J R Coll Physicians Edinb 2009; 39:43–6

Adolescent inflammatory bowel disease: assessment, treatment and transition

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ABSTRACT Paediatric inflammatory bowel disease (IBD) most usually evolves during adolescence, a time of great challenge. For the adolescent, the disease should be thoroughly assessed by upper gastrointestinal endoscopy and ileo-colonoscopy, preferably performed under general anaesthetic or conscious sedation, with relevant radiological examination. This will enable the determination of diagnosis, IBD subtype and extent. Growth also needs to be assessed and the effect of disease on academic and social functioning must be explored. Unlike adult IBD, there is a poor evidence base for the medical and nutritional management of adolescent IBD. However, within the UK it is common practice to use exclusive enteral nutrition rather than corticosteroids for the induction of Crohn's remission, and to have early recourse to immunomodulation with azathioprine (and methotrexate for azathioprine/6MP intolerance or non-response) unless remission is rapidly induced and maintained. There should be close collaboration with paediatric and colorectal surgeons. Adolescents need higher relative drug doses than the literature suggests for adult IBD patients. Transition clinics are vital for adolescent care and provide a helpful source of second opinion for the paediatric gastroenterologist. Adolescents with IBD are best looked after by the paediatric gastroenterology multidisciplinary team (or in shared care with that team). In this overview we highlight these key areas of assessment, treatment and transition.

KEYWORDS Crohn's disease, paediatric inflammatory bowel disease, ulcerative colitis

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***August 2008***

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INTRODUCTION

Paediatric inflammatory bowel disease (IBD) most usually evolves during adolescence, a time of great challenge due to the need for growth, pubertal development and educational attainment, together with the ability to establish self-esteem and peer relationships. The incidence of Crohn's disease in Scotland has trebled over the past 30 years, and ulcerative colitis (UC) has continued to rise, albeit at a lower rate; the incidence of paediatric-onset Crohn's disease in Scotland is the highest in the UK and one of the highest in the world. There is a male predominance of paediatric IBD until at least 14 or 15 years of age. The evidence base for the assessment and treatment of paediatric IBD is limited compared with that in adult IBD. Our approach is representative of that in most tertiary paediatric gastroenterology centres in the UK. The British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) has produced consensus-based guidelines for the management of paediatric and adolescent IBD in 2008.[1]

ASSESSMENT OF ADOLESCENT IBD

The first step in assessment is to recognise the compatible clinical presentation. In the UK prospective inception cohort of paediatric IBD of 1998–99, 72% of children and adolescents had abdominal pain, 56% had diarrhoea, 22% had blood in the stool, 58% had decreased weight, but of importance only 25% had the classic triad.[2] There are other presentations of Crohn's disease in adolescence such as isolated short stature alone, or resistant iron deficiency anaemia. Most adolescents with UC have pancolitis at presentation and there are frequent upper gastrointestinal findings, including focally enhanced gastritis. As well as having extensive IBD at presentation, children and adolescents show rapid progression of disease.[3]

The majority of children under eight years of age who present with IBD have isolated colonic disease (Crohn's disease, UC or indeterminate colitis) and although this colonic predominance continues through to adolescence, there is a gradual rise particularly in the ileocolonic phenotype. These sometimes occult forms of presentation of Crohn's disease, together with a lack of recognition of its development in adolescence, explain a mean of 11 months from symptom onset to diagnosis for this UK conception cohort. Of course, other causes of inflammation such as infection need to be considered and excluded. Primary immunodeficiencies can present with chronic intestinal inflammation and recurrent infections (chronic granulomatous disease, glycogen storage disease type 2a, Wiskott-Aldrich syndrome) and

TABLE 1 Tanner staging for pubertal status

Tanner stage	Breast staging (girls)	Genital staging (boys)	Pubic hair (boys and girls)
1	Pre-adolescence: elevation only of the papilla of the nipple	Pre-adolescence: testes, scrotum and penis the same as early childhood	Pre-adolescence: no pubic hair
2	Breast bud stage: elevation of the breast and papilla as a small mound	Enlargement of the scrotum and testes with reddening of scrotal skin and change in texture with little or no enlargement of the penis	Sparse growth of long, slightly pigmented downy hair, straight or slightly curled, chiefly at the base of the penis or along the labia
3	Further enlargement of the breast and areola, with no separation of the contours	Enlargement of the penis, which at first occurs mainly in length with further growth of testes and scrotum	Darker, coarser and more curled pubic hair which spreads sparsely over the junction of the pubis
4	Projection of the areola and papilla to form a secondary mound above the level of the breast	Increased size in the penis with growth in breadth and development of the glans; the testes and scrotum are larger with darker scrotal skin	Hair which is more adult in type but the area covered is considerably smaller than in the adult and there is no spread to the medial surface of the thighs
5	Mature stage: projection of the papilla only, due to recession of the areola to the general contour of the breast	Male genitalia are adult in size and shape	Adult in quantity and type with distribution of a horizontal pattern to form an inverse triangle, and spread to the medial surface of the thighs but not up the linea alba or above the base of the inverse triangle

it is therefore important to consider the differential diagnosis of intestinal inflammation, although of course the primary immune deficiencies are likely to have been associated with recurrent severe sepsis in earlier life, such as skin abscesses and bacterial pneumonias.

