# Managing problematic severe asthma: beyond the guidelines

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## ABSTRACT

This review discusses issues related to managing problematic severe asthma in children and young people. A small minority of children have genuinely severe asthma symptoms which are difficult to control. Children with genuinely severe asthma need investigations and treatments beyond those described within conventional guidelines. However, the majority of children with poor symptom control despite high-intensity treatment achieve improvement in their asthma control once attention has been paid to the basics of asthma management. Basic asthma management requires optimisation of inhaler technique and treatment adherence, avoidance of environmental triggers and self-management education. It is also important that clinicians recognise risk factors that predispose patients to asthma exacerbations and potentially life-threatening attacks. These correctable issues need to be tackled in partnership with children and young people and their families. This requires a coordinated approach between professionals across healthcare settings. Establishing appropriate infrastructure for coordinated asthma care benefits not only those with problematic severe asthma, but also the wider asthma population as similar correctable issues exist for children with asthma of all severities. Investigation and management of genuine severe asthma requires specialist multidisciplinary expertise and a systematic approach to characterising patients' asthma phenotypes and delivering individualised care. While inhaled corticosteroids continue to play a leading role in asthma therapy, new treatments on the horizon might further support phenotype-specific therapy.

## ASTHMA AND PROBLEMATIC SEVERE ASTHMA

More than 1 million children in the UK are diagnosed with asthma[1] and direct healthcare costs associated with asthma treatment exceed £1.1 billion.[2] Asthma is characterised by recurrent wheezing, breathlessness and cough, together with variable expiratory airflow limitation. Symptoms are frequently associated with airway inflammation and bronchial hyper-responsiveness[3] Achieving symptom control and reducing exacerbation risk are the central aims of asthma management guidelines, including those of the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN)[4] and the Global Initiative for Asthma (GINA).[3] Poorly controlled symptoms limit school and leisure activities, and impair sleep and quality of life.[5 6] Children with poorly controlled asthma are at risk of exacerbations, school absence, hospital admission and death, most of which are preventable.[7]

While the majority of children and young people with asthma can be adequately managed using conventional guidelines, a minority have problematic severe asthma (PSA) which is difficult to control despite guideline-based management. The exact prevalence of PSA is unknown, although estimates from two Scandinavian birth cohorts suggest that 2%–5% of children with asthma might be considered to have severe disease.[8 9] These children have the greatest morbidity, and their management accounts disproportionately for asthma costs. Problematic severe asthma, defined as poor asthma control despite high-intensity therapy, can be subdivided into two groups.[10] The majority are considered to have 'difficult to treat asthma'; control is difficult to achieve either because the diagnosis is incorrect, treatment is inadequate, not adhered to or inhaler technique is poor, or exacerbating comorbidities or environmental conditions are present. A smaller number of children have symptoms which are genuinely difficult to control with standard medications, even after efforts to address modifiable factors. These patients have 'severe asthma' and require specialist investigation and management.[11 12] Paediatric severe asthma is not well understood and the evidence base for management guidelines is incomplete, relying to some degree on extrapolation from adult studies. This is likely to be inappropriate as children with severe asthma present a different, more atopic, phenotype to that of severe asthma in adults.[13]

## CO-ORDINATED CARE

There is a need for a change in attitude regarding asthma management. Asthma needs to be treated as a chronic ongoing disease rather than a series of acute illnesses. For example, there is little evidence that patients are followed up within 48 hours after hospital treatment for acute asthma as recommended in BTS/SIGN[4] and the National Institute for Health and Care Excellence (NICE) Asthma Quality Standard.[14] For children with severe asthma, care should be co-ordinated by a specialist respiratory team.[15] However, co-ordinated care should extend across community, primary, secondary and tertiary care, and include accident and emergency departments and urgent care centres as well as pharmacies and schools. To promote optimal health and development, care for children and young people with asthma needs to be integrated horizontally between health, education and social services, acknowledging the impact of difficulties in each of these domains on the other. Care also needs to be integrated vertically between primary, secondary and tertiary care so that specialist care is rapidly accessible for those



