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Ulcerative Colitis in Children and Adolescents

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1. Introduction

Ulcerative colitis (UC) is a chronic gastrointestinal inflammatory disorder and is one of the inflammatory bowel diseases (IBD) along with Crohn disease (CD). CD can involve any area of the gastrointestinal (GI) tract and has features of transmural disease, skip lesions and mucosal granulomata. UC, on the other hand, principally involves the colon for a variable length, and comprises confluent superficial inflammation. In addition, some individuals may be termed to have IBD unclassified (IBDU): a situation where there are clear diagnostic features of IBD, but no definitive features of either UC or CD. Over time many individuals with IBDU are reclassified as UC or CD. At present CD and UC are considered to be incurable, although colectomy can be seen as a surgical cure for UC. Furthermore, the pathogenesis of these conditions remains unclear, although understanding is increasing rapidly.

The onset of UC can be in any age, from the first year of life. The peak age of onset, however, is between 15 and 35 years of age. Overall rates of UC climbed through the last decades of the 20th century. Recent paediatric data suggests that rates of UC have been static in a number of countries. In some, however, UC incidence has continued to increase. In countries where IBD was previously uncommon, UC incidence rates are also noted to be increasingly recently. When diagnosed in children of any age, these individuals face a long-term condition with remitting-relapsing features. Children may have significant interruption to daily activities and consequent impact upon quality of life (QOL). A number will have complications of disease and some will require colectomy during childhood. Because of the multiple aspects of UC and the various adverse impacts, children and adolescents with UC should be considered separately to adults with UC and require a multidisciplinary approach to management to ensure that all aspects are considered in optimal fashion.

2. Pathogenesis of IBD

2.1 Current hypothesis of causation of UC

At the present the precise cause of IBD is unknown. The best accepted hypothesis is that UC develops in individuals at genetic risk as a result of interactions between the intestinal

microflora and the host innate immune responses, leading to dysregulated immune responses and to consequent inflammation. Environmental factors are also important.

2.2 Genetic influences in the development of UC

The familial nature of UC and of CD has been recognised for many years. Over the last decade or so, international collaborative groups have focused on identifying the genetic elements contributing to the risk of IBD, with many key discoveries. Over 100 loci are now reported in association with IBD. There is some overlap with many loci important for both CD and UC. However, more than 20 loci are specific for UC. These include genes encoding for cytokines (e.g. interleukin (IL)-10, IL-22 and IL-26) and others whose function are unclear (e.g. ARPC2) (Thompson and Lees 2011; Cho and Brant 2011).

Recent studies have used genome wide association studies (GWAS) to examine particular genetic elements important in early-onset (paediatric) UC and have demonstrated the involvement of several particular genes (Anderson et al 2011; Henderson et al 2011a). Important mutations have been shown in IL-27 (implicated in Th17 cell function), CAPN10 (involved in endoplasmic reticulum stress responses), MTMR3 (component of autophagy reactions), and several other genes.

2.3 The intestinal flora and UC

The intestinal flora is clearly critical in the development of IBD. In specific animal models of gut inflammation, exclusion of the bacterial flora prevents or delays the onset of the inflammatory changes. In the human setting, excluding the flow of faecal effluent from an involved segment of bowel (i.e. defunctioning a segment of the bowel) leads to improvement of inflammation. Furthermore, antibiotic treatment of individuals with active CD can lead to improvement, whilst probiotic therapies that modify the intestinal flora have similar effects in the setting of UC.

At present, however, there is no evidence for one specific organism or group of organisms being the causative agent(s) of IBD. Candidate organisms include *Mycobacterium paratuberculosis* (MAP), *Escherichia coli*, and mucous-associated flora. Recent work has focused on several mucous-associated flora and indicates high rates of specific organisms in children with active IBD compared to controls. *Campylobacter concisus* is one example of a bacterium that may play roles in the development of IBD. Our work in Australian children has illustrated that this organism is frequently present at the time of diagnosis of CD in children (Man et al 2010). Ongoing studies from the UK also indicate that this organism is more often present in newly diagnosed UC than in controls (Mukhopadhya et al 2011). However, at present there is not sufficient data to indicate that this pathogen is the specific causative agent in IBD.

2.4 Other environmental factors

Other environmental factors are also relevant to the development of UC. Appendectomy for appendicitis is associated with lower rates of UC, whilst smoking also can be protective (Bastida et al 2011). Exposure to second-hand smoke (passive smoking) in children does not appear to provide any protection against the development of UC (Mahid et al 2007). However, one series suggested that patients with UC exposed to passive smoke had increased extra-intestinal manifestations (van der Heide 2011), but this has not been

described by others. Other factors that are shown to be protective against UC include having a vegetable garden as a child and breast-feeding (Gearry et al 2010).

2.5 Dysregulated immune responses

Disrupted innate defence mechanisms in the gut are also critical to the development of the chronic inflammation as seen in IBD. Many of the genes implicated in IBD encode for proteins involved in innate protection of the mucosa. Altered barrier function, leading to increased epithelial permeability, is clearly described. It is unclear if this is a primary event, or if it occurs secondary to gut inflammation. Variation in innate antibacterial proteins, such as defensins, may contribute to altered host responses (Ramasundara et al 2009). Altered immune responses are likely also important. T helper cell type 1 (Th1) responses have traditionally been implicated in CD, whilst Th2 or a combination of both pathways seen as relevant to UC. More recent understanding suggests that T regulatory cells (Tregs) have key roles in UC.

3. Epidemiology of UC in children and adolescents

UC can occur in children of any age, but rates tend to increase with age. Most large cohorts illustrate that UC comprises around 25-30% of paediatric IBD (the majority of children with IBD are diagnosed with CD). Family history of IBD (CD or UC) is commonly seen in children diagnosed with UC.

Two large cohorts have examined the epidemiology of paediatric UC in different areas of the USA. The earlier study retrospectively reviewed 171 children diagnosed with UC in two academic centres in North-East USA (Hyams et al 1996). The children in the cohort ranged from the second year of life to almost 18 years of age (mean 11.7 yrs). Just over one third of the group were aged less than 10 years at diagnosis. The gender distribution slightly favoured males (55%) and the population was predominantly Caucasian (95%). A first degree family history was present in 11%. Most had symptoms for less than 3 months, but 18% had symptoms for more than 6 months duration before diagnosis. At diagnosis, mild disease was present in 43%, with moderate or severe disease in 57%. The majority of the mild group had proctitis or proctosigmoiditis, whilst almost the entire moderate/severe group had left-sided or pan-colonic disease. Ninety percent of the mild group and 80% of the mod/severe group had cessation of symptoms within the first six months of therapy. Almost two thirds of the mild group had inactive disease in the second six-month period after diagnosis, with only one child having continuous disease in this time period. Over the same period, 11% of the moderate/severe group had continuous disease, with a further 44% having intermittent/chronic disease course. Disease distribution did not appear to influence this course. Twenty-seven percent of the mild group received corticosteroids by 12 months after diagnosis, contrasting with 70% of the moderate/severe group needing this therapy over the same time. Overall, the one year colectomy rate in this group of children was 9% at 12 months and 19% at 5 years. Age less than 10 years did not influence colectomy rates, but initial disease severity was associated with increased risk for colectomy overall.

