Retrospective study recommends endoscopy when diagnosing lymphocytic colitis or eosinophilic gastrointestinal disorder in children with abdominal pain

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Title:
Retrospective study recommends endoscopy when diagnosing lymphocytic colitis or eosinophilic gastrointestinal disorder in children with abdominal pain

Short, running title:
Severe recurrent abdominal pain in children

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The authors have no conflicts of interest to declare.

ABSTRACT
Aim: This study assessed the prevalence, clinical presentation and outcome of lymphocytic colitis (LC) and eosinophilic gastrointestinal disease (EGID) in children with severe, recurrent abdominal pain (RAP), by describing the predominant symptoms, diagnostic approaches and treatment options.

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Methods: We performed a retrospective follow-up study at a Danish regional hospital by reviewing the histology reports of the children who had undergone gastrointestinal endoscopy for RAP. Data were retrieved from the medical records of those who met the diagnostic criteria for LC and, or, EGID from 2011-2016. The study population comprised 381 patients who underwent a diagnostic process to clarify RAP.

Results: A total of 74 patients (39 females) aged 2-17 years, with severe RAP as the most predominant symptom underwent gastrointestinal endoscopy. This identified 16/74 (21.6%) with LC (n=6) and, or, EGID (n=11), which equated to 4.2% with RAP. No biochemical patterns of abnormalities were found. Medical treatment and, or, diet generally induced and maintained clinical remission.

Conclusion: We found 16 children with LC and, or, EGID. The predominant symptom was severe RAP. All patients had a macroscopically normal mucosa at endoscopy, a specific histopathological feature and no characteristic biochemical findings. Endoscopy should be considered in these cases.

Keywords: Eosinophilic gastrointestinal disease, Histopathology, Lymphocytic colitis, Paediatric, Recurrent abdominal pain.

Abbreviations:
LC: Lymphocytic colitis
EGID: Eosinophilic gastrointestinal disorder
RAP: Recurrent abdominal pain

Key Notes
- This study assessed lymphocytic colitis (LC) and eosinophilic gastrointestinal disease (EGID) in 381 children aged 2-17 years with severe, recurrent abdominal pain (RAP).
- Of the 381 patients who underwent gastrointestinal endoscopy, 16/74 had LC (n=6) and, or, EGID (n=11), which equated to 4.2% with RAP.
• Endoscopy should be considered in such cases, as all patients had macroscopically normal mucosa, a specific histopathological feature and no characteristic biochemical findings.

INTRODUCTION

Abdominal pain in children is a common paediatric issue and a prevalence of 71.1% has been reported in children and adolescents aged 3-17 over a three-month period (1). Recurrent abdominal pain (RAP) refers to a period of at least three months with episodes of pain that are severe enough to affect daily activities of the affected individual (2). With advances in medical technology and a better understanding of the pathophysiology of abdominal pain, more and more organic causes may be identified. The severity and frequency of pain is not related to aetiology. However, the most common cause of RAP in children is still of functional origin (2,3).

It has become apparent that microscopic colitis and eosinophilic gastrointestinal disease (EGID) may cause gastrointestinal symptoms in children, such as abdominal pain and diarrhoea. Microscopic colitis covers collagenous colitis, lymphocytic colitis (LC) and paucicellular colitis.

Chronic inflammation in the lamina propria is a mandatory finding in microscopic colitis. LC and paucicellular colitis are characterised by an increase of intraepithelial lymphocytes in the surface epithelium. Collagenous colitis is further characterised by a thickening of the subepithelial collagen band (4,5). The clinical features of the microscopic colitis subtypes are indistinguishable, characterised in adults by chronic relapsing non-bloody watery diarrhoea, abdominal pain, weight loss and a macroscopically normal or slightly oedematous mucosa in the colon.

Primary EGID represents eosinophilic infiltration of the gut wall in the absence of known causes. The symptoms of EGID are not disease-specific. Patients most commonly report abdominal pain, but may also experience nausea, vomiting, poor appetite, weight loss and diarrhoea at the time of diagnosis. Previous studies have reported that EGID is a rare disorder in children, with a prevalence of 28 per 100,000 (6) and an unknown prevalence of microscopic colitis, possibly due to limited research (7,8).
Detection, diagnostics and treatment are important, but low levels of awareness of microscopic colitis and EGID may lead to delayed diagnosis and thus a prolonged course of disease and a decreased quality of life for the affected children and their families.

The aim of the present study was to assess the frequency of microscopic colitis and EGID in children with recurrent and chronic abdominal pain, with or without diarrhoea, by describing the predominant symptoms, diagnostic approach and treatment options.