One of the major differences in adolescent IBD is the need to understand normal growth and pubertal staging, given the major disruptive effect on both that can result from the development of adolescent IBD. There are three phases of normal growth in childhood: a rapid infant stage of growth which ends by two years of life; a much slower and steady childhood phase of growth; and the third phase of a pubertal growth spurt beginning at a variable time, although rarely before 11 years of age. Inflammatory bowel disease is most likely to present in adolescence, and therefore disrupt the pubertal phase of growth, which is itself influenced not only by nutrition and growth hormone but also by sex hormones. It is vital to measure and correctly plot weight and height on an appropriate centile chart for age and sex, obtain pre-illness growth parameters and calculate the mid-parental height centile to get an idea of genetic potential for growth. The mid-parental height is calculated by averaging the height of the child's mother and father and then either adding or subtracting 7 cm, given that the mean difference in parental height between men and women in the UK is 14 cm.[4] The parental height is obviously plotted at the limit of the childhood growth chart.

Pubertal status is checked by Tanner staging (see Table 1). This is based in girls on breast development and pubic hair, and in boys on genital development and pubic hair.

With normal linear growth, the peak height velocity (growth in cm per year) in girls occurs at the stage of early breast development but in boys occurs much later during the advanced changes of puberty and before development of facial hair and shaving. There can be major disruption of growth in adolescent IBD, particulary in Crohn's disease, due to a combination of decreased nutrient intake, inflammation and steroid therapy after diagnosis. The pro-inflammatory cytokine cascade released from intestinal inflammation has effects via insulin-like growth factor 1 (IGF-1) on the growth plate of the long bones and in a negative feedback loop on the hypothalamus and pituitary, interrupting growth hormone release.

Delayed growth, therefore, can either be constitutional (associated with a familial tendency to late linear growth and pubertal development) or may be due to disruption of growth by chronic inflammation. A bone-age estimation by left-hand X-ray will give the constitutional age expressed as a centile value of the chronological age at the time of radiology. Height velocity is the most sensitive marker of abnormal growth, showing the value of serial measurements of height with plotting on centile charts. In 45% of Tanner stage 1 and 2 adolescents with Crohn's disease, there is decreased height velocity before onset of gastrointestinal symptoms; at diagnosis

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of IBD in adolescence there is decreased weight in 85% of patient's with Crohn's disease and 65% of those with UC. A sustained increase in height velocity is a good indicator of successful treatment in clinical practices.

Despite the absence of high-quality evidence, both current practice and informed recommendations by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[5] for endoscopic assessment of IBD in adolescents is to have full upper gastrointestinal endoscopy with ileo-colonoscopy and multiple biopsies. We repeatedly hear from adolescents of their shock when subjected to unprepared sigmoidoscopy in clinics, and there are often major psychological sequelae from this. Therefore, a full assessment should be done under general anaesthetic or deep sedation with propofol infusion.

In adolescent Crohn's disease, upper gastrointestinal lesions confirm the diagnosis which would otherwise have been classified as indeterminate colitis or UC in 11–29% of cases. In adolescent UC, it is recognised that there is often unusual histology at presentation and that the vast majority of patients have pancolitis, emphasising the need to have full colonoscopy. If treatment has begun in the community or clinic prior to colonoscopy, treatment effects will give occasionally normal histology or patchy lesions, confusing the diagnosis. Lastly, Crohn's colitis classically has rectal and sometimes sigmoid and rectal sparing, so limited sigmoidoscopy may miss the diagnosis of IBD. Full clinical, endoscopic, histopathological and radiological examination will enable determination of the diagnosis of adolescent IBD, the subtype of IBD and its extent. Radiology should be performed unless it is a clear-cut case of UC, usually by small bowel follow-through, but more recently magnetic resonance imaging of the small bowel is replacing this in some centres. Labelled white cell scans are of poor diagnostic utility and are not recommended for full assessment of adolescent IBD.

TREATMENT OF ADOLESCENT IBD

The treatment goals for IBD in adolescence are to relieve symptoms without side effects, maintain remission and avoid complications. Optimisation of growth and pubertal development is important, particularly in Crohn's disease. We aim to facilitate a return to normal lifestyle in terms of school attendance and achievement, sports, leisure and family events. In the longer term, the need to attain full educational potential and gain appropriate employment is vital. To meet these, we work within the context of a multidisciplinary paediatric IBD team. Having assessed the adolescent with IBD, we wish to, very importantly, reduce the burden of steroids, stem the pro-inflammatory cytokine tide and promote growth. Adolescents need higher relative drug doses than the literature suggests for adult patients: for example, we use azathioprine at 2.5 mg/kg, and infliximab is given in three doses of 5 mg/kg for induction of luminal inflammatory as well as fistulising disease. The evidence base for paediatric IBD treatment is very limited compared with the large amount of systematic reviews and randomised controlled trials available as evidence in adult IBD.