More recently was a study of prospectively recruited children with diagnosis of IBD from across the state of Wisconsin for the first two years of the 21st century (Kugathasan et al 2003). Sixty children with UC were identified within a total of 199 children with IBD (30% of the total). The UC cohort had an average age of 11.8 yrs and 55% were male. There was no

association between UC and rural or urban location and 87% were Caucasian. Eleven percent had a first or second-degree family member with IBD. Ninety-eight percent of this group had diarrhoea at diagnosis, with bleeding in 83%, pain in 43% and weight loss in 38%.

The mean period of symptoms prior to diagnosis was 3 months in this group. Most of the group (90%) had pan-colonic disease, with the rest having left-sided location. ESR was normal in 35% and albumin was normal in 68% of the cohort.

Follow-up data including response to therapy, or other outcomes were not reported in this cohort.

A recent report examined the incidence of UC across Scotland in two distinct time periods (1990-95 and 2003-8) (Henderson et al 2011b). Compared to the earlier time period, the incidence was greater in the more recent cohort (1.59/100,000/yr versus 2.06/100,000/yr; p=0.023). This equates to a 30% increase in paediatric UC over this period. There was a male predominance overall and age-adjusted incidence figures showed increases in males but not females over time. Another recent study utilised Canadian health data and demonstrated a modest rise on the prevalence of UC from 16.2 to 19.7/100,000 over the period of 1994 to 2005 (Benchimol et al 2009).

The overall trends in the rates of UC were reviewed recently (Benchimol et al 2011). This article assessed 139 studies reporting rates of paediatric-onset IBD across 32 countries, both developing and developed. Overall, rates of IBD were clearly shown to be increasing with varied rates between countries. Not all the studies applied statistical analysis to changing rates over time: overall one-fifth of the studies showed increasing UC in children.

A recent report has characterised patterns of UC in Japanese children with direct comparison to adults in that country (Ishige et al 2010). A long-standing register was examined for the patterns of disease in children and adults. In total, 37,846 individuals with UC were included: 5.9% were aged less than 16 years of age. The children more commonly had positive first-degree family history, more severe disease at diagnosis and had more extensive colitis than adults. Family history of IBD was seen in 4.3% of the children (less than in comparable European cohorts).

Reports from the middle part of the 20th century illustrate a predominance of UC in cohorts of IBD. As noted above, most recent cohorts reported in the western world demonstrate much higher rates of CD than UC. One study has however, demonstrated that this is not a universal change (Lehtinen et al 2011). This study of rates of paediatric IBD in Finland over 16 years showed increasing rates of IBD over this time (rates increased by 6.5% per annum. In addition, rates of UC increased from 4/100,000 to 9/100,000 over the period from 1992 to 2003. These regional differences illustrate the importance of environmental factors in the development of UC.

Interestingly, recent reports from Asia, where IBD was previously considered to be rare, have shown increasing rates of UC (more so than with CD) (Goh and Xiao 2009). This pattern of differing rates across the globe also illustrates the importance of environmental factors.

4. Phenotypic features of UC

UC has traditionally been seen as a chronic inflammatory condition of the colon, with inflammation extending for variable distances from the anus. Disease patterns include proctitis (distal changes only), left-sided colitis or pan-colitis.

Inflammation is superficial, with acute and chronic changes. This pattern contrasts with CD, where disease can involve any section of the gastrointestinal tract (from mouth to anus), with trans-mural inflammatory changes and the presence of the specific findings of granulomas. Perianal disease is a feature of CD and not UC.

The adult-based Montreal disease classification system for IBD included three types of UC: proctitis (E1), left-sided disease (E2) or disease proximal to the splenic flexure (E3) (Silverberg et al 2005). The recent Paris classification has adjusted the Montreal system for paediatric UC by the addition of E4 (disease proximal to hepatic flexure), and S1 (ever severe UC) (Levine et al 2011).

Recent studies demonstrate that non-specific gastritis may be seen in combination with colonic disease in UC (Hori et al 2008). Homing of lymphocytes from the colon to the stomach may explain some of these events (Berrebi et al 2003). In addition some authors describe so-called "back-wash" ileitis, with minor changes present in the distal ileum, as an occasional feature of UC.

UC is associated with various extra-intestinal manifestations (EIM) of disease, such as skin, eye and liver disease. EIM were noted in 285 of a cohort of 1009 newly diagnosed patients with IBD – most of these occurred within the first 12 months after diagnosis (Dotson et al 2011). In a cohort of 211 children with UC from the UK, 1 had skin manifestations and 5 had liver disease at diagnosis (Sawczenko et al 2003).

Several studies of large paediatric cohorts have illustrated key phenotypic features of UC. These studies demonstrate that many children have pan-colitis at diagnosis, with few having proctitis and a small number having left-sided disease. Furthermore, many children with limited disease at initial assessment have extension to pan-colonic disease over the first 2-3 years of their disease. This pattern in children contrasts greatly with adult UC, where proctitis is prominent and pan-colitis seen less commonly.

A study based in Scotland evaluated the features of 99 children with UC at diagnosis and over the subsequent years, and compared these features of a cohort of adult-onset UC (Van Limbergen et al 2008). UC was extensive (pan-colonic) in 82% of the children at the time of diagnosis. In contrast, this pattern was seen in just 48% of adults ($p < 0.0001$). Almost half (46%) of the children without extensive disease initially progressed to develop extensive colitis during follow-up. One third of the group required immunomodulatory therapy within 12 months of diagnosis. In addition, the median time to first surgery was substantially shorter in the patients with childhood-onset than in adult-onset patients.