METHODS
We performed a retrospective cross-sectional study in a paediatric outpatient clinic at Børnelægeklinikken v/Karen Tilma, Northern Region, Denmark. The study population consisted of 381 patients referred to the clinic from general practice for evaluation of chronic RAP during the study period 1 December 2011 to 30 December 2016. They underwent a diagnostic process, appropriate for their age, which was based on the steps outlined in Table 1. In 74 patients, the following conditions were excluded as reasons for RAP: other inflammatory bowel disease, infection, infestation, psychosomatic issues, presumed functional abdominal pain, helicobacter pylori, celiac disease, congenital lactose intolerance, malformations, metabolic disorders, constipation, malignancies, abdominal migraine, food allergies and adverse drug effects. Due to unexplained severe RAP that compromised their daily life, these patients underwent gastroscopy and colonoscopy at a surgical department. Despite normal macroscopic appearance of the mucosa, biopsies were obtained and investigated at a pathological department.

Furthermore, enzyme activity testing of duodenal disaccharides was performed from small bowel tissue samples. This clarified any occurrence of lactase deficiency as a possible cause of RAP and any possible association between lactase deficiency and LC or EGID (9). Samples were evaluated at a biochemical department. Abnormal level of lactase was defined as below 15.0 units when defined by myM/min/g protein. This practice had not been implemented as a routine examination at the start of the study period, hence, data is not complete due to incomplete testing. As awareness increased, this was made a routine examination in the hospital endoscopy department. Biopsies were obtained...
from multiple areas of the gastrointestinal tract to increase the detection rate, even in cases of macroscopically normal mucosa (4,10).

We reviewed the histology reports of patients undergoing endoscopy for RAP and recorded results of endoscopy, age, gender, histopathological findings, enzyme activity testing and genetic lactase deficiency tests.

From the medical records of patients meeting the diagnostic criteria for LC and EGID, we recorded multiple variables: relevant symptoms, date of diagnosis, cause of referral, comorbidity, gender, age, treatment, including medication, clinical course, biochemical data, results of endoscopy, histopathological findings and enzyme activity test results.

The diagnosis of LC was made according to European Consensus Criteria (4), based on a diffuse increase of more than 20 intraepithelial lymphocytes per 100 surface epithelial cells and an increase of lamina propria inflammatory cells. One of the children had a histological finding of 18 intraepithelial lymphocytes per 100 epithelial cells and the same clinical characteristics and endoscopic appearance. He was included in the study because the European Consensus (4) states that the exact number of intraepithelial lymphocytes needed for diagnosis has not been determined and varies between 10 and 20 per 100 surface epithelial cells, normally ranging between four and ten. In addition, reports suggest that LC, and the incompletely fulfilled criteria for LC, which is called incomplete LC or paucicellular colitis, are so similar in histopathology that intra-observer and inter-observer variability diminishes a clear distinction between these, while LC and non-LC are firmly distinguished (11). Another study suggested classifying LC, collagenous colitis and incomplete LC as one entity, with the same clinical characteristics and treatment effect (5).

The diagnosis of EGID was based on histologic features above 20 eosinophils per high power field, the absence of secondary causes of eosinophilia, such as parasite infections, drug reactions, food allergies and malignancies, and symptoms of the gastrointestinal tract, such as predominantly abdominal pain, diarrhoea or nausea, depending on the location involved (10,12-15).

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In all cases diagnosed with EGID, the histopathological picture was inflammation with eosinophilia above 40 eosinophils per high power field, based on the assessment by an experienced gastrointestinal pathologist.

**Ethical adherence**
The study was conducted according to Danish Law and ethical regulations regarding patient privacy, data security and anonymity. No patients underwent any interventions related to the study, as only retrospective data were collected through medical records without the use of central registries. Data collection was decided by the doctor responsible for the child’s treatment and did not require further formal approval.

**RESULTS**
In the study period, 381 patients referred for evaluation of RAP underwent an age-relevant diagnostic process (Table 1). In 74 patients (19.4%), 39 females, aged 2-17 years, this investigation did not identify the cause, and an endoscopy including biopsies and histopathological examinations was performed. We identified 16 patients with LC (n=6) or EGID (n=11) and one patient had both, first EGID and later LC. This group comprised 10 males and six females with a median age at diagnostic endoscopy of 10.8 years (range 2.9 to 15.1). All 16 patients had a macroscopically normal mucosa. Therefore, the incidence of LC and EGID in patients referred for RAP was 16/381 (4.2%) and the proportion of LC and EGID in patients who underwent endoscopy was 16/74 (21.6%).