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| A. Asthma symptom control | | Level of asthma symptom control | | |
|---|---|---|---|---|
| **In the past 4 weeks, has the patient had**: | | **Well controlled** | **Partly controlled** | **Uncontrolled** |
| • Daytime asthma symptoms more than twice/week? | Yes☐ No☐ | None of these | 1–2 of these | 3–4 of these |
| • Any night waking due to asthma? | Yes☐ No☐ | | | |
| • Reliever needed for symptoms* more than twice/week? | Yes☐ No☐ | | | |
| • Any activity limitation due to asthma? | Yes☐ No☐ | | | |

| B. Risk factors for poor asthma outcomes | |
|---|---|
| Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations.<br>Measure $FEV_1$ at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment. | |
| Potentially modifiable independent risk factors for flare-ups (exacerbations)<br>• Uncontrolled asthma symptoms<br>• High SABA use (with increased mortality if >1 x 200-dose canister/month)<br>• Inadequate ICS: not prescribed ICS; poor adherence; incorrect inhaler technique<br>• Low $FEV_1$, especially if <60% predicted<br>• Major psychological or socioeconomic problems<br>• Exposures: smoking; allergen exposure if sensitized<br>• Comorbidities: obesity; rhinosinusitis; confirmed food allergy<br>• Sputum or blood eosinophilia; elevated FENO (in adults with allergic asthma)<br>• Pregnancy<br>Other major independent risk factors for flare-ups (exacerbations)<br>• Ever intubated or in intensive care unit for asthma<br>• ≥1 severe exacerbation in last 12 months | **Having one or more of these risk factors increases the risk of exacerbations even if symptoms are well controlled.** |
| Risk factors for developing fixed airflow limitation<br>• Lack of ICS treatment<br>• Exposures: tobacco smoke; noxious chemicals; occupational exposures<br>• Low initial $FEV_1$; chronic mucus hypersecretion; sputum or blood eosinophilia | |
| Risk factors for medication side-effects<br>• *Systemic*: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors<br>• *Local*: high-dose or potent ICS; poor inhaler technique | |

$FEV_1$: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; OCS: oral corticosteroid; P450 inhibitors: cytochrome P450 inhibitors such as ritonavir, ketoconazole, itraconazole; SABA: short-acting $beta_2$-agonist.

*Excludes reliever taken before exercise. For children 6–11 years, also refer to Box 2-3, p.30. See Box 3-8, p.50 for specific risk reduction strategies.

This consensus-based GINA control classification corresponds to that in GINA 2010–2012, except that lung function now appears only in the 'future risk' assessment. 'Current clinical control' has been renamed 'symptom control', to emphasize that these measures are not sufficient for assessment of disease control – future risk assessment for adverse outcomes is also needed. 'Independent' risk factors are those that are significant after adjustment for the level of symptom control. Poor symptom control and exacerbation risk should not be simply combined numerically, as they may have different causes and may need different treatment strategies.

**Figure 1** Assessing asthma control and future risk. ©2017 Global Initiative for Asthma (www.Ginasthma.org). Reprinted with permission.

suspected of having problematic severe symptoms.[16] The need for specialist care is based not only on the amount of treatment required but also consideration of current control, exacerbation history and future risk of loss of control, exacerbation and harm from treatment (figure 1).[17] Specifically, a referral should be made if there is significant patient or family anxiety or there is uncertainty about diagnosis, uncontrolled symptoms or exacerbations despite adequate therapy (and inhaler technique). A referral should also be made if there has been a previous severe attack, there is risk of sudden fatal attack due to anaphylaxis or food allergy, or there are concerns about medication side-effects, including growth delay or adrenal suppression.[3 4] Longitudinal integration is needed to link paediatric and adult services and to ensure smooth transition for adolescents. Planned longitudinal care is needed which supports the development of self-management and resilience.[18]

Networks can support specialist centres to overcome many of the practical problems associated with delivering a centralised service. Networked care acknowledges that the majority of patient contacts occur in primary or secondary care, rather than