A similar cohort was described from France, in which 112 children were characterised at diagnosis and their progress followed for at least 2 years (Gower-Rosseau et al 2009). At diagnosis, 28% of the children had proctitis, 35% left-sided colitis, and 37% extensive colitis. The disease course of this group also was characterized by disease extension in 49% of patients. Delay in diagnosis for more than 6 months and a positive family history of IBD were associated with an increased risk of extension of disease. Eight percent of this group had colectomy within 12 months of diagnosis. By 3 years, 15% had colectomy and by 5 years 20% had undergone colectomy. The risk of colectomy was increased if EIM were present at diagnosis (hazard ratio = 3.5 (1.2-10.5)). In addition, with regards the group with less extensive disease initially, those who had disease progression had much greater risk of needing colectomy than those who continued to have restricted disease. These two well-described cohorts of children from Europe have illustrated a number of key aspects of the

natural history and outcomes of paediatric UC, and have emphasised that paediatric-onset disease has many key differences from the same disease beginning in adulthood.

5. Presentation patterns of UC

Bloody diarrhoea is the most common presenting feature in paediatric UC. However, children may also have less specific symptoms of abdominal pain, anaemia, or lethargy.
In a large cohort of British children (n=172) newly diagnosed with UC, diarrhoea was seen in 72%, bleeding in 84%, pain in 62%, weight loss in 31%, and lethargy in 12% (Sawczenko et al 2003). Arthropathy, nausea and secondary amenorrhoea were seen less commonly.
Idiopathic acute pancreatitis (AP) is a further atypical pattern of presentation with UC. Broide et al (Broide et al 2011) retrospectively evaluated a cohort of 12 individuals with IBD who had presented initially with AP: 10 of these were children. Eight of these 10 children had colonic disease (four with UC). Although the median time between the episode of AP and the onset of IBD was 24 weeks, the longest duration was 156 weeks.
Acute severe UC (or fulminant colitis) can be seen at diagnosis or at subsequent exacerbations in adults or children with UC. In adults this pattern is defined as more than six bloody motions daily along with tachycardia, fever, anaemia or elevated ESR (one of these required for the definition). In children acute severe colitis can be defined as Pediatric Ulcerative colitis activity index (PUCAI) of 65 points or greater.
Historically, acute severe colitis was seen as a medical emergency with a high case fatality rate. It remains a life-threatening condition, with risk of various complications. Hence early recognition and optimal management of this condition is critical.

6. Growth and nutrition in paediatric UC

Children with UC commonly have weight loss at presentation. Case series suggest that up to 65% of children with UC have a history of weight loss at diagnosis (Griffiths et al 2004). In addition to weight loss and/or failure to continue gaining weight normally, children diagnosed with UC may also have a history of interrupted or impaired linear growth. As many children with UC are diagnosed in adolescence, before or during their pubertal growth spurt, perturbation of normal linear growth at the time of the expected pubertal growth spurt can be a significant complication of paediatric IBD. For these reasons, ongoing attention to growth and nutrition from the time of diagnosis and thereafter, is a crucial aspect of management of UC in children and adolescents. These concerns, however, are even more pertinent in children with CD, which has much greater impact on growth and nutrition than in paediatric UC.

6.1 Overweight and obesity in IBD

Although most concern about the nutritional impact of IBD in children is with regards under nutrition, recent data indicates that more children are overweight (BMI > 85%) and/or obese (BMI > 95%) at the time of diagnosis of IBD. These changes may simply reflect recent overall changes in weight in children and adolescents across many countries (i.e. increasing overweight/obesity). However, overweight/obese status has important implications for children with IBD.
In a group of 166 children with newly diagnosed IBD in Wisconsin, USA, 17.6% of the children with UC were overweight/obese (Sondike et al 2004). More recently, 23.3% of a

separate group of 1598 American children with known CD and UC were noted to be overweight/obese (Long et al 2011). The rate of over nutrition was markedly greater (30%) in the children with UC in this group than the children with CD. In this cohort recruited from a number of paediatric centres, overweight/obesity status was associated with African-American ethnicity and Medicaid insurance. In addition, prior surgical intervention was linked with overweight/obese status in the children with CD, suggesting that the presence of over nutrition may be associated with a more severe disease course. Overweight/obese status may also make medical therapies more difficult, and increase surgical morbidities. In addition, it may increase psychological outcomes in the setting of children with a chronic disease, making them stand out even more from their peers.

7. Investigation and diagnosis of UC in children and adolescents

7.1 Consideration of diagnosis of IBD

The diagnosis of UC relies firstly upon consideration of the diagnosis. Children with atypical symptoms may be reassured and symptoms not assessed further if practitioners are not aware that UC can present at any age. As noted above, presentation patterns in children with UC vary, with most typical symptoms being bleeding, diarrhoea and pain. Family history of IBD (especially in first degree family members) should further raise suspicion of possible IBD.

A presentation with bloody diarrhoea in a child requires a series of assessments. In infants, the differential of this presentation includes eosinophilic (allergic) colitis, infection, surgical conditions (such as intussusception) and complications of congenital conditions (such as Meckels diverticulum). In older children, infection is an important differential. Functional constipation with bleeding from distal causes (anal fissures) and perianal Streptococcal infection may be important to exclude.

7.2 Approach to possible IBD/UC

A detailed history should clarify the features of the gastrointestinal symptoms, especially patterns of pain and bowel habit. Appetite, energy levels (lethargy), and weight changes should be documented clearly. The presence of any extra-intestinal features should be detailed, including skin, eyes, joint and systemic symptoms. Past history of gastrointestinal symptoms and diseases should be noted, along with family history of IBD or other GI conditions. The extent to which the child has been able to continue daily activities should be carefully documented also: this includes attendance at school, school performance, social interactions, ability to undertake sports or other hobbies, and general interest in these activities. Clarification of current immunisations status is important and a catch-up plan arranged if required. Confirmation of past history of varicella or of antibody protection against this infection will be relevant if this vaccine is not included in the routine schedule.

Physical examination should include a search for extra-intestinal manifestations of IBD (skin for erythema nodosum or pyoderma gangrenosum, joints for arthalgia/arthritis and mouth for ulceration or lip swelling), documentation of oedema, anaemia and clubbing, and comprehensive examination of abdomen and perianal region. The abdomen should be examined for signs of organomegaly, tenderness and mass. Perianal region should be examined for signs of skin tags, fissures, fistulas or collections. Examination of lower spine and ileo-sacral region may be relevant if back pain is a feature.

In addition, to these undertakings a close examination of growth and nutrition is also relevant. This should begin with detailed examination for nutritional deficiencies, such as anaemia, oedema and skin changes. Current weight and height measurements should be recorded and plotted on a standard age-appropriate growth chart. BMI should be calculated. Retrieval of past weight and height measurements is often helpful to fully document the child's growth history and patterns over time. These measurements can be used to calculate recent height velocity. Parental and family growth patterns are also important to define. In peri-pubertal children Tanner stage should be documented to clearly define current pubertal status. Establishment of the child's current bone age (using radiograph of the child's left wrist) will be helpful in interpreting any linear growth delay.

