Greater Manchester and Eastern Cheshire SCN

Asthma in Pregnancy Guideline

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Document Control

Ownership

Role	Department	Contact
Project Clinical Lead	GMEC SCN	Sarah.vause@mft.nhs.uk
Document author	Akila Anbazhagan GMEC Maternal Medicine Network Group Dr Robert Niven, Consultant Respiratory Physician, Wythenshawe Hospital Dr David Allen, Consultant Respiratory Physician, Wythenshawe Hospital	akila.anbazhagan@mft.nhs.uk
Project Manager	GMEC SCN	Sarah.west20@nhs.net

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Dr Sarah Vause
Consultant in Fetal and Maternal Medicine
Chair of the Greater Manchester & Eastern Cheshire SCN Maternal Medicine Group

Contents

1. Introduction

The majority of women with asthma have normal pregnancies and the risk of complications is small in those with well-controlled asthma. Adherence to asthma treatment is essential and pregnant women need to receive clear education that asthma treatment is safe in pregnancy.

During pregnancy asthma control often changes, presumably related to hormonal influences, though it is unpredictable. Many women's asthma control improves in pregnancy, whilst others get significantly worse. In general, one third gets better, one third worsens and one third stays the same during pregnancy. The course of asthma tends to be similar in successive pregnancies.

Symptoms of breathlessness in those with severe or poorly controlled asthma tend to worsen during pregnancy, owing to the added physiological burden due to reduced lung volumes and increased metabolic demands in those who are already compromised. Studies suggest that 11–18% of pregnant women with asthma will have at least one emergency department visit for acute asthma and of these 62% will require hospitalisation. Exacerbations are more common between 24 and 36 weeks, with peak incidence from 32-34 weeks, but less likely to occur in last 4 weeks of pregnancy.

2. Clinical Features

Symptoms

- Breathlessness, cough, wheeze, chest tightness, nocturnal waking due to cough

Signs

- Raised respiratory rate, wheeze, use of accessory muscles, tachycardia

Triggering Factors

- Pollen, animal fur, dust, exercise, cold, emotion, upper respiratory infections, medications (aspirin, beta blockers)

3. Diagnosis:

- History and examination consistent with the symptoms and signs listed above; history of atopy (personal or family)
- Measurement of FEV_1 (forced expiratory volume) and FVC (forced vital capacity) by spirometry. Ideally this will be supplemented by evidence of reversibility (12% improvement to a bronchodilator or inhaled steroid or oral steroids)
- ≥ 20% diurnal variation in PEFR (peak expiratory flow rate) for 3 or more days per week during a 2 week period of monitoring is a diagnostic criteria
- A raised FeNO (fractional exhaled nitric oxide) is a marker of airway inflammation
- In complex cases, assessment by a specialist team might be needed
- It would be unusual to diagnose de novo asthma in pregnancy for the first time.The MBRRACE report highlights areas where a diagnosis of cardiac disease was missed due to the erroneous attribution of new onset SOB and cough etc to respiratory disease

4. Classification of asthma severity in pregnancy

Table 1. Classification of Asthma Severity and Control During Pregnancy

Asthma Severity	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Asthma Control	**Well Controlled**	**Not Well Controlled**		**Very Poorly Controlled**
Symptom frequency and SABA use	≤2 days/wk	>2 days/wk	Daily	Several times/day
Nighttime awakenings	≤2 times/mo	>2 times/mo	>1 time/wk	>4 times/wk
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
FEV_1 or PEF	>80% predicted or personal best	>80% predicted or personal best	60%-80% predicted or personal best	<60% predicted or personal best

FEV_1: forced expiratory volume in 1 second; PEF: peak expiratory flow; SABA: short-acting beta agonist.
Source: Reference 1.

