include metastases from colorectal, gastric and appendiceal cancers. Peritoneal surface malignancy has historically been associated with dismal prognosis. Colorectal peritoneal metastases (CRPM) for example when treated with standard therapy has a median survival of less than 17 months while in gastric cancer median survival less than 8 months⁽¹⁾.

However, advances in treatment modalities in the last two decades, has begun to offer hope for survival in patients once upon a time condemned to palliation. Chief among these treatment strategies has been the combination of surgical tumour cytoreduction with intra-operative delivery of heated chemotherapy to the peritoneal cavity. This approach pioneered by the likes of Paul Sugarbaker of the Washington Cancer Institute has showed significant improvement in the overall survival rates of peritoneal metastases from ovarian, colorectal, appendiceal and gastric carcinoma as well as from malignant peritoneal mesothelioma. It has also emerged as the standard of care in the management of peritoneal dissemination of low-grade mucinous neoplasms of the appendix, a condition known as pseudomyxoma peritonei (PMP).

What is the rationale behind this procedure?

With advances in surgical techniques, a complete macroscopic removal of the peritoneal metastases (Cytoreduction) is technically feasible in a number of patients. However there remains the possibility of microscopic tumour deposits giving rise to future recurrences. This is explained as the theory of tumour entrapment. Standard intravenous chemotherapy has had limited efficacy on peritoneal surface malignancy due to poor penetration. However direct intra-peritoneal instillation of chemotherapy can theoretically overcome this disadvantage. It was subsequently discovered that heat augmented the cytotoxic effects of chemotherapy⁽²⁾. This led to the development of the concept of Hyperthermic intra-peritoneal chemotherapy

(HIPEC). In order for HIPEC to be effective however, the peritoneal disease burden must be reduced to a level where intra-peritoneal chemotherapeutic agents can successfully penetrate remaining tumour cells. This underlies the rationale for combining cytoreductive surgery (CRS) with HIPEC in the management of peritoneal surface malignancy. In addition, there is a significant proportion of patients where the metastasis is limited to the peritoneum with no evidence of systemic disease.

A number of factors appear associated with the treatment efficacy. These include the volume of peritoneal metastases, the completeness of cytoreduction and the type of malignancy⁽¹⁾.

Technique

Cytoreductive Surgery

The aim of cytoreduction is to ensure complete macroscopic removal of all peritoneal disease. In order to achieve this, the surgical procedures are performed include;

1. Segmental peritonectomy
2. Resection of disease affected viscera
3. Diathermy ablation of disease
4. Resection of structures with high risk of recurrence (Target organ resection)

Peritonectomy includes stripping of all areas of the peritoneum affected by tumour deposits. This may include stripping of the pelvic peritoneum, stripping of the under-surface of the diaphragm and stripping of the paracolic gutter. Areas of peritoneum with no macroscopic disease are preserved.

All affected organs or those with potential risks that can be safely sacrificed are also resected. This may include removal of the spleen, gall-bladder, appendix, uterus and ovaries as well as colonic and rectal resection.

High energy diathermy is used to ablate disease which may not be safely stripped or resected. This technique is used to achieve technical clearance of disease on the surface of the liver.

Certain structures are at high risk of developing peritoneal metastases. This includes the omentum which studies have shown may have a receptive vascular micro-environment for tumour attachment. Therefore, cytoreductive procedures include resection of the greater and lesser omentum, ligament of teres, ovaries and in certain situations the gallbladder even if unaffected by macroscopic disease.

Cytoreduction is conventionally performed via midline laparotomy. However, evidence is emerging that in low volume disease a laparoscopic approach may also be effective.

Hyperthermic intra-peritoneal chemotherapy

The cytoreductive procedure is then followed by the delivery of intraperitoneal chemotherapy. This is delivered via specifically designed or modified perfusion machines which circulate the chemotherapeutic agents within the peritoneal cavity for periods between 30-90 minutes. A number of drugs have been used for HIPEC and these vary depending on the primary tumour as well the history of prior chemo-sensitisation. The commonly used agents include mitomycin C, oxaliplatin, cisplatin and carboplatin⁽³⁾. Chemotherapeutic infusion is delivered at temperatures between 41-43 °C. The HIPEC can be delivered with abdomen open (Figure1) or closed.