7.3 Initial investigations

The first investigations in the setting of possible UC include the collection of multiple stool samples for microscopy and culture to exclude enteric infection. Testing should include the request for specific organisms including *Clostridium difficile*. Further tests should include blood tests for serum markers of inflammation (as per below section), and stool inflammatory markers (see below section) if available.

Other tests may be indicated in the initial work-up depending on the clinical context – two further examples are investigations for possible Coeliac disease (tissue transglutaminase and total immunoglobulin A) and tests for pancreatitis (amylase and lipase).

If infection is excluded and the results of initial tests indicate inflammatory events, then endoscopic assessment should next be undertaken. International guidelines recommend colonoscopy (with terminal ileal intubation) and upper gastrointestinal endoscopy for the assessment of possible IBD in children. Multiple biopsies from all segments of the upper and lower gut are required to ensure full assessment of the GI tract.

Assessment of the small bowel is also required to exclude the presence of small bowel CD and to distinguish from UC. The preferred test in many centres is now small bowel magnetic resonance imaging (MRI), known either as MRI enterography or small bowel series MRI. This modality has better sensitivity and specificity than some other modalities that been used in the past, such as barium meal and follow-through or technetium-labelled white cell scan. Capsule endoscopy and positron-emission tomography (PET scanning) also have high test utility, but remain less available or more expensive options at present.

7.4 Further baseline assessment after confirmation of UC

Other baseline testing should include assessment of renal function (serum urea and creatinine), liver chemistry (Bilirubin, ALT, AST, GGT, ALP and albumin), electrolytes and minerals (sodium, potassium, chloride, calcium, phosphate, magnesium and zinc), and nutritional or absorptive markers (iron, ferritin, vitamin B12, folate and Vitamin D).

Serological markers may be helpful in differentiating between CD and UC if these are available. The presence of anti-neutrophil cytoplasmic antibodies (p-ANCA) is more common in UC, whereas anti-*Saccharomyces cerevisiae* antibodies (ASCA) are more frequently found in CD.

It also may be appropriate to define TPMT activity at the time of baseline assessment, so that this result is available in the event of future prescription of thiopurines.

7.5 Endoscopic and histologic features of UC

The typical endoscopic appearance in UC is of confluent disease extending proximally from the rectum for a variable distance. Ulcers, erythema, loss of normal vascular pattern, granularity, increased friability and the presence of pseudopolyps are common findings (**Figure 1**). An absence of skip lesions is one aspect to assist in excluding CD. Although rectal sparing is typically seen as a feature of CD, some authors have suggested that this may be present in UC (Rajwal et al 2004).

Histologically, typical changes of UC include a continuous pattern of acute and chronic mucosal inflammation, with crypt distortion, crypt abscesses, and goblet cell depletion. The absence of granulomas or of patchy changes helps to exclude from CD.

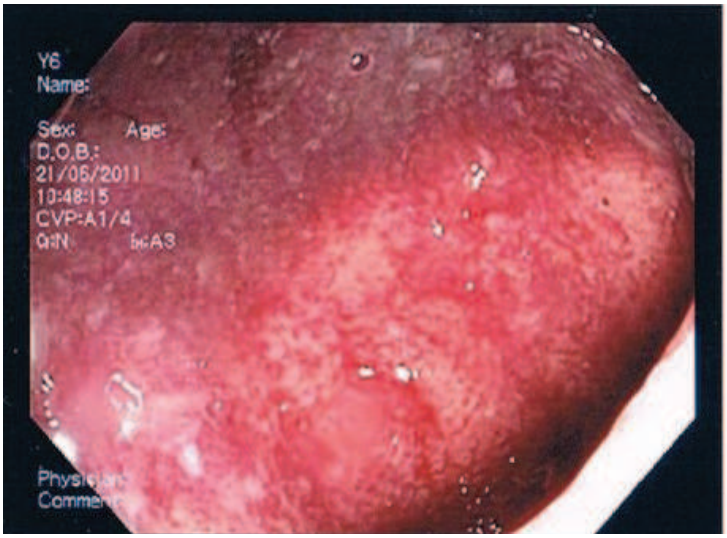

Fig. 1. Typical endoscopic appearance of severe colitis, with loss of normal mucosal vascular patterns, oedema, friability and ulceration

7.6 Radiologic findings in UC

As mentioned above, examination of the small bowel should be included as an essential part of the work-up for likely IBD. The principal rationale is to define the extent or presence of small bowel CD, which may not be evident on standard endoscopic assessment. In UC, the small bowel radiology assessment would be expected to be normal.

Plain abdominal radiographs may show changes of colitis in UC, with thumb-printing, wall thickening or featureless mucosal surface. Plain radiographs should also be considered in the assessment of fulminant (acute severe) colitis where abdominal tenderness or distension is present to ascertain if toxic megacolon is present. Abdominal ultrasound may also be used to define colonic wall thickening and due to improved sensitivity is being considered more.

In the event of incomplete colonoscopy (such as in the settings of colonic stricture or very severe mucosal disease), imaging may be helpful to confirm the proximal extent of the colonic involvement. Magnetic resonance imaging or labelled white cell scans may be

helpful. Barium enema examinations can be considered if other tests are not feasible or are unhelpful, but are no longer first-line investigations in children.

7.7 Differentiation between CD and UC

A full assessment is important to definitively establish a diagnosis of IBD and also to assist in distinguishing between UC and CD. Almost two thirds of children with CD have upper gut and/or small bowel changes at diagnosis. These may be the only locations of disease, or may help to delineate the diagnosis in the setting of pan-colitis where there are no other defining features of UC or CD present.

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) established the Porto criteria in 2005 (ESPGHAN 2005). This consensus statement provided a set of recommendations for the key elements for the diagnosis of IBD and also considered the important features to distinguish between CD and UC. A Spanish group has subsequently reviewed a cohort of 108 patients according to the application of the Porto criteria (Martin De Carpi et al 2011). Overall they noted that these criteria had been followed in 49% of the children (with a higher percentage after the publication of the criteria than prior to this). Ileocolonoscopy was undertaken in 85.2% of children with multiple biopsies obtained. Upper endoscopy was undertaken in 39% of children prior to and 72% of the group after the publication of the Porto criteria. These authors noted that the introduction of the criteria lead to a change in clinical practice.