5. Indications requiring referral

Uncontrolled asthma symptoms which will require referral into a joint multidisciplinary obstetric respiratory clinic in a tertiary setting include (see appendix 1):

- Daytime asthma symptoms in spite of titrated inhaled corticosteroids (ICS) therapy already commenced at primary care

- Night time waking (defined as waking with asthma symptoms one or more times per week)
- Need for additional preventer therapy – patients requiring add on therapy beyond an inhaled short-acting β2 agonist (SABA) and ICS
- Patients with persistent poor control
- Asthma attacks and exacerbations requiring frequent oral corticosteroids or more than one hospitalisation in a year
- Limitation of daily activity
- FEV_1< 80% of expected

6. Pre-pregnancy care

All professionals providing care for women of childbearing age including general practitioners and obstetricians should be aware that:

- Control of asthma should be optimised before conception
- There is some evidence that the course of asthma is similar in successive pregnancies
- Women need to receive clear education that the risk of harm to the baby from severe or chronically undertreated asthma outweighs any small risk from the medications used to control asthma
- Safety data regarding commonly used asthma medication can be found in appendix 2

7. Effect of pregnancy on asthma

- Asthma may improve, worsen or remain unchanged in pregnancy
- Women with mild asthma are unlikely to experience problems relating to their asthma or its treatment in pregnancy
- An asthma attack during labour is extremely unlikely (perhaps due to increased production of endogenous steroids) so consider other causes of acute respiratory distress should it occur in labour
- The most common cause of deterioration in disease control in pregnancy is caused by reduction, or even complete cessation, of medication due to fears about its safety. This is actually the biggest risk to the baby
- During pregnancy FEV_1, FVC and PEFR do not change significantly, but residual volume and functional residual capacity (FRC) fall, along with total lung capacity (TLC) in the last trimester. The minute ventilation increases during pregnancy.

8. Effect of asthma on pregnancy

- In the majority of women if asthma is well controlled throughout pregnancy there is little or no increased risk of adverse maternal or fetal complications
- Poorly controlled asthma may adversely affect the fetus with a small but significant increase in risk of complications
- There is some association between asthma and the following conditions:
    - pregnancy induced hypertension & pre-eclampsia
    - preterm births and preterm labour
    - fetal growth restriction
    - neonatal morbidity (transient tachypnoea of new born, admission to neonatal unit, seizures)

  Most of these are entirely caused by poor asthma control and by the treatments used.

9. Management

9.1 Antenatal

Education

- Women should be encouraged to stop smoking. Referral to smoking cessation programs is helpful where indicated. Women should also be counselled that gestational exposure to side stream cigarette smoke or second hand smoke promotes transgenerational transmission of exacerbated allergic asthma and bronchopulmonary dysplasia. Other members of the household should also be encouraged to stop smoking or to avoid smoking in the vicinity of the pregnant woman

- The Greater Manchester Smoke free Pregnancy Programme initiative supports women in quitting smoking and recommends carbon monoxide monitoring at booking in all pregnant women with a recommended cut off point. A carbon monoxide reading equal to/greater than 4ppm is raised.
    - Women can find useful information regarding smoking from the following links:

      https://www.nhs.uk/Conditions/pregnancy-and-baby/smoking-pregnant/

      https://www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/pregnancy/pi-smoking-and-pregnancy-2.pdf

- Women should be assessed for inhaler technique. Technique with metered dose inhalers is often less than ideal and a spacer is strongly recommended. Further information and video demonstration of the correct inhaler use can be found at - https://www.rightbreathe.com/
- Non-adherence with preventer therapy needs continuous assessment in women who remain poorly controlled. In addition, consider using suppression testing using monitored inhalers for patients who continue to have high levels of airway inflammation. FeNO suppression testing using monitored inhalers should be considered
    - Studies show that intrauterine growth restriction, low birth weight and maternal malnutrition may lead to altered lung growth and development antenatally and in early childhood. Subsequent lung injury and further gene-environment interaction may result in airway obstruction predisposing to chronic obstructive airway disease
    - It is essential to counsel about indications for an increase in inhaled steroid dosage and, if appropriate in a selected few motivated women an emergency rescue supply of oral steroids may be considered (appendix 2/4 BTS guidance)
- Women should be advised about the importance of getting the flu vaccination during pregnancy as early as possible in the flu season. It is important that any previous children in the household aged over 2 are vaccinated. This is because adult vaccination is only partly effective and the woman will have extra protection if her children are protected.