Of the 58 patients who underwent endoscopy but did not have LC or EGID, two had oedema and histopathological features of non-specific lymphoid growth in the caecum. One patient had lymphocytic infiltration in the duodenal mucosa and another had a non-specific inflammation in the gastric mucosa. All the others presented with macroscopically normal mucosa.

Biopsies were enzymatically tested in 39 of the 74 patients (52.7%) who underwent endoscopy and these included 10/16 (62.5%) patients with. In the LC and, or, EGID group, 10 patients were
investigated enzymatically (62.5%), revealing 4/10 (40.0%) had absent or insufficient lactase production. In the remaining patients in the endoscopy group, 7/29 (24.1%) had absent or insufficient lactase production. The levels of additional disaccharides, maltase and sucrose were normal. Data from the LC or EGID group concerning diagnosis, histopathology, gender and age are summarised in Table 2.

In the LC or EGID group, the most prominent symptom was severe RAP, with or without diarrhoea, which compromised daily activities. The symptoms at referral are shown in Figure 1, with the distribution illustrated as a percentage of the 16 patients in this group. With regard to abdominal pain, the only patient who did not present with abdominal pain at referral, was the patient who first presented with EGID and then with LC. He initially presented with discomfort and distention and was treated for EGID, but was referred with RAP at a later stage when he developed LC. Therefore, abdominal pain at referral did not reach 100% in Figure 1.

The median duration of symptoms in these 16 patients before the first consultation was 21 (range 1-72) months. There was one patient who had experienced one month of abdominal discomfort, which did not qualify for chronic pain, but the patient had had bloody stools and thus went through an accelerated diagnostic process.

The median diagnostic duration for the LC or EGID group was 205 (range 57-551) days, which covered the time from the first consultation in the paediatric clinic regarding abdominal symptoms until the diagnosis of LC and, or, EGID. The patient’s age at consultation was not correlated to the duration of symptoms (p=0.52).

Biochemistry

All patients presented with normal levels of haemoglobin and inflammatory markers according to their age. Ferritin levels were available in nine patients and below normal in two patients. Peripheral blood eosinophilia was elevated above 0.50*10^9/litres in six patients and within the normal range in 10 patients. There was no difference in duration of symptoms between these two groups,
(p=0.624). We found no differences in blood eosinophils in patients with LC when they were compared to patients with EGID.

Plasma total immunoglobulin E was increased in four patients and within the normal range according to age in the remaining 12 patients. We found no correlation between increased immunoglobulin E and eosinophil counts (p=0.84) or between any clinical features.

Allergies were present in five patients with confirmed specific immunoglobulin E for grass, birch, house mites and dust mites. These patients were all well treated for atopic symptoms during abdominal diagnostics. Standard food allergy tests with specific immunoglobulin E were negative in all patients.

Faecal calprotectin was available for all patients and five patients, four with LC and one with EGID, had slightly elevated levels above 50 microgram per litre, ranging from 65-154.

All LC or EGID patients had a normal lactase gene test of congenital lactase deficiency.

In the non LC or EGID endoscopy group, one Syrian girl had congenital lactase deficiency, but all the others had normal lactase gene test results.

**Treatment effects**

The medical treatment for the six cases of LC was budesonide (Entocort 9mg/50 kg bodyweight per day) for four weeks, followed by weaning off for two weeks leading to clinical remission. One had a relapse after one year and was treated with budesonide again without having a relapse.

Medical treatment for the one case of EGID with inflammation restricted to the colon (n=1) was budesonide (Entocort 9mg/50 kg bodyweight per day) for four weeks, followed by weaning off for two weeks with clinical remission without relapse. Two patients with more widespread EGID were treated with prednisolone (1 mg/kg/day) for four weeks, followed by weaning off for two weeks, also with clinical remission without relapse.
One patient with primary oesophageal EGID was treated with an elimination diet free of milk, eggs, soy and wheat, swallowed budesonide inhalation and proton pump inhibitor, according to recommendations. He had no relief of symptoms, underwent additional endoscopy with findings of eosinophilic inflammation of the caecum and colon and was referred to a tertiary hospital for further treatment.

Three patients with EGID and no lactase activity in the intestinal mucosa were treated with lactrase (Lactaid) or a lactose-free diet with clinical remission without relapse. One patient with EGID was only treated with an empiric elimination diet, since no specific allergen was found, leading to clinical remission without relapse. Two patients with EGID spontaneously remitted without specific treatment.