A report from a NASPGHAN working group considered the key elements in differentiating between UC and CD in children or adolescents (NASPGHAN 2007). This report aimed to address controversies in the assessment of IBD in children and to develop an algorithm to enhance practitioner agreement and consistency in the diagnosis and classification of CD and UC. Clarification of the features of IBD-Unclassified (IBDU) was also undertaken.

8. Inflammatory markers and disease activity in paediatric UC

8.1 Assessment of disease activity: Pediatric UC Activity Index

Recently the Pediatric UC activity index (PUCAI) has been developed as a standardised measure of activity in children with UC (Turner et al 2007). A well-defined process was used to identify six critical elements (from an initial group of 41 variables). These six variables are abdominal pain, rectal bleeding, stool consistency, nocturnal stools, number of stools each 24 hours and interruption to normal activities. The PUCAI correlates closely with other indicators, such as physician global assessment and endoscopic scores (Turner et al 2009). This validated score, which is simple and non-invasive, can now be used to assess disease activity and to monitor changes in activity following intervention. It can also be used to guide management decisions, such as in the context of acute severe UC.

8.2 Relapse and remission in paediatric UC

UC tends to follow a relapsing and remitting course, with periods of disease control interrupted by relapses or flares of symptoms. Active disease in children with UC can be defined in terms of symptoms, serum or faecal markers of inflammation and increased mucosal inflammatory changes. In contrast, remission in children can be defined clinically or symptomatically (resolution of symptoms), biochemically (normalisation of abnormal inflammatory markers) and histologically (mucosal healing). Mucosal healing is

increasingly recognised as an important goal in the initial management of IBD, especially in children with many years of disease ahead of them. Attaining mucosal healing may in turn lead to modification of the long-term disease course in UC (Colombel et al, 2011). Although mucosal healing is now seen as an ideal state, in terms of long-term outcomes, this degree of monitoring requires repeated endoscopic and colonoscopic assessment, which is often not feasible or possible in children.

8.3 Standard serum inflammatory markers

Standard serum markers of inflammation include ESR, CRP, platelets and albumin. These markers are easy to measure in most routine clinical laboratories, but tend to have low specificity and sensitivity for gut inflammation in children with UC. Mack et al measured ESR, platelet count, albumin level along with haemoglobin in 134 children with newly diagnosed UC (Mack et al 2007). All four of these markers were normal in 54% of the children with mild UC, whilst 4.3% of those with moderate-severe UC had normal tests. ESR was the most useful test in this cohort. In addition, disease extent was linked with the number of abnormal tests.

In a small cohort of 30 children with diagnosed with UC at Sydney Children's Hospital (Sydney, Australia), 54% had elevated ESR, whilst platelets were elevated in 13%, CRP high in 29% and albumin abnormal in 33% (Day et al, unpublished data). There was no correlation between disease location and the number of abnormal results in this group.

In a further, recently reported, cohort of 102 Canadian children with newly diagnosed UC, CRP levels were found to be elevated in 41% of those with mild disease and 60% of those with moderate-severe disease (Tsampalieros et al 2011).

8.4 Faecal markers of inflammation

Stool samples can be used to measure various markers of gut inflammation. The presence of faecal white cells can indicate the presence of gut inflammation but are also present in various enteric infections. Faecal white blood cells may be degraded if the sample is not viewed promptly. Elevated levels of faecal α-1-antitrypsin, a protein that is stable in stool, can reflect mucosal inflammation as a breach of the epithelium may lead to a protein losing state. Neither of these indicators has adequate sensitivity and specificity.

Other faecal markers of inflammation include calprotectin, S100A12, and lactoferrin. Although these three markers are not yet universally available, they provide a less-invasive method to assess gut inflammation. Normalisation of these markers can be used as markers of the success of therapy. Each of the measures can be used to assess the response to therapeutic intervention in children with UC. Calprotectin can also be helpful in assessing the risk of subsequent relapse of disease (Costa et al 2005).

9. Principles of management of UC in children

The overall aims of management of UC in children and adolescents are to control inflammation and to maintain remission, whilst ensuring that the child has normal growth and development. Ongoing inflammation will likely adversely impact upon growth in children and adolescents.

As well as optimising growth, management should ensure normal pubertal development, and normal social and psychological health. Treatment side-effects must be avoided or

minimised: especially those side-effects that may in turn interfere with growth and development. Thus, therapeutic choices must be seen in the context not just of the child's current disease status and disease location, but also in terms of growth, puberty, bone health, family setting, and psychological wellbeing. In addition to the critical importance of growth and nutrition in children, it is also crucial to ensure the avoidance of side effects in children who will face many years of disease and exposure to medications. One other element of the long term nature of these diseases, when commencing in childhood, is that reduction and control of the disease burden may help to avoid long-term disease related complications. One example of this is the increased risk of colonic cancer seen in the setting of long-standing colitis (colitis associated carcinoma), especially when uncontrolled.

Due to the complex medical and social issues involved in the management and treatment of children and adolescents with CD or UC, care should be provided in a multi-disciplinary manner. In addition to the management of medical aspects by specialist paediatric gastroenterologists, universal attention must be paid to many other issues. These include growth and nutrition, normal development, attention to schooling and learning, psychosocial issues, coping and adjustment issues, and general well-being. In addition to the various direct effects of chronic UC upon the child or adolescent patient, these chronic illnesses may also impact adversely upon siblings and parents.

These wide ranging and important issues mean that many key non-medical personnel also should be closely involved in the care of these children. These individuals include nursing staff (to provide key liaison and coordination roles), dietitians (growth and nutrition), social workers and psychologists (psychosocial and coping aspects). Paediatric surgeons, pathologists and radiologists experienced and skilled in relevant aspects of paediatric UC also comprise key personnel contributing to the care of children with UC. The child's general practitioner also plays an important role in the care of these children. Thus the management of all children with CD or UC should be facilitated within a context that provides access to each of these professionals. The system of care needs to be able to provide coordination of services, with good clear lines of communication between personnel.

Further to the personnel requirements for an environment caring for children with CD and UC, appropriate support is also necessary. This includes adequate administration support (such as secretarial, outpatient booking staff and medical record staff), along with adequate record and database systems. This may include systems to ensure regular checking of required blood tests, or annual blood tests, or providing for clear records of complications or events. This might include the use of diagnostic checklists, pre-clinic review meetings, proformas for clinic review and systems to ensure regular monitoring requirements. These database and record keeping resources will provide for smooth seamless clinical management, and also for eventual transition to adult services and audit or research activities.