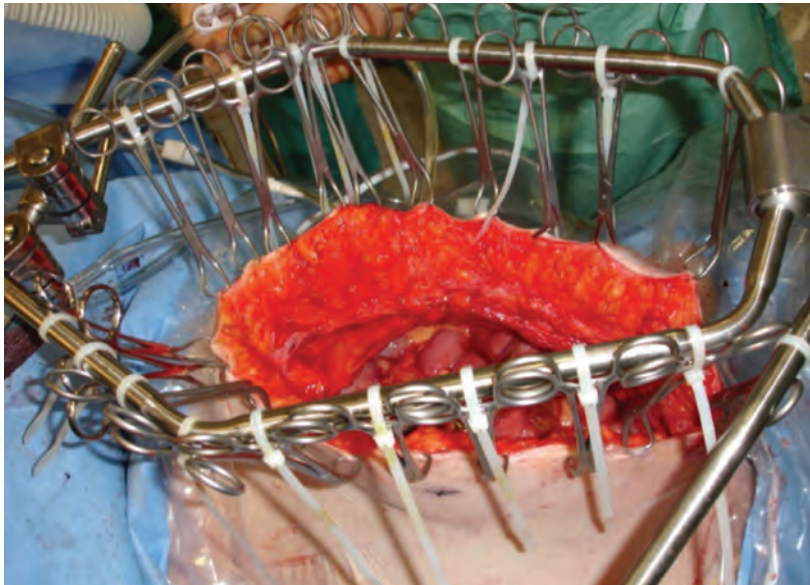


Figure 1: Open 'Coliseum' technique for HIPEC

Due to the complexity of procedure which usually exceeds 5-6 hours, there is high risk of complications. Nevertheless, results from high volume centres show that this can be performed with acceptable morbidity and mortality (<1%)⁽⁴⁾.

What evidence do we have that it works?

Evidence for the efficacy of CRS and HIPEC in the management of this rather heterogenous group of conditions comes from a multitude of sources.

In general, the efficacy of this technique depends on several factors. The most important of these is the completeness of cytoreduction and extent of tumour burden. Tumour burden is objectively assessed by the Peritoneal Carcinomatosis Index (PCI Score) as proposed by Sugarbaker⁽⁵⁾. This gives a score of between 1 and 3 to thirteen regions of the peritoneal cavity based on the extent of tumour in each region (Figure 2) The higher the PCI score the less chance that CRS and HIPEC would be effective.

In addition to this the outcome benefit of each procedure varies based on the nature of the primary cancer.

Peritoneal Cancer Index

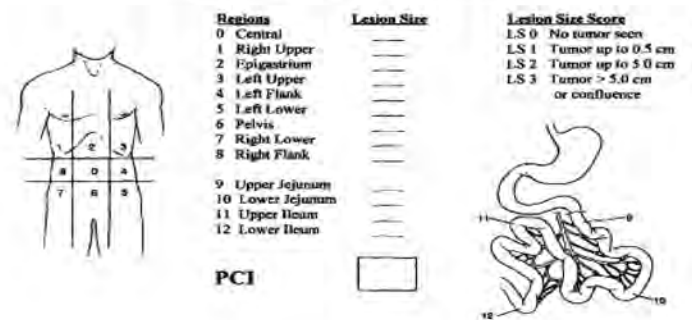


Figure 2: Peritoneal Carcinomatosis Index (After Sugarbaker⁽⁵⁾)

Although there is a paucity of level 1 evidence to examine the effect of each of its components there is no doubt about its efficacy in Pseudomyxoma peritonei (PMP), appendix adenocarcinoma and malignant peritoneal mesothelioma. PMP is rare condition characterised by the presence of mucinous ascites and mucinous peritoneal deposits. The condition is mainly due to peritoneal dissemination of perforated mucin producing appendiceal neoplasms. The spectrum of this condition ranges from peritoneal dissemination of relatively indolent low-grade appendiceal mucinous neoplasms (LAMN) to mucinous adenocarcinoma. CRS and HIPEC has been showed to have excellent results in PMP due to LAMN lesions with 5-year survival rates in the region of 70-90%⁽⁴⁾. It now recommended as the standard of care for this condition. It is also offered in some centres as a risk-reducing procedure for perforated LAMN lesions with no obvious signs of peritoneal spread as an alternative to surveillance. CRS and HIPEC also has showed good results in malignant peritoneal mesothelioma with 5-year survival of up to 80%⁶.