Asthma Control

- Avoid known trigger factors
- Reassure pregnant women to continue their asthma medications. This will improve treatment adherence for the duration of pregnancy
- Encourage personalised self-management plans

Monitoring

- Monitoring of FeNO during pregnancy has been associated with better outcomes as it directs appropriate and adequate anti-inflammatory control
- If an acute severe attack occurs, then this should be treated as an emergency in hospital (appendix 4)
- Serial growth scans should be performed in women with severe asthma from 28 weeks onwards 4 weekly

- Early referral to the anaesthetic team should occur if asthma is severe or poorly controlled. This is to allow timely discussion and planning for labour analgesia and peripartum anaesthesia. For optimisation of asthma management see Section 5 above

9.2 Intrapartum

- Asthma attacks or exacerbations are exceedingly rare in labour due to endogenous steroids
- Women should not discontinue their inhalers during labour as there is no evidence to suggest that β2 agonists inhalers will impair uterine contractions. Whilst the woman is on an inhaled SABA there is very minimal systemic absorption of SABA to warrant monitoring blood glucose levels in the baby after birth
- Women receiving oral corticosteroids of 7.5mg/day for more than 2 weeks prior to delivery should receive parenteral hydrocortisone 100mg 8 to 12 hourly to cover the stress of labour
- Oxygen should be delivered if the maternal oxygen saturation falls below 94% in order to prevent maternal and fetal hypoxia. If this occurs, help should be sought from respiratory, or preferably asthma, specialists
- Prostaglandin E2 is safe to use, when needed (appendix 2)
- Use of prostaglandin F2α (haemobate) to treat life threatening postpartum haemorrhage may be unavoidable, but it can cause bronchospasm and should be used with caution (intensive care and respiratory teams should be involved when they are being used)
- All analgesic options for pain relief can be used in asthma, but epidural analgesia may be particularly beneficial in cases where there is poor control or severe symptoms
- Continuous fetal monitoring should be performed when asthma is uncontrolled or severe
- Ergometrine may aggravate bronchospasm especially when general anaesthesia is used
- Where possible, regional rather than general anaesthesia is preferable because of the decreased risk of bronchospasm, chest infection and post-operative atelectasis
- Caesarean section is reserved largely for obstetric indications. In certain situations where the asthma is severe a decision to perform a caesarean delivery may be made in close conjunction with the respiratory physician, to ensure a safe pre-term delivery
- When interpreting arterial blood gases in pregnancy, it should be remembered that the progesterone-driven increase in minute ventilation may lead to relative hypocapnia and a respiratory alkalosis, and higher PaO_2, but oxygen saturations are unaltered

9.3 Postnatal

- Most of the medications, including oral corticosteroids are safe in breast feeding mothers, however if the woman is restarted on azithromycin, breastfeeding should not be encouraged.
- The risk of atopic disease developing in the child of a woman with asthma is about 1 in 10, or 1 in 3 if both parents are atopic. There is some evidence that breast feeding may reduce the risk of asthma in the baby.

Appendix 1: Common drugs used in pregnancy and their effects on asthma

Common drugs used in pregnancy that may have effect on asthma

Prostaglandin E2	Propess®, Prostin E2® is a bronchodilator and is safe.
Prostaglandin F2α	Carboprost ® should be used with caution as it may cause bronchospasm.
Nitrous Oxide	Safe to use
Epidural analgesia/Spinal anaesthetic	Safe to use
General anaesthetic	Increased risk of bronchospasm, chest infection, atelectasis and barotrauma
Opiates	Should be avoided in acute exacerbation of asthma, safe to use at other times
Ergometrine	Can cause bronchospasm, particularly in association with general anaesthesia**.** Syntometrine (oxytocin/ergometrine) is less problematic
Nonsteroidal anti-inflammatory drugs (NSAIDs) and Aspirin	Avoid if known sensitivity to these drugs (only about 10% of patients with asthma are sensitive to NSAIDs)

Women can be referred to the BUMPS (Best use of medicines in pregnancy) website created by UK teratology Information Service (UKTIS) which contains patient information leaflets (PILs) for different medicines in pregnancy:

http://www.medicinesinpregnancy.org/a

Appendix 2: Evidence for the continuation of asthma medications during pregnancy and breastfeeding

The Commission on Human Medicines (CHM) and the MHRA encourages the reporting of all suspected reactions to newer drugs and vaccines, which are denoted by an inverted Black Triangle symbol (▼) or if drug reaction is suspected through www.mhra.gov.uk/yellowcard