For adolescent Crohn's disease, our first-choice therapy is exclusive enteral nutrition, usually as six weeks of an oral polymeric feed with a period of three days to one week of return to full diet at the end. If there has been no response by two weeks, clinically and in terms of inflammatory markers, it usually means that enteral nutrition therapy is unsuccessful. We use nutrition support in all adolescents with IBD when relevant. We have early recourse to immunomodulator therapy and would also use biological agents for severe recalcitrant disease or chronic inflammation that fails to settle despite use of azathioprine/6MP and then methotrexate immunomodulation.

At all stages of change of therapy we consider the need for surgery, with repeat endoscopy and radiology and surgical consultation if necessary. We use growth-promoting agents such as growth hormone and sex steroids when relevant. Although 'step-down' therapy with aggressive use of biological agents and immuno-suppressants at diagnosis may appear attractive compared with the classical 'step-up' treatment paradigm, there are increasing long-term concerns about the safety of the biological agents. In particular, there has been the description of 15 cases of the nearly always fatal hepatosplenic T-cell lymphoma in cases of paediatric-onset IBD treated with infliximab and azathioprine (information from Schering-Plough, April 2008). Natural history shows that surgery will allow achievement of pre-morbid height in early puberty in Crohn's disease but has much less effect in late puberty, demonstrating again the importance of pubertal staging, bone age estimation and close liaison with surgical colleagues.

Issues for the IBD team in managing adolescents include the amount of time spent talking to the teenage patients together with the large degree of explanation often needed by his or her parents. We provide age-appropriate literature from the Crohn's in Childhood Research Association (CICRA) and the National Association for Colitis and Crohn's Disease (NACC), and involve clinical psychology and social workers in our multidisciplinary management. An explanation is needed to guide teachers at school to facilitate optimal school performance, and very early on in adolescence the process of transition to the adult clinic should begin.

TRANSITION OF ADOLESCENT IBD

Transition is a process, not an event, and the timing of this is based on the adolescent and their family's wishes, their emotional maturity, psychological and educational

issues, pubertal development and stage of linear growth. In Edinburgh's Royal Hospital for Sick Children, transition IBD clinics were established in early 1998. This has been invaluable for the paediatric IBD team, not only for streamlined care of the adolescent IBD patient but also for increasing our knowledge of some of the wider issues of IBD medicine in adult practice. Problems such as liver disease in IBD are rare in adolescence, and the transition clinic gives us a valuable opportunity for second opinions, either on complications, which are rare in adolescent IBD, or in difficult cases. The earliest we have had an adolescent transfer fully to the adult IBD team is 13 years of age and the oldest is 19 years of age, but generally this is done at the end of schooling, a time that seems to suit most teenagers and their families. The advantages of chronic disease transition clinics for teenagers are many, and are summarised in recent Department of Health documents.[6,7]

CONCLUSIONS

High-quality care of the adolescent with IBD is typified by appropriate initial assessment (clinical assessment, endoscopy and biopsies under general anaesthetic or deep sedation, radiology, pubertal staging, growth staging), and repeated assessments if the adolescent is not maintaining remission or has frequent relapses. We aim for growth promoting and steroid-sparing therapy with the use of exclusive enteral nutrition as a primary treatment in adolescent Crohn's disease, nutrition support in all, early immunomodulation with azathioprine or methotrexate, use of biological agents, early consultation with surgical colleagues and the use of growth-promoting agents such as growth hormone and sex steroids.

In our opinion, all adolescents with IBD should be either managed only by a multidisciplinary paediatric IBD team or in shared care with this team. The transition process must be explicit, adolescent-centred and flexible. The collaboration of colleagues in paediatric and adult IBD care provides a rich clinical environment and an important research base.

KEY POINTS

- Paediatric inflammatory bowel disease most usually evolves during adolescence, a time of great challenge due to the need for growth, pubertal development and educational attainment, together with the ability to establish self-esteem and peer relationships.
- Adolescents with inflammatory bowel disease must be looked after either completely by or in shared care with the paediatric gastroenterology multi-disciplinary IBD team.
- Appropriate initial assessment of the adolescent with inflammatory bowel disease involves clinical assessment, full upper gastrointestinal endoscopy with ileo-colonoscopy and biopsies under general anaesthetic or deep sedation by propofol infusion, radiology, pubertal staging or growth staging; repeated assessments are necessary if the adolescent is not maintaining remission or has frequent relapses.
- Therapy is growth-promoting and steroid-sparing, with use of exclusive enteral nutrition as a primary treatment in adolescent Crohn's disease, nutrition support in all, early immunomodulation with azathioprine (or methotrexate if azathioprine and 6MP resistant/intolerant), the use of biological agents, early consultation with surgical colleagues and the use of growth-promoting agents such as growth hormone and sex steroids when relevant.
- Transition is important for adolescents; it is a process, not an event, and the timing of this is based on the adolescent and their family's wishes, their emotional maturity, psychological and educational issues, pubertal development and stage of linear growth.

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Originally published as part of the Gastroenterology module in the RCPE Online Continuing Medical Education Programme. Online CME, including self-asessment MCQs, is available to Fellows and Members at: http://www.rcpe.ac.uk