CRS and HIPEC has been attempted as treatment for colorectal peritoneal metastases (CRPM) since the 1980's and a growing body of mostly level II and III evidence shows promising



Figure 3: Low-volume colorectal peritoneal metastases (green arrows)

results in carefully selected patient groups with relatively low-volume disease (Figure 3). In 2003, Verwaal et al presented data from a Dutch RCT which showed significantly improved survival for CRS and HIPEC over standard chemotherapy (Median survival 22.3 months v 12.6 months)⁽⁷⁾. However, questions have been raised whether it is the complete cytoreduction which is responsible for the improved outcome as opposed to addition of HIPEC. This was the subject of investigation in the multicentric French RCT PRODIGE 7. This compared CRS and HIPEC for low to moderate volume CRPM versus CRS alone. The results of this study presented as an abstract at the American Society of Clinical Oncology (ASCO) meeting in 2018, concluded that while CRS significantly improves survival in CRPM, addition of HIPEC does not have any additional benefit⁽⁸⁾. These results have caused some controversy although several criticisms have been made of the methodology of PRODIGE 7 including the fact that it is under-powered and also included data from low-volume centres.



Figure 4: Extensive peritoneal disease with 'omental cake'

Cytoreduction for peritoneal metastases from ovarian cancer has been performed historically since the 1930s⁽²⁾. Following its use in gastro-intestinal cancer, CRS and HIPEC has been extended to ovarian cancer as well. Unlike in colorectal cancer, there is level 1 evidence that addition of HIPEC augments the effectiveness of cytoreduction⁽⁹⁾. A recent multicentre open label Dutch RCT comparing CRS and HIPEC versus CRS alone demonstrated improved overall and disease-free survival with the addition of HIPEC (OS 42 months versus 33 months)⁽¹⁰⁾.

PRIMARY TUMOUR	5-YEAR SURVIVAL AFTER CRS AND HIPEC FOR PERITONEAL MATASTASES
PMP / Appendix	70 – 90 %
Ovarian carcinoma	42 – 68 %
Colorectal carcinoma	13 – 51 %
Gastric carcinoma	13 %
Malignant peritoneal mesothelioma	40 – 50 %

Table 1: 5-year survival following CRS and HIPEC

While results in gastric cancer are relatively modest, it does appear that CRS and HIPEC offers some hope in this notoriously aggressive disease.

It must be noted that CRS and HIPEC is not a panacea for all situations. High volume disease (Figure 4), inability to achieve complete cytoreduction, presence of non-responsive systemic disease are instances where this procedure will not alter outcome.

In the United Kingdom, there are two centres established to manage these patients. One is at the Christie and the 2nd at Basingstoke. These two units provide high volume service through a multi-disciplinary process to ensure those patients requiring this surgery are treated in a safe and effective way.

Conclusion

Peritoneal metastasis is a notoriously difficult condition to treat with a long history of poor prognosis. The emergence of cytoreduction and HIPEC has begun to offer hope to selected groups of patients with this condition.

References:

1. Sugarbaker PH, editor. Cytoreductive surgery & perioperative chemotherapy for peritoneal surface malignancy. Textbook and video atlas. Woodbury, CT: Cine-Med Publishing; 2016.
2. Sugarbaker PH. Laboratory and clinical basis for hyperthermia as a component of intracavitary chemotherapy. *Int J Hyperthermia* 2007; 23:431-42.
3. Helderan RF, Löke DR, Kok HP, Oei AL, Tanis PJ, Franken NA, Crezee J. Variation in clinical application of hyperthermic intraperitoneal chemotherapy: A review. *Cancers* 2019; 11(1):78
4. Ansari N, Chandrakumar K, Dayal S, Mohamed F, Cecil TD, Moran BJ. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 1000 patients with perforated appendiceal epithelial tumours. *Eur J Surg Onc* 2016; 42(7):1035-41.
5. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res* 1996; 82: 359-374.
6. Baratti D, Kusamura S, Cabras AD, Bertulli R, Hutanu I, Deraco M. Diffuse malignant peritoneal mesothelioma: long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Cancer* 2013; 49(15):3140-8.
7. Verwaal VI, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Onc* 2003; 21(20):3737-43.
8. Quenet F, Elias D, Roca L, Goere D, Ghouti L, Pocard M, Facy O, Arvieux C, Lorimier G, Pezet D, Marchal F. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7.
9. Wang Y, Ren F, Chen P, Liu S, Song Z, Ma X. Effects of Cytoreductive surgery plus hyperthermic IntraPeritoneal chemotherapy (HIPEC) versus Cytoreductive surgery for ovarian cancer patients: A systematic review and meta-analysis. *Eur J Surg Onc* 2018 Oct 24.
10. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med* 2018; 378:230e40.