Asthma medication	Drug safety
Short acting $\beta_2$agonists	• No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome • Excessive doses can cause maternal and fetal tachycardia • There is no statistically significant reduction in frequency of uterine contractions with IV salbutamol
Inhaled corticosteroids (ICS)	• No significant association has been demonstrated between major congenital malformations or adverse perinatal outcome and exposure to ICS • Inhalers can be safely used in breastfeeding
Long acting β_2 agonist (LABA)	• Human safety data for vilanterol (LABA used in combination inhaler Relvar) lacking, but adverse effects not noted in animal studies • Inhalers can be used safely during breastfeeding
Leukotriene receptor antagonists	• Safety data in pregnancy limited, but no increase in teratogenicity observed in animal studies with montelukast • Recommend continuing therapy in women who have demonstrated significant improvement in asthma control with these agents prior to pregnancy and during breastfeeding if benefits outweigh the risks
Theophyllines	• Can be used as preventer therapy or intravenously (IV) for management of acute severe asthma • Monitoring of levels is recommended as decreased protein binding in pregnancy leads to increased free drug levels • In most individuals, a plasma-theophylline concentration of 10–20 mg/litre (55–110 micromol/litre) is required for satisfactory bronchodilation, although a lower plasma-theophylline concentration of 5–15 mg/litre may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre • Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment. A blood sample should usually be taken 4–6 hours after an oral dose of a modified-release preparation.

Asthma medication	Drug safety
	• Check blood levels in only in pregnant women with acute severe asthma and in those who are critically dependant on therapeutic theophylline levels • When stopping smoking, a reduction in theophylline dose of up to 25-33% might be needed after one week. However, it may take several weeks for enzyme induction to dissipate • There is a potential for fetal tachycardia and irritability at the time of delivery
Oral/systemic glucocorticoids	• Steroid tablets should be used as normal when clinically indicated for severe asthma during pregnancy • Prednisolone remains the steroid of choice throughout pregnancy (10% delivered to the placenta – much lower than dexamethasone (33%) and hydrocortisone (15%) • There is limited conflicting data regarding risk of cleft lip / palate associated with first trimester use – steroids should not be withheld because of this • Studies have shown an association between glucocorticoid use and gestational diabetes and pregnancy induced hypertension • Studies have also shown an association between oral steroid use and pre-term labour and low birth weight (< 2500g) - however severe asthma may be a confounding variable in these studies and the benefit to the mother and fetus for treating a severe exacerbation justify the use of steroids in pregnancy • If high dose of steroids (prednisolone >80mg/day) being administered avoid breast feeding for 4 hours after last dose
Antibiotics	• Doxycycline should not be used during pregnancy but short courses during breastfeeding is acceptable • For patients with severe asthma and a mucus phenotype on long term low dose azithromycin, consider switching to nebulised hypertonic saline • Refer to local guidelines regarding appropriate antibiotics
Omalizumab	• The Xolair Pregnancy Registry (EXPECT) examined the safety of omalizumab during pregnancy. EXPECT, a prospective, observational study of pregnant women exposed to ≥1 dose of omalizumab within 8 weeks prior to conception or at any time during pregnancy, included 191 women and outcomes from 169. 14.5% were born prematurely and 3.2% of full term infants had low birth weights. The incidence of congenital abnormalities was 4. 4% (compared with a background risk in all pregnancies of ~3%) • Data from the registry suggests that if women are already established on therapy when they get pregnant, they should continue treatment following a multidisciplinary discussion with the team and

Asthma medication	Drug safety
	the patient but that omalizumab shouldn't be started in pregnancy unless there are no alternatives • There is no information available on its use during breastfeeding
Mepolizumab	• No safety data for the use of anti-IL-5 monoclonal antibody (mab) therapy in pregnancy is available to date. The consensus is that mepolizumab should be continued during pregnancy as stopping treatment may lead to de-stabilisation of asthma control and requirement for high dose oral steroids • Therapy with mono-clonal antibodies doesn't tend to be an issue in early pregnancy as placental transfer of mabs tends to occur from the third trimester. Anti-eosinophilic mabs such as mepolizumab may affect eosinophil counts in the new-born and monitoring of counts should be considered • There is no information on its use during breastfeeding
Magnesium sulphate	• Magnesium sulphate can safely be used in pregnancy as the dose uses in asthma is much lower than that used in preeclampsia prophylaxis or for neuroprotection in preterm labour