**DISCUSSION**

**Key findings**

This study reported the findings of 16 children: six diagnosed with LC and 11 with EGID, including one with both entities. The predominant symptom was severe RAP with or without diarrhoea. All patients had a macroscopically normal mucosal appearance at endoscopy, a specific histopathological feature and no characteristic biochemical findings.

LC and EGID are still known as rare diseases (10,16) and microscopic colitis or LC is a fairly recent disease entity, which was first described in the 1970s. As a result, information on the incidence of LC may be underreported. EGID was first described in 1936 (17), but the condition may still be under-diagnosed.

We found a prevalence of 4.2% for LC and, or, EGID in children referred to the paediatric clinic with RAP. Of the 74 patients with RAP who underwent an endoscopy, we found that 21.6% had LC and, or, EGID. Apparently, this is a higher frequency than earlier described (6,7,8).
We found that biochemical markers had no value in the diagnostic process and no correlation to symptoms. All our patients presented with normal haemoglobin levels according to their age, C-reactive protein, erythrocyte sedimentation rate and albumin levels. The ferritin level was slightly decreased in two patients, with no impact on haemoglobin levels.

These findings indicate that normal inflammation markers and haemoglobin levels can be unaffected in the case of LC or EGID, and, therefore, they are of little use as screening factors in the diagnostic process (10). Faecal calprotectin performed poorly as a marker of gastrointestinal inflammation in the patients with LC or EGID in our study and was slightly elevated in five patients, ranging from 65-154 mg/kg. This did not qualify for further evaluation, since regional recommendations state that a faecal calprotectin level below 200 is harmless (18).

Previous studies have suggested that both LC and EGID present in adults with gastrointestinal symptoms and a variety of biochemical indicators and key screening factors. These include allergies, atopy, anaemia, elevated blood immunoglobulin E, elevated faecal calprotectin, peripheral hyper-eosinophilia and hypo-albuminaemia (7,10,12). We could speculate that these might be due to sustained disease, as well as signs of prolonged malabsorption or insufficient food intake.

Because there are no valid biochemical markers that can be used to diagnose LC or EGID, gastroscopy and colonoscopy should be considered in children with RAP when daily life is compromised and their abdominal pain is still unexplained, despite a relevant diagnostic process (Table 1).
In our study, the decision to perform endoscopy might have selected the children with more severe symptoms or those with additional factors prompting the clinician to investigate. While 21.6% of those who had an endoscopy had pathology, this only represented 4.2% of the total. This should prompt further prospective studies in which all children presenting with chronic unexplained abdominal pain are similarly investigated.

Additional findings
We noted that 10/16 (62.5%) of patients in the study group diagnosed with LC or EGID had an enzyme activity test from biopsies obtained by endoscopy. These revealed 4/10 cases of lactase deficiency: one with LC and three with EGID. The three patients with EGID and lactase deficiency achieved clinical remission simply by being treated with Lactaid or avoiding dairy lactose products as the only therapy. Of the 58 patients who underwent endoscopy and did not have LC or EGID, 29 had enzyme activity tests and these revealed seven (24.1%) cases of lactase deficiency. Genetically determined adult type hypolactasia was excluded in all but one case and thus lactase deficiency seemed secondary to small bowel pathology (19).

The difference in prevalence of insufficient lactase production in the patients with and without LC and EGID could indicate that there was an association between these two conditions and insufficient lactase production, as found in other studies (9). Thus, it seems important to screen for lactase deficiency in LC and EGID, as some cases may be linked to lactase deficiency, primary or acquired, and may be treated effectively by a lactose-free diet (9,19).

It is unknown if lactase deficiency is transitional or secondary to some other unidentified aetiology of LC or EGID, but generally, besides LC and EGID, gastrointestinal endoscopy in patients with RAP can reveal insufficient lactase production and the RAP can be eliminated with a lactose free diet (9,19).

EGID has been associated with atopic conditions including food allergies, hyper Immunoglobulin E, asthma and atopic dermatitis (10,13,20). One patient in our study experienced relief of symptoms on a diet free of citrus, tomatoes and food dyestuff, which was recommended because of atopic
dermatitis. She had significant clinical remission of her gastrointestinal symptoms, but her symptoms recurred following food provocation. However, we did not find any specific food allergen-antibodies namely immunoglobulin E, in our patients. This was consistent with studies that reported that the majority of adult and paediatric patients with EGID did not respond to a restricted diet (10,13). Earlier findings suggested that patients with EGID had greater poly-sensitisation to multiple aeroallergens than foods, in contrast to patients with eosinophilic oesophagitis (20).

The value of an elemental and elimination diet is the