Did you know?

The UK is ranked 15th by the 2016 Euro health consumer index. The issue is the lowest score on accessibility to health care. "waiting times" and "an autocratic management culture" are responsible for this performance. The Netherlands and Switzerland lead the way in providing good, consumer friendly healthcare.

The UK has 300 beds per 100,000 population; in the Irish Republic it's 500; in Belgium 650; in France it's over 700.



Penile Cancer

A Case Report

Dr G C Sinha
Grove Park Surgery
Maidstone

Introduction

Men's attitude towards their illness differs from the women's. Men quite often hide their illness thinking it may appear as a weakness against their "macho" image¹.

According to a recent study from Glasgow, women between the ages 16 – 60 had higher rates of contact with their GPs than men, discounting consultations for reproductive reasons². The reason why men are reluctant to contact their GPs and seek medical advice is deeply rooted in their biological and psychological factors as well as their work conditions accepting risks acquired through social role and behaviour³. Prominent hypothesis indicate that men over react to minor problems and under react to severe issues or symptoms, which they tend to hide. The latter sometimes leads to disastrous consequences.

Penile cancer is one of the prime examples, which is quite often diagnosed late because of the behavioural attitudes amongst men.

Case Report

Mr A is a retired 74 year old gentleman, who lives with his wife, who suffers from advanced COPD. He is her carer.

Mr A has a history of hypertension, gout and CKD.

He attended his GP surgery in October 2017 for routine check up for hypertension by the nurse. He had his yearly routine blood tests, which showed a HB of 73. He denied any upper or lower GI symptoms. This necessitated a rectal examination at the surgery, which was negative. He was referred to the hospital for endoscopy.

CSSU confirmed the presence of Pseudomonas infection, although he denied any urinary symptoms. 3 weeks later endoscopy was performed, which showed a small hiatus hernia and mild erosive gastritis.

He attended surgery 4 weeks later complaining of dribbling of urine, but was unable to give any further details of his symptoms. Clinical examination revealed a fungating mass with total disappearance of the penis (Fig 1). On further questioning he admitted that this had appeared only in the past 2 weeks.

Carcinoma was suspected and an urgent referral was made to the Consultant Urologist. He underwent specialist surgery in January 2018 with Panpenectomy and bilateral groin dissection with wide excision of

the inguinal lymph nodes; this has been followed by radiotherapy (Fig 2). He remains under follow up.

Penile Cancer

The incidence of penile cancer is 0.9 – 2.1 in 100,000 in the male Caucasian population in Europe⁴. It peaks in the 6th decade. The presentation is equally spread with 50% in the prepuce and 50% in the glans.

95% are of squamous cell carcinoma type, originating in the prepuce or the glans. Other malignancies (melanoma, sarcoma) or metastases are extremely rare at the penis. Carcinogenesis is associated with human papilloma virus (HPV) infection and with chronic inflammation⁴.

Patients note changes of the glans or foreskin, but experience no pain. In many cases, the diagnosis of exophytic penile cancer is established by inspection. Superficial stages of penile cancer are often limited to surface changes. Early suspicion and biopsy are necessary to prevent delays in treatment initiation.

Confirmation of the diagnosis by biopsy and tumour staging are both required for treatment planning.