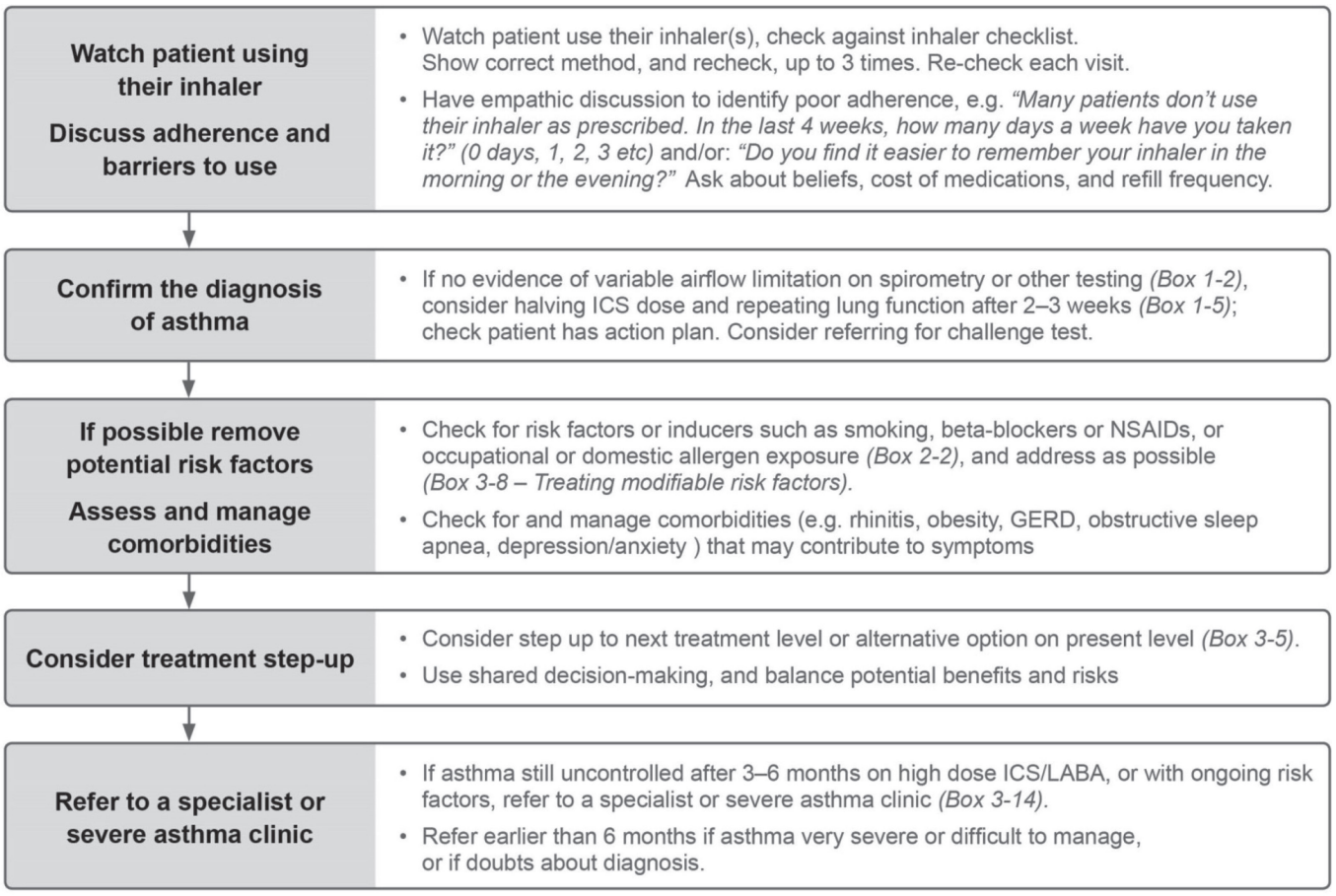


**Figure 2** Assessment of children and young people with poor asthma control and pathway to specialist referral. ©2017 Global Initiative for Asthma (www.ginasthma.org). Reprinted with permission.

in a specialist tertiary centre which might be some distance from patients' homes and schools. Professional education and shared protocols (including specialist referral criteria) are essential to encourage appropriate referrals, facilitate communication and ensure responsibilities are explicit (figure 2). The importance of recognising children and young people at risk and of sharing information is highlighted in the National Review of Asthma Deaths.[7] A co-ordinated approach helps to identify risk factors, such as increased prescription of short-acting bronchodilators (SABA), insufficient preventer prescription or collection, past exacerbations and poor consultation attendance, particularly where parents fail to collect prescriptions or to bring their children for follow-up after attacks.[4 7] The success of the national asthma programme in Finland has proven that targeted professional education across healthcare networks can improve the basics of asthma care and reduce both hospitalisations and costs.[19] New and innovative platforms are needed to ensure timely and consistent communication between the various professionals involved in each child's care.