A further key principle in the management of children with UC is that care needs to be firmly family focused. A child with UC needs to be seen in the context of their family. Parents and sometimes siblings will attend outpatient appointments with their child. Parents and the patient will be together involved in decision making or consideration of therapeutic choices. Furthermore, parents and the patient's siblings will be directly and indirectly affected by the child's condition.

10. Medical management of paediatric UC

10.1 Induction and maintenance of remission in UC

The therapies proven to have roles in the induction of remission of active UC in children are less numerous than those available for CD. Overall therapies can be considered as those used to induce remission and those used to maintain remission (**Table 1**).

INDUCE REMISSION	MAINTAIN REMISSION
Corticosteroids	Corticosteroids (especially topical)
ASA	ASA
Tacrolimus (or cyclosporin)	Azathioprine / 6-mercaptopurine
Infliximab	Methotrexate
?Adalimumab	?Tacrolimus
	?Infliximab

Table 1. Standard Therapies for UC in children and adolescents

As in CD, the goal in the long term management of UC in children is to maintain remission and control of disease, along with ensuring optimisation of normal life events, whilst ensuring that medical therapy does not lead to adverse consequences.

CS are most commonly used to induce remission, although ASA may have a role in mild disease. Tacrolimus, cyclosporin and infliximab may have roles in severe UC, as second line (rescue) therapy. Two therapies that have roles in paediatric CD (exclusive enteral nutrition and antibiotics) probably do not have roles in UC.

5-ASA drugs often comprise the initial therapy used to maintain remission in childhood UC. When disease is not well-controlled with ASA drugs, then immunosuppressives would be indicated. Thiopurines (azathioprine or 6-mercaptopurine) are more often utilised, but methotrexate also has a role. Tacrolimus may also have benefits as a maintenance drug to keep control.

10.2 Corticosteroids

CS can be utilised in various routes for active UC. Oral CS in mild to moderate UC may lead to more rapid improvements than those seen in CD. CS (including topical delivery) may have roles in maintenance of remission.

Standard CS therapy to induce remission involves oral prednisone or prednisolone with once daily dosing in the morning (doses as per **Table 2**). Budesonide, which has advantages over prednisone with less systemic absorption and side-effects, has been demonstrated to have a role in the management of ileal CD. The role of budesonide in the management of UC has been considered in several studies. Three of these studies were reviewed together in a recent Cochrane review: budesonide was shown to not be helpful for UC (Sherlock et al 2011). Interestingly, however, budesonide as a MMX preparation was shown to be helpful in a study reported in abstract form at Digestive Diseases Week 2011 (Sandborn et al 2011).

IV Steroids	2 mg/kg/day (max 40 mg/day) once daily in morning (starting dose, then wean as appropriate)
Budesonide	6-9 mg/day (then wean as appropriate)
IV Steroids	Hydrocortisone 2-4 mg/kg/day (q6h); Methylprednisolone 1-1.5 mg/kg/day (q12h)
Sulphasalazine	50-60 mg/kg/day (up to 3-4 grams daily)
5-ASA	30-50 mg/kg/day
Azathioprine	Start 1 – 1.5 mg/kg/day, Increase to approx 2.5 mg/kg/day (max 200 mg/day)
6-MP	Start 1 mg/kg/day, increase to around 1.5 mg/kg/day
Methotrexate	15 mg / m2 (max 25 mg) weekly subcutaneous injection
Tacrolimus	Commence at 0.1 mg/kg/day in 2 divided doses orally
	Usual dose 0.2 mg/kg/day in 2 divided doses (ongoing dose dependant on levels)
Cyclosporin	3-8 mg/kg/dose Q12H

Table 2. Standard doses for drugs used in Paediatric UC

Severe UC often requires the administration of IV CS. Typically this would be given as methyprednisolone, with one or two doses daily, or six-hourly hydrocortisone. Methylprednisolone has the advantage of less mineralocorticoid effects.

One study from Japan has evaluated pulse steroid therapy in children with UC (Kudo et al 2011). This group retrospectively compared outcomes from children with UC treated with conventional methylprednisolone dosing to another group treated with megadose pulse therapy (20-30 mg/kg/day, to max of 1000 mg). Pulse therapy lead to more rapid response, with quicker reduction in PUCDAI scores, without any increase in side-effect profile. Pulse therapy, however, did not alter outcomes over the first 12 months after diagnosis compared to standard therapy. This retrospective data in a small group of patients would require replication and confirmation before broader use of this approach. Other data looking at larger doses of corticosteroids have not suggested benefits.

Topical CS is more often helpful in distal UC, where it has advantages of less systemic absorption and being directed straight to the area of inflammation. Steroid suppositories may be helpful in very distal disease, whereas enemas or foam preparations may have effects in left-sided disease. In these instances, topical CS may have benefits in treating active disease and in maintaining control. However, children may not tolerate the per-rectal administration route.

10.3 Amino-salicylates

This group of therapies includes sulphasalazine and the 5-aminosalicylate (5-ASA) drugs. Delivery routes include oral and rectal (suppository or enema). Packaging of the 5-ASA

drugs can provide distribution of the drug at different locations in the gastrointestinal tract. More recent variations of the 5-ASA drugs enable once daily dosing with equivalent efficacy to multiple dosing regimens.

These drugs have roles in the induction and maintenance of remission in UC (Ford et al 2011). Although there are many studies demonstrating efficacy of 5-ASA agents in adults with UC, there are few in children or adolescents. One study demonstrated 80% clinical remission with sulphasalazine at 1, 2 and 3 months and lower response to olsalazine at the same time points (Ferry et al. 1993).

10.4 Thiopurines

Azathioprine or 6-mercaptopurine are the most commonly used immunosuppressives in paediatric IBD. Although well-established as agents that modify disease course in children with moderate-severe CD when used early, there has been little data in paediatric UC. Seventy-five percent of a group of 32 children with UC in a British series received azathioprine (Howarth et al 2007). Recently a prospective multi-centre study evaluated the outcomes of thiopurines in paediatric UC (Hyams et al 2011). This report included 394 children with UC recruited at diagnosis from paediatric centres in USA. One hundred and ninety seven of this group received thiopurines (half within the first 3 months of diagnosis). Due to difficulties in follow-up or other reasons, just 133 of this cohort were re-evaluated after 12 months. Sixty-five of these 133 children were in remission at this time, without CS or rescue therapy.