Figure 1: Penile Cancer

Phimosis
HPV genital warts
HIV
UV light treatment of Psoriasis
AIDS
Premalignant conditions:
Erythroplasia of Queyrat
Bowen's disease
Lichen sclerosus (Balanitis Xerotica obliterans)

Table 1: Risk Factors (American Cancer Society)

The risk factors are given in Table 1. Circumcision reduces the risk. The reason for the lower risk in circumcised men is not entirely clear, but it may be related to other known risk factors. For example, men who are circumcised can't develop the condition called phimosis, and they don't accumulate material known as smegma.

Treatment

Surgical treatment of penile cancer is guided by the following principle: as much organ preservation as possible and as much radicality as necessary. The options are given in Table 2.

Approximately 20% of patients have palpable inguinal lymph nodes at the time of diagnosis⁵. In obese patients clinical differentiation can be challenging. This requires further imaging techniques. Non-enlarged regional lymph nodes contain micrometastasis in up to 25% of cases and require investigations and invasive surgical evaluation. Those with limited lymph nodes metastasis one would consider radical lymphadenectomy with adjuvant chemotherapy. This plan and treatment is decisive for the prognosis.

The success of focal treatment should be confirmed by a follow-up biopsy. In most cases, local recurrences occur within 1 to 2 years after the initial treatment, most frequently after laser ablation (10–48%), less frequently after glans resurfacing (0–6%) and very rarely after glansectomy (0–2%)⁶.

Conclusion

Penile cancer has devastating mutilating and psychological consequences for those affected individuals and their partners.

New generation and new initiatives like Men's Health check up might help to change the men's reluctance to seek advice and use the health care system early to reduce the concerns raised.

It is important to raise awareness of this condition and encourage men to come forward early enough as soon as they notice any skin changes in the penile organ. Mr A had very few contacts with health professionals. At neither the recent GP attendances nor when he went to the hospital for his endoscopy did Mr A disclose of any growth or skin changes on his penis. Mrs A agreed that her husband seemed to have a male ego and he was not prepared to accept his illness until it was diagnosed late.

Penile cancer is curable in all early stages with the appropriate treatment, but its prognosis depends crucially on the proper management of the regional (i.e., inguinal) lymph nodes.



Figure 2: Post Surgery

STAGES	SURGERY	ALTERNATIVES
Early Glans lesion: Superficial tumours limited to epithelium Or Recurrence or persistence of superficial lesions	Glans resurfacing	Glans sparing techniques Focal Chemotherapy Immunotherapy Laser ablation Radiation therapy
Lesion in inner layer of prepuce	Radical circumcision	
Large tumours involving the corpus spongiosus pT2 or cavernosus pT3	Glans amputation	
Lesion in inner layer of prepuce	Partial amputation of penis / Panpenectomy	

Table 2: Surgical Options

References:

1. Reporterlinker. Men's health - Changing male attitudes to health to improve prognosis and outcome May 19, 2015
2. Wang Y et al. Do men consult less than women? An analysis of routinely collected UK GP data. *BMJ Open* 2013
3. The Conversation. Men more reluctant to go to the doctor - and its putting them at risk. May 1, 2016
4. Hakenberg OW et al. The diagnosis and treatment of Penile Cancer. *Dtsch Arztebl Int.* 2018 Sep; 115(39):646-652
5. Perrson B et al. The national Penile cancer register in Sweden 2000-2003. *Scand J Urol Nephrol* 2007;41:278-82
6. Imamura M et al. Surgical management for localised penile cancer. *Cochrane Database Syst Rev* 2015;3 CDO11533



Medical Quiz



Can you identify this skin condition?

Image courtesy
DermNetNZ.

- a) Ichthyosis vulgaris
- b) Impetigo contagiosa
- c) Xeroderma pigmentosum
- d) Psoriasis vulgaris