Appendix 3: British Thoracic Society step-up guidance on asthma medications

Advice should be given regarding:

- In general, medicines used to treat asthma are safe in pregnancy
- The risk of harm to the fetus from severe or chronically undertreated asthma outweighs any small risk from the medications used to control asthma
- Use all the drugs mentioned below as normal in pregnancy including oral steroid tablets
- Perform blood levels of theophylline in pregnant women with acute severe asthma and in those critically dependent on therapeutic theophylline levels
- No adverse perinatal outcome exposure to sodium cromoglicate and nedocromil sodium has been documented.

Step 1 - Mild intermittent asthma

- Inhaled short-acting beta agonist as required

Step 2 - Regular preventer therapy

- Add inhaled corticosteroid 200-800 micrograms/day 400 micrograms is an appropriate starting dose for many patients

Step 3 - Initial add-on therapy

- Add inhaled long-acting beta agonist (LABA)
- Assess control of asthma:
    1. Good response to LABA - continue LABA
    2. Benefit from LABA but control still inadequate - continue LABA and increase inhaled corticosteroid dose to 800 micrograms/day
    3. No response to LABA - stops LABA and increase inhaled corticosteroid to 800 micrograms/day. If control still inadequate, start other therapies as leukotriene receptor antagonist (LRA) or SR (sustained release) theophylline