10.5 Methotrexate

Methotrexate is also well established a second or third line agent for the maintenance of remission in CD. Only recently, however, has it also been considered for the maintenance of remission in UC. Two clinical trials are assessing the role of methotrexate in adult UC (Carbonnel 2011). A recent retrospective report described the outcomes of methotrexate in a group of Canadian children with UC (Willot et al 2011). Four of the 16 children with UC or IBDU were in remission after six months of methotrexate therapy. A further report from Italy evaluated 32 children with UC who were treated with methotrexate (Aloi et al 2010). Response or remission was seen in 72% of the children by 3 months, with 50% at 12 months. Almost all of the children receiving steroids at the start of therapy were able to cease steroids by six months. Both these studies, however, were retrospective assessments of this drug in relatively small cohorts. Prospective studies are required to clarify the role of methotrexate in paediatric UC.

Methotrexate is given as a once weekly subcutaneous injection. Six weeks is usually expected before onset of action, and sixteen weeks would be required before expecting the benefits of the drug. Folate supplementation (but not on the day of methotrexate administration) is required to prevent folate deficiency – this also may decrease upper gut side-effects.

10.6 Infliximab and adalimumab

The anti-Tumour necrosis factor-(TNF) alpha inhibitor Infliximab has been evaluated in adult and paediatric UC.

A recent report demonstrated the benefits of infliximab in paediatric UC (Hyams et al 2010). The outcomes of 52 children recruited prospectively across several sites in USA were

followed for a median of 30 months. CS-free remission was seen in 38% of these children at 12 months, with remission in 21% after 24 months. After 2 years of followup, 39% of this group had undergone colectomy. An Italian study has also reviewed their experience with infliximab in children with UC (Cucchiara et al 2008). These 22 children had been treated with infliximab using a three dose induction course and ongoing maintenance dosing (eight weekly). Some of the children had acute severe colitis with no response to CS, whilst others had a protracted course with/without CS dependency. Overall, 12 of the 22 children had full response with CS-free remission after 12 months and 6 others had partial response. Seven children required colectomy (only one during the acute period).
A report in adults with UC unresponsive to CS demonstrated that adalimumab is also safe and effective in this context (Reinisch et al 2011). However, there is not yet data looking at adalimumab or other biologics in paediatric UC.

10.7 Tacrolimus and cyclosporin (CSA)

These calcineurin inhibitors are most typically used as rescue therapy in acute severe UC. Although CSA is favoured in adult protocols, tacrolimus has advantages of oral administration, quicker onset of action and a more tolerable side-effect profile. In the context of acute severe UC, tacrolimus can be used a bridge to allow the introduction of long-term immunosuppressive therapy (such as azathioprine). In addition, tacrolimus may have a role in the management of grumbling colitic symptoms and/or as a longer-term drug to maintain remission.
Tacrolimus was evaluated in an open label multi-centre study as rescue therapy in children with UC (Bousvaros et al 2000). Two thirds of the 14 children responded, but less than half had long-term remission. More recently, a cohort of 46 children managed with tacrolimus was reviewed retrospectively (Watson et al 2011). Ninety-three percent of this group were discharged without requiring colectomy, and the probability of colectomy after tacrolimus therapy was 40% at 26 months. Side-effects in this cohort included hypertension, headaches, seizures, tremor and nephrotoxicity. Although not reported in this cohort, hypomagnesaemia is a further common side-effect. Tacrolimus therapy requires close monitoring of serum levels (aim to achieve 8-10 initially), with ongoing close monitoring of renal function, electrolytes, blood pressure, blood sugar and urinalysis. Magnesium supplementation may be required.

10.8 Exclusive enteral nutrition

This therapy involves the exclusive administration of a liquid diet for 6-8 weeks as sole therapy to induce remission. This therapy is well established as standard induction therapy for newly diagnosed CD in children. Although this therapy has benefits in colonic CD, there is less evidence for a role in UC.

10.9 Novel therapies for UC

Along with the roles of standard medical and surgical therapies has been increasing interest in novel therapies. Foremost of these is probiotic therapies. There is convincing animal and human evidence indicating that modifications to the intestinal flora can prevent or modulate gut inflammation. Recent studies have focused on VSL#3, a high-potency probiotic mixture, in adult and paediatric UC. A recent Italian study in adults with UC demonstrated that

VSL#3 supplementation was safe and effective, with reduction in disease activity scores and symptoms (Tursi et al 2010). An earlier paediatric study evaluated the same probiotic therapy in 29 children with newly-diagnosed active UC using a randomised placebo-controlled design (Miele et al, 2009). Remission was observed in 93% of the children treated with VSL#3, compared to 36% of those who did not receive the probiotic. Less children receiving the probiotic relapsed over the followup period, and no adverse effects were attributed to the probiotic. It is not clear if these findings are specific to VSL#3, or able to be achieved with other probiotics, but are clearly encouraging as a safe and effective therapy for UC.

11. Severe acute colitis

Several recent publications have highlighted key aspects of acute severe colitis in children. Most important of these was a prospective multi-centre study conducted in North America (Turner et al 2010a). This study included 128 children admitted to one of 10 centres for severe UC – both as initial presentation and as subsequent relapse of disease. These children were assessed serially in terms of clinical and laboratory findings, disease activity scores and outcomes, both during hospitalisation and for up to 12 months subsequently. All children were treated with intravenous corticosteroids as initial therapy. Thirty-seven children did not respond to corticosteroids: these children proceeded to receive secondary medical therapy (cyclosporin or infliximab) or underwent colectomy. Overall 9% of children had colectomy by discharge and 19% required this by 12 months follow-up. PUCAI scores calculated during hospitalisation in all children were predictive of response and outcomes. A score of greater than 45 on day 3 of admission predicted lack of response to corticosteroids. In contrast a score of greater than 70 on day 5 guided the start of rescue therapy.

Serial stool samples in this cohort of children were analysed for a suite of faecal inflammatory markers (Turner et al 2010b). All four of the markers (calprotectin, S100A12, M2PK and lactoferrin) were greatly elevated in these children. M2PK provided the best predictive value for response to corticosteroids. However, none of these markers performed better than the PUCAI in this context. A further assessment of a subset of samples from this group of children evaluated faecal osteoprotegrin (OPG): when measured at day three faecal OPG was a good predictor of response to corticosteroids (Sylvester 2011). This marker has previously been evaluated in children with CD (Nahidi et al 2010).

More recently a consensus statement from key European groups has been prepared (Turner et al 2011). This document outlines key recommendations and management pointers for acute severe colitis in children (**Table 3**).