Answer on page 25

Welcome to new BIDA members

Name	Membership No.	Division
Dr A Ahmed	10598	Stoke-on-Trent
Dr S Sultana	10599	Stoke-on-Trent
Dr S Hafi	10600	Manchester
Dr A Sindhi	10601	Manchester
Dr S Mir	10602	Stoke-on-Trent
Mr B Ononuze	10603	North East
Dr S Maiti	10604	Blackburn
Dr M S Shaheen	10605	Stoke-on-Trent
Mr P Govind	10606	North Wales
Dr M Muddiyavar	10607	North Wales
Dr A Reddy	10608	North East
Dr P Mangalore	10609	North East
Dr S Shenoy	10610	North Wales
Mr M Chawda	10611	North Wales
Dr S Dondapati	10612	Stoke-on-Trent
Dr S Roy	10613	Wolverhampton
Dr S Shetty	10614	Wolverhampton
Dr M H Mohamed	10615	Wolverhampton
Dr A Krishnamurthy	10616	Wigan
Dr B Navqi	10617	North East
Mr Sahadevan	10618	Newcastle-upon-Tyne
Dr Sasi	10619	North East
Dr O Hussain	10620	Stoke-on-Trent
Dr V Machineni	10621	Stoke-on-Trent
Dr S Pydah	10622	North East
Dr A Rajan	10623	Stoke-on-Trent
Dr R Kumar	10624	Stoke-on-Trent

BIDA 2019 ARM & AGM

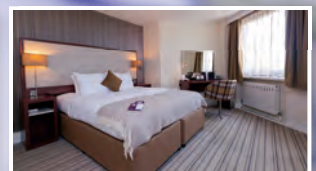
BIDA AGM 2019

A REMINDER - WE'LL SEE YOU THERE!

The 44th Annual General Meeting of the
British International Doctors' Association
will be held on **Sunday 22nd September 2019**
at the **The Salmesbury Hotel**, Preston New Road,
Salmesbury, Preston, Lancashire PR5 0UL

Hosted by BIDA's Blackburn Division.

(All fully paid members are
cordially invited to attend, but please note
that prior notification to Central Office is required).



Congratulations!

Dr Shikha Pitalia

Congratulations to Dr Shikha Pitalia, who has been honoured with the prestigious "Inspiring Women Awards"

Dr Shikha Pitalia, Secretary of the Wigan BIDA Division was announced as the winner in the 'Business' category at the 2019 Inspiring Women Awards. The awards were founded in 1993 to recognise and celebrate the inspiring achievements of women. Dr Pitalia was congratulated for her passion for the health service, in a quest to influence change in the NHS.

Dr Shikha Pitalia is already an award-winning entrepreneurial doctor who has pioneered federated working and helped many doctors and their practices to thrive and remain sustainable. Her contribution to the NHS was featured on BBC

1 and BBC World news to showcase some examples of innovative solutions such as flexible working, skill mix and new models of care. These changes have helped GPs who might otherwise have retired earlier or even emigrated, to remain in primary care and enjoy being a doctor again. Shikha is convinced that without this model, some of these practices risked closure and many doctors were at risk of burnout.

Shikha believes that the next iteration of change is the formation of Primary Care Networks. She is confident that if allowed to be properly configured, these PCNs offer huge potential for collaboration between various health and social care organisations for the benefit of patients and to genuinely provide the resilience which General Practice so desperately needs.



Dr Pitalia is the Chair of the Wigan GP Alliance, Director of SSP Health and co-founder of SSP Health Charitable Trust, raising funds for local, national and international health-related charities.



Prof Nirmal Kumar

Congratulations to Prof Nirmal Kumar, who has been honoured as President ENT (UK)

Professor Nirmal Kumar, an active member of Wigan BIDA Division has been elected as President, ENT UK by his national peers after serving 2 years as President-elect. As a proud BIDA member for 20 years he wants to emphasise to colleagues that such positions are now open to BME doctors but obviously decided purely on merit.

He commenced his two year tenure at the inaugural ceremony in Chester at the annual spring meeting of ENT UK with the message *"I shall dedicate my time as President to nurture the next generation of ENT specialists and help foster improved international links and co-operation"*. He encouraged members to engage with ENT UK and help deliver a strategy to improve quality of care for our patients.

Nirmal is a Consultant ENT surgeon and Director of Medical Education at Wrightington, Wigan & Leigh NHS Foundation Trust. Regionally, he leads the NW CRN research network for ENT in addition to being Honorary Professor at Edge Hill University Medical School where he has led a MCh academic programme in otolaryngology for 10 years. He was a very successful Training Programme Director for ENT, North West Deanery for 8 years. Nationally, he is FRCS (ORL) examiner of the Royal College of Surgeons, Fellow of the Academy of Medical Educators and until recently Vice-Chair for Specialist Advisory Committee (SAC) in Otolaryngology.