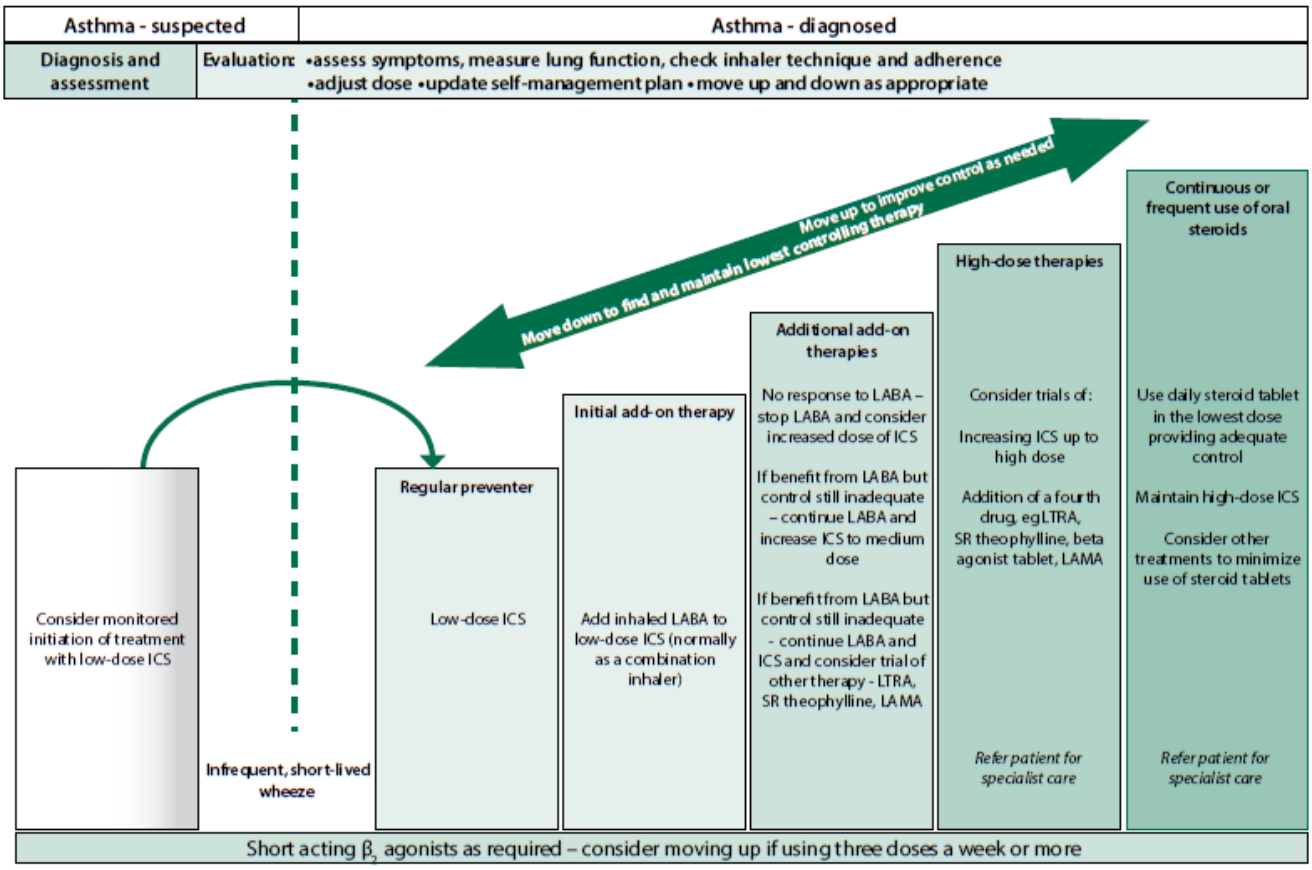
Step 4 - Persistent poor control

- Increasing inhaled corticosteroid up to 2,000 micrograms/day
- Addition of fourth drug e.g. LRA, SR theophylline, beta 2 agonist tablet

Step 5 - Continuous or frequent use of oral steroids

- Use daily steroid tablet in lowest dose providing adequate control
- Maintain high dose inhaled corticosteroid at 2,000 micrograms/day

The current BTS guidelines advocate the following:



Appendix 4: Management of acute asthma in pregnancy/labour

Acute severe asthma in pregnancy is an emergency and should be treated vigorously in hospital.

A diagnosis of acute severe asthma is made when:

- PEF 33-50% best or predicted
- Respiratory rate ≥25/min
- Heart rate ≥110/min
- Inability to complete sentences in one breath

Life threatening asthma

In a patient with severe asthma any one of:

- PEF <33% best or predicted
- SpO_2 <92%
- PaO_2 <8 kPa
- Normal or raised $PaCO_2$ (4.6-6.0 kPa)
- Silent chest, cyanosis, poor respiratory effort
- Arrhythmia, exhaustion, hypotension, altered consciousness

Near fatal asthma

- Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures

Treatment of acute and severe asthma

Severe asthma in pregnancy is a medical emergency and should be vigorously treated in hospital in conjunction with the respiratory physicians.

- Treatment of severe asthma is not different from in non-pregnant patients
- Treatment should include the following:
  - High flow oxygen to maintain saturation of 94- 98%
  - Beta-2 agonists administered via nebulizer which may need to be given repeatedly
  - Nebulised ipratropium bromide should be added for severe or poorly responding asthma
  - Corticosteroids (IV hydrocortisone 100mg) and /or oral (40-50mg prednisolone for at least 5 days)
  - Chest radiograph should be performed if there is any clinical suspicion of pneumonia or pneumothorax or if the woman fails to improve
- Management of life threatening or acute severe asthma that fails to respond should involve consultation with the critical care team and consideration should be given to the use of IV beta-2 agonists, IV magnesium sulphate and IV aminophylline

Appendix 5: Providing asthma care in pregnancy in the North West

Hospital	Respiratory consultants	Obstetric Consultants	Asthma Nurse	Pharmacist
Manchester Royal Infirmary and Trafford St Mary's at Oxford Road Campus	Dr Waseem Khan	Dr Dyan Dickens	Jackie Sheppard Leanne Tomlinson	
Manchester Foundation Trust St Mary's at Wythenshawe	Dr Rob Niven Dr David Allen Dr Top Pantin	Dr Akila Anbazhagan Dr Andrea Pilkington	Leanne Holmes	Lynn Elsey
Pennine Acute NHS Trust	Dr Nita Sehgal		Karl Balance Sarah Johnson	
Salford, Bolton, Wigan	Dr Ronan O'Driscoll Dr Shruti Khurana Dr Imran Aziz			
Lancashire Teaching Hospitals	Dr Aash Vyas			

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