1. Stool evaluation should include standard culture and specific screening for *C difficile*
2. CMV infection should be excluded endoscopically in children with steroid resistant disease
3. Disease activity should be monitored regularly during admission, with frequent assessment of vital signs, completion of PUCAI scores daily and monitoring of key blood tests (ESR, full blood count, albumin and electrolytes) at admission and at subsequent intervals

4. Initial treatment should be with intravenous corticosteroids, with methylprednisolone (1-1.5 mg/kg/day, to max of 60 mgs as 1 or 2 daily doses) favoured due to less mineralocorticoid effect.
5. Antibiotics are not indicated routinely but should be considered when sepsis suspected or when toxic megacolon present
6. There is no evidence for the routine use of prophylactic heparin to prevent thromboembolic events
7. 5-ASA therapies should be interrupted at admission in known patients, or introduction delayed in newly diagnosed patients
8. Regular diet should be continued, but nutritional support (enteral or parenteral) considered if inadequate oral intake. Oral intake should be ceased when surgery imminent and is contraindicated in toxic megacolon.
9. Complications (such as perforation or toxic megacolon) should be considered in children with increasing or severe pain. Narcotics or non-steroidal anti-inflammatory drugs are not recommended in the setting of acute severe colitis.
10. PUCAI scores can be used to monitor response and the need for secondary therapy. A score of >45 at day 3 indicates likely poor response to corticosteroids and a need to prepare for rescue therapy. A score of >65 on day 5 indicates a need to commence rescue therapy on that day. In children with PUCAI scores of between 35 and 60 at day 5, steroids can be continued for a further 2-5 days before secondary therapy should be considered. Children with scores of less than 35 points on day 5 are not likely to require rescue therapy
11. Plain radiographs of the abdomen should be obtained in any child with clinical signs of toxicity and subsequently as indicated. The diagnostic criteria for toxic megacolon comprise radiological evidence colonic dilatation (>=56 mm) along with signs of toxicity. Urgent surgical review is required in all children with toxic megacolon. Conservative management is appropriate if the child has stable vital signs and there are no signs of sepsis. If signs of toxicity worsen, then immediate colectomy should be undertaken. Rescue medical therapies are not indicated in the setting of toxic megacolon.
12. Rescue therapies include medical (infliximab or calcineurin inhibitors) and surgical (colectomy) options.
13. Sequential medical rescue therapies are not recommended in children
14. If colectomy is required in acute severe colitis in children, subtotal colectomy and ilesotomy is recommended. Pouch formation can subsequently be considered.
15. Surgical complications can be reduced by avoiding delays in colectomy to enhance nutrition or to wean corticosteroids and the use of perioperative broad spectrum antibiotic coverage.

Table 3. Recommendations from Consensus statement for the management of acute severe colitis in children (abridged from reference: Turner 2011)

12. Surgical management

Colectomy may be required during childhood in children with UC. Indications include fulminant UC unresponsive to medical therapy, severe colitis complicated by toxic megacolon and/or perforation, chronic colitis unresponsive to medical agents and when pre-cancerous changes develop. One retrospective study has assessed clinical factors that might help in prognosticating the risk of colectomy (Moore et al 2011). In a cohort of 135 children with UC, these authors showed that white blood count and haematocrit values at diagnosis were associated with colectomy at 3 years. A UC Risk Score was derived from these measurements. Risk assessment such as this required further prospective assessment in large numbers of children.

Colectomy may be followed by ileal pouch formation as one or more steps. A two-step procedure might include colectomy and end-ileostomy initially followed by pouch formation. A new pouch may be protected by a defunctioning ileostomy, which is subsequently reversed (third step). Pelvic dissection in young individuals, as required for total colectomy, may be complicated by disruption to pelvic nerves and consequent effects upon fertility.

A condition known as pouchitis may complicate an ileal pouch. Probiotics can be used to prevent or treat pouchitis. Antibiotics (e.g. metronidazole) are also useful for pouchitis.

The outcomes of surgical management of UC in children have been considered in some recent reports. Newby et al reported that 17.6% of 72 children with UC underwent 1 or more major operations over the period of study, with a mean time of 1.92 years to the first procedure (Newby et al 2008). Fraser et al (Fraser et al 2010) retrospectively compared the outcomes of laparoscopic and open colectomy in a group of 44 children aged up 18 years of age. Twenty-seven of this group were diagnosed with UC – the remainder had various other surgical diagnoses. There were no differences between the technique in terms of postoperative abscess or sepsis, would infection of small bowel obstruction. The children having laparoscopic ileoanal reanastomosis and pouch formation had less pouchitis than those having open pouch formation ($p=0.03$).

A second study (Lillehei et al 2010) evaluated QOL scores in children undergoing proctocolectomy and pouch formation. The children with UC and their parents reported low QOL scores pre-operatively that improved substantially with resection. This report did not evaluate other aspects of the outcomes of surgical intervention.

13. Transition of adolescents with UC to adult services

One of the last components of the management of adolescents with UC is preparing them for the move on from paediatric care to adult care. This transition is increasingly recognised as an important step in the overall management of young people with chronic diseases, such as UC (Viner 2008). The move from a family-focused multi-disciplinary model of care in the paediatric setting to the adult setting that typically features an individual-focused approach that may be office based and more rigid, with expectations of patient involvement. Preparation for this transition can include review of understanding of medications, knowledge of key aspects of disease management, and practical aspects of health care (such as renewal of scripts, learning how to organise appointments and health benefit applications if appropriate). A successful transition should lead to a more confident young person able to

better care for their own health and willing to take charge of their care. Further, it should also mean that less young people "fall between the cracks", and ultimately lead to better quality of life and health outcomes.

14. Conclusions

Children and adolescents should be considered a distinct and special group of patients with numerous important clinical features, and with particular management needs and requirements. At this point in time, genetic evaluation is not part of routine clinical management. In time, however, analysis of mutations in key relevant genes will likely be considered routine. Such developments will serve to further differentiate paediatric UC from the condition in older individuals and perhaps will also assist in defining clinical subgroups that may indicate specialised therapeutic needs and/or provide key prognostic information.

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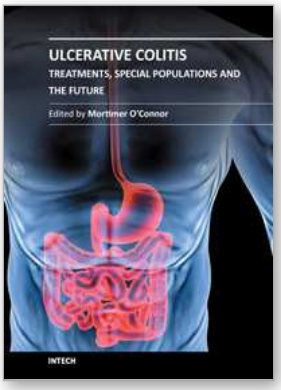

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This book is intended to act as an up to date reference point and knowledge developer for all readers interested in the area of gastroenterology and in particular Ulcerative Colitis. All of the chapter authors are experts in their fields of publication and deserve individual credit and praise for their contributions to the world of Ulcerative Colitis. We hope that you will find this publication informative, stimulating and a reference point for the area of Ulcerative colitis as we move forward in our understanding of the field of medicine.

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