Nirmal has published extensively in the medical literature with more than 100 publications in peer reviewed journals and is greatly interested in supporting Quality Improvement (QI) in medical practice.



Medical Quiz Answer

Answer: (c) Xeroderma pigmentosum

Xeroderma pigmentosum is a rare skin condition which affects about 1 in a million people worldwide. Affected children are extremely sensitive to ultraviolet rays of sunlight. It is an autosomal recessive genetic condition and manifests soon after birth. Exposure to sun leads to severe sunburn resulting in dry skin (xeroderma) and pigmentation (pigmentosum). The risk of developing skin cancer is extremely high and most children develop their first cancer by age 10. The eyes may be particularly sensitive to UV light and without adequate sun protection the cornea becomes cloudy, eyelashes fall and eyelids get thinned out. The incidence of eye cancer is very high. About 30% of affected children also develop neurological abnormalities in addition like hearing loss, impaired movement and loss of intellectual function. Apart from avoiding exposure to sunlight (Children of the Dark) there is no definite treatment for this condition and most children sadly die before the age of 20.



Why I joined BIDA



Dhuni Soren
Retired GP and Trainer in
General Practice.
Merseyside BIDA

"I joined the association in the late sixties when it was called Overseas Doctors Association more for a social reason and then it turned out to be more for equal rights and opportunities and against discrimination of overseas-qualified doctors. Then it grew and the name was changed to BIDA to be more inclusive and to include all overseas-qualified doctors and became like a trade union."

I personally did not need any help over the years but was able to help few fellow overseas doctors in their training in General Practice. I strongly recommend all ethnic doctors even if they qualify from here to join the BIDA to safe guard their rights and future."



Nikhil Kaushik
FRCOphth
Consultant Ophthalmologist
North Wales BIDA

"I was first introduced to BIDA (then ODA) via an Educational event, the contents of which impressed me immensely. It was to become a forum for me to keep up with specialities other than my own, with the added bonus of meeting and socialisation with like-minded professionals. It has over the years provided to me a platform for social and professional interaction and serves a valuable tool to connect with the wider medical world."



Ram Karan Singh
Consultant Anaesthetist
North East BIDA

"I joined BIDA because I believe BIDA speaks for the international doctor's interest and highlights their problems. We face some of the problems that local doctors do not go through nor do they understand these issues e.g., visa requirements, racial discriminations etc. BIDA has got grips with these issues. BIDA publishes a journal, which is informative and covers a wide area of practice. On top, BIDA provides a network for professional advice and support."

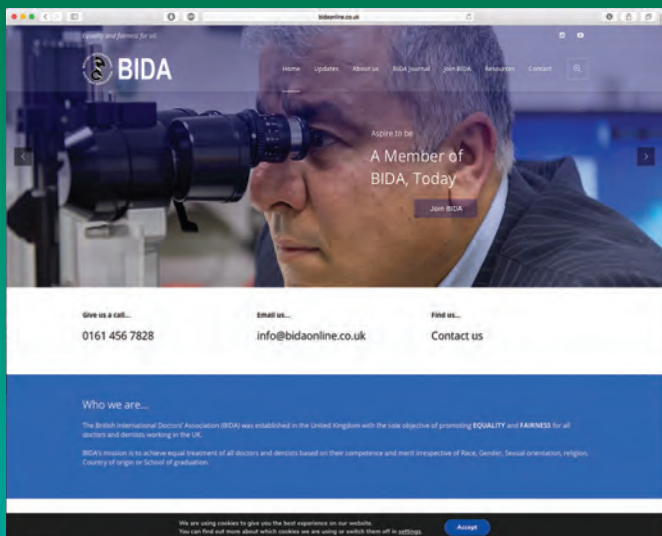


Amit Sinha
FRCS (Trauma & Ortho)
Co-Editor, BIDA Journal.
Consultant Orthopaedic
Surgeon.
North Wales BIDA

"BIDA embodies the aspirations and ideals of all International doctors. BIDA is our voice and its strong image provides a platform, which represents our welfare. My interest has been mainly its educational activities through the Journal and regular medical meetings. It's an opportunity to meet up with colleagues of differing nationalities and specialities, which makes up this organisation."