## 'ASTHMA BASICS'

### Diagnosing asthma and exacerbating conditions

Symptoms commonly attributable to asthma, including wheeze, cough, chest tightness and shortness of breath, are non-specific and may also be features of many other conditions. While there is no single diagnostic test for asthma, objective evidence of reversible airways obstruction or airway inflammation can be used to support a clinical diagnosis.[4] If, despite good inhaler technique, standard asthma therapy fails to improve symptoms or there are other atypical features, alternative diagnoses should be investigated such as suppurative lung disease, developmental lung anomalies, recurrent aspiration, foreign body inhalation or congenital heart disease.[20] Diagnoses such as rhinitis, gastro-oesophageal reflux, obesity and dysfunctional breathing are more challenging, as they not only imitate asthma symptoms but also frequently coexist with, and variably impact upon, problematic severe asthma.[20] There is also a complex interplay between asthma and mental health, emotional well-being and family function.

A more realistic appraisal of a child and their family's ability to manage their symptoms can sometimes be made during a visit to the patient's home rather than in the clinic. During a home visit, an assessment can be made of exposure to likely triggers, including allergens or environmental tobacco smoke. Advice on allergen control can be offered and referral to smoking cessation services encouraged for parents/carers, or children or young people who are themselves smoking. A home visit can provide a more relaxed environment within which to enquire about

adherence and psychosocial issues, including financial, health or other concerns within the family.[21]

## DRUG DELIVERY AND ADHERENCE

Once the correct device has been selected, thorough and repeated training is required to support correct inhaler technique and adherence should be monitored.[22] Common mistakes include prescribing a metered-dose inhaler without a spacer, using a spacer with a mask in a child who is able to use a mouthpiece (most children are able do so from approximately 3 years of age) or failing to prescribe an age-appropriate inhaler device.

Suboptimal adherence is the most common reason for treatment failure and can lead to unnecessary investigations and treatment escalation. It is often poorly estimated by healthcare professionals, however.[23] Adherence rates of 30%–70% have been reported among children with asthma.[24 25] Adherence rates <75% are associated with increased risk of exacerbation, worse control and increased healthcare use and costs.[26] Non-adherence can be erratic, unwitting or deliberate[27], reflecting, respectively, practical difficulties associated with administering regular medication, poor understanding of treatment rationale, or a lack of confidence in or dislike of medication.

Unfortunately, despite the importance of treatment adherence, no perfect adherence monitoring tool exists and the evidence base for interventions to improve adherence is limited. In research studies, objective monitoring methods, such as electronic monitoring devices, are considered the most accurate.[28] These devices might overestimate adherence due to the influence of monitoring on behaviour and high costs limit their use. Prescription refill rate is a useful cheaper alternative. Pick up of <50% of preventer medication is clearly indicative of suboptimal adherence; however, good refill rates provide no information about how much medication is actually taken. Pick up of reliever inhalers can also be assessed using prescription data; prescription of ≥3 SABA inhalers a year is associated with increased hospital admissions and >12 is a risk factor for asthma death.[7 27] Review by a practitioner with respiratory expertise within 2 working days of treatment for an asthma attack would enable adherence to be assessed in those at risk of future exacerbations and could help identify other preventable factors.[4 14]

Asthma-related knowledge does not appear to be the main barrier to adherence as most caregivers and older children can accurately recall the names and purpose of the medications prescribed to them.[29] For this reason, interventions focused solely on increasing patient knowledge are likely to be unsuccessful.[30] A tailored approach in partnership with children and their families is necessary to overcome personal adherence barriers, this includes provision of an agreed personal asthma action plan and coordinated care. Practical behavioural strategies can include goal setting and helping patients to link medication with daily activities or reminders, as well as helping parents to develop a reward system and to positively reinforce adherence.[31]

## SPECIALIST INVESTIGATIONS

Investigation within a specialist service is directed towards excluding remaining alternative diagnoses and identifying remaining exacerbating factors. Beyond this, the aim of specialist investigation is to assess inflammatory phenotype and response to steroid therapy. Tests of sensitisation help to identify possible exacerbating allergens. Although baseline spirometry is poorly correlated with asthma severity in children, spirometry can be useful to demonstrate the presence of reversible airway obstruction. Specialist lung function tests include tests of airway hyper-responsiveness, which in conjunction with careful history taking and examination might help rule out asthma in the face of severe symptoms but normal spirometry. Fractional exhaled nitric oxide (FeNO) is a useful non-invasive marker of eosinophilic airway inflammation.

Bronchoscopy in selected cases can be helpful to assess anatomy, including evidence of external compression, and to collect bronchoalveolar lavage and endobronchial biopsy samples. These samples can identify infection and provide information about inflammatory response and airway remodelling.[32] Measuring airway inflammation before and after intramuscular triamcinolone allows assessment of steroid response independent of drug delivery and adherence.[33] Intramuscular triamcinolone can be administered under the general anaesthetic required for bronchoscopy and other uncomfortable procedures, including placement of an impedance probe to investigate gastro-oesophageal reflux, can be completed at the same time. Following intramuscular triamcinolone improvement in asthma control test or forced expiratory volume in 1 s or reduction in bronchodilator reversibility (BDR) or FeNO can be used to assess the response. Alternatively, induced sputum analysis can be used to asses the characteristics and intensity of the inflammatory response without the need for a second bronchoscopy.[34] Further specialist investigations are used in selected patients. Continuous laryngoscopy during exercise can be used to assess vocal cord movement and to identify exercise-induced laryngeal obstruction.[35] Where unusual clinical features such as digital clubbing, weight loss, productive cough or crackles suggest an alternative or additional diagnosis, such as bronchiectasis or interstitial lung disease CT scanning can be useful but there is little evidence to suggest CT provides a marker of severity in paediatric asthma.[36]

## SEVERE ASTHMA TREATMENT

Within specialist centres the anti-IgE monoclonal antibody omalizumab can be used on a trial basis in children aged ≥6 years with severe allergic asthma. The National Institute for Health and Clinical Excellence supports a 4-month trial in appropriately aged children with an IgE of 30–1500 IU/mL, who have had four or more severe exacerbations requiring oral corticosteroids or hospitalisation in the previous year.[37] If neither symptom control, exacerbation frequency, unscheduled healthcare use, nor quality of life improves during this period, then continuing this therapy is unlikely to be associated with benefit. For those continuing omalizumab therapy there are limited data on long-term use at present, particularly in children.[38] Randomised placebo controlled trial data suggest that omalizumab has a steroid-sparing effect.[39 40] Given the negative effects of corticosteroids on adrenal function, growth and bone health, efforts to decrease oral or inhaled steroid maintenance therapy should be made in those with a favourable response to omalizumab.

The choice of licensed add on therapy is limited for those not showing a clinical response or not eligible for omalizumab. There may be some benefit from high-dose inhaled corticosteroids, new steroid preparations or alternative inhaled steroid dosing regimens. However, for most children relentlessly increasing the dose of inhaled corticosteroid is unlikely to be effective, particularly once the plateau of the dose–response curve has been reached.[41] Newer inhaled corticosteroids, ciclesonide and mometasone, generate smaller particle sizes, reach the peripheral airways at lower doses, and potentially incur fewer side effects than their predecessors. These preparations require once-daily dosing which is believed to contribute to better adherence.[42] A Cochrane Review, however, was unable to refute or

confirm superiority in terms of asthma control, exacerbations or side effects when comparing ciclesonide to budesonide and fluticasone.[43] Symbicort as Maintenance And Reliever Therapy (SMART) dosing regimen has been shown to reduce the risk of severe exacerbations in adults with asthma. The efficacy and safety of SMART in adolescent asthma patients has been demonstrated to be similar to that in adults.[44] In this regimen, a single inhaler (budesonide and formoterol) is used as regular therapy and for exacerbations of symptoms. The effects on asthma control have generally been small, however, and when trialled in adolescents no significant effects on hospitalisations, asthma control days, need for rescue treatment or symptom-free days were found.[45] For a small number of children, oral corticosteroids may be effective but any benefit must be weighed against the risk of side effects. For this reason, an objective assessment of steroid response is essential before committing a child to long-term systemic steroids.[33]

Alternatives to corticosteroid treatment include theophylline or macrolide antibiotics. Adult studies suggest that theophylline inhibits the late-phase response to aeroallergens, increases neutrophil apoptosis and reduces steroid resistance.[46–48] In children, however, only modest clinical benefits are seen.[49] Studies of macrolide antibiotics have been conducted in children. These were small studies but they demonstrated reduced sputum neutrophilia and improved bronchial hyper-responsiveness.[50] Given the likely importance of altered airway microbiome in the development of asthma, the antibacterial effects of macrolides might also be beneficial.

Although yet to be licensed for use in children, much current interest is focused on long-acting muscarinic antagonists (LAMAs). These may confer bronchodilator effects and improved control when used as add-on therapy. Muscarinic antagonists induce bronchodilation[51] and have been suggested to have anti-inflammatory properties.[52] Tiotropium Respimat has recently been incorporated into the BTS treatment strategy as an alternative for adult patients who do not respond to inhaled corticosteroids plus long-acting beta-agonist[4] and the evidence from paediatric phase II trials is encouraging. Two randomised, double-blind, incomplete crossover studies in children and young people with moderate symptomatic asthma have found that once-daily tiotropium add-on therapy improved lung function compared with placebo.[53 54]

A number of immunomodulatory steroid-sparing treatments, including methotrexate, azathioprine and ciclosporin, have been used in children. There is little evidence of benefit and no randomised controlled trials. These agents are not licensed for use in paediatric asthma and should only be considered as a last resort and commenced as an n=1 trial assessed according to objective evidence of response. More promising are a number of novel monoclonals, including mepolizumab (anti-interleukin (IL)-5) and reslizumb (anti-IL-5), which have recently been licensed for use in adults with asthma in the UK, and a number of others (eg, dupilumab, anti-IL-4), which are likely to be licensed in the near future. Currently, only mepolizumab is NICE approved (for adults) and none of the existing European licences extend to those <16 years. Access to, and funding for, these drugs will have to be considered on a case-by-case basis for the foreseeable future.

## NON-PHARMACOLOGICAL TREATMENTS

Non-pharmacological approaches are generally directed at avoiding or removing asthma triggers. Temperature-controlled laminar airflow devices are a non-pharmacological treatment designed to substantially reduce allergen exposure. These devices distribute filtered cooled air from the breathing zone overnight. Significant improvements in quality of life, airway inflammation and systemic allergy were demonstrated in children with persistent allergic asthma recruited to a clinical trial of these devices, although it was not possible to evaluate the effect on exacerbations due to the small number of participants experiencing an exacerbation during the trial.[55] This approach might provide an alternative for children ineligible for omalizumab therapy. Within the specialist multidisciplinary team, psychological expertise is essential to identify and treat depression or anxiety, to help children recognise and counter the effect of stress on asthma symptoms, and to cope with the stigma and practical impact of chronic illness. Specialist physiotherapy input is also important and can be invaluable in the identification and treatment of dysfunctional breathing.[56]

## CONCLUSIONS

While asthma is a common childhood disease for which evidence-based management guidelines exist, a small minority of children have symptoms which are difficult to control with conventional therapies. The reasons for poor control are variable and likely reflect unique biological as well as environmental, behavioural and psychosocial factors. For some children there is a genuine failure of conventional treatments to control their disease and investigations and treatments beyond those described in conventional guidelines are required. For the majority of children, however, preventable factors such as adherence to medication advice, poor inhaler technique or failure to avoid or reduce the effect of triggers are evident. For this reason, lessons learnt in the care of children with severe asthma could be used to improve the care of all children and young people affected by asthma. Co-ordinating care across healthcare providers is an effective way to achieve this by sharing knowledge, improving communication and agreeing care pathways.

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