**Do you want to see the clearer picture?
Would you like to know what's going on?
Then keep in touch!**



For all the BIDA news, views, reviews and a great deal more, simply go to www.bidaonline.co.uk

Divisional News

Bolton Division NHS Pensions Meeting

BIDA's Bolton Division held a meeting discussing NHS Pensions on 22 May 2019.

Dr Anjani Kumar chaired and welcomed the members, who attended in large numbers. In what turned out to be a very interactive and interesting evening, Dr. Alka Trivedi, National Vice President, also updated the attendees on BIDA.



Above: Delegates at Bolton Division's meeting, including Dr Alka Trivedi (centre).

BIDA Sports Events 2019

National Badminton & Table Tennis Tournament

This year's BIDA Sports events are now in full swing. Both the BIDA National Badminton Tournament and BIDA National Table Tennis Tournament, hosted this year by BIDA's Wolverhampton Division, took place on 19th of May. This year's winners are as follows:

National Badminton:

Singles **Jivitesh** - (Winner)
Maghan - (Runner Up)

Doubles **Narasimha Rao & Jivitesh** - (Gold Medal)



Congratulations to the winners and thank you to all the players who participated in the games, and also to the family members.

President's Cup Cricket Tournament



The draw for the President's Cup Cricket Tournament has now been made and the first set of matches have already taken place on the 2nd of June. The next set of matches is scheduled for the 7th of July.

Divisional Winner

Congratulations to **Dr Sunil Sapre**, who is seen here receiving his trophy following his recent success in winning the 2018-19 Liverpool and District Table Tennis League Division 5 Singles title.



MYSTICAL LAND OF PERU



8 Days from £ 1450 pp

Highlights -Lima | Cusco | Sacred Valley | Machu Picchu | Vistadome Train | Lake Titicaca

15 Days from £ 2500 pp

Highlights -Lima | Cusco | Sacred Valley | Machu Picchu| Tambopata Rain Forest
Inca Trail | Vistadome Train | Lake Titicaca | Ballestas Island | Nazca Lines

**Book by
31st July 2019
& get £50 off
Your Holiday.**

**Cruise | Honeymoon | Beach | Safari | Couples | Groups
Conferences | Destination Wedding & many more Holidays**

Please Contact us on

020 8144 2276 / 07588 463 505

sales@boltontravel.com

www.boltontravel.com

bolton travel

BEST OF JAPAN



7 Days from £ 1400 pp

Highlights - Tokyo City Tour | Tea Ceremony Experience | Sumida River Cruise
| Mt. Fuji & Lake Ashi Cruise | Kyoto Shrines & Nara Park

10 Days from £ 2100 pp

Highlights - Tokyo City Tour | Tea Ceremony Experience | Sumida
River Cruise | Kamakura Tour | Nikko Park | Mt. Fuji & Lake Ashi Cruise |
Kyoto Shrines & Nara Park | Hiroshima & Miyajima Osaka City Tour

TOGETHER, WE ARE STRONGER



The **British International Doctors Association (BIDA)** is a professional doctors' association. Its sole objective is promoting **Equality** and **Fairness** for all doctors and dentists working throughout the UK.

BIDA's mission is to achieve equal treatment of all doctors and dentists based on their competence and merit, irrespective of their race, gender, sexual orientation, religion, country of origin or school of graduation.

If you believe in this mission and would like to be part of this endeavour, join us!

- ◆ You will make professional contacts, gaining the opportunity to network with people who can impact your profession, and giving you access to new opportunities, friends and information.
- ◆ *In addition to being part of a group of like-minded professionals, and having the recognition of your peers, specific member benefits include:*
 - Attending BIDA-organised international, national and regional conferences, seminars, meetings, and many other educational and social activities
 - Constant access to pastoral support
 - Nominations for excellence awards
 - BIDA Journal, our scientific journal, complete with news, interviews and much more.



If you are interested in joining BIDA, or would simply like to know more about us, please either write to **BIDA, ODA House, 316A Buxton Road, Great Moor, Stockport, Cheshire SK2 7DD, U.K.**, e-mail us at bida@btconnect.com, or contact us through our website at www.bidaonline.co.uk

We look forward to hearing from you!



www.bidaonline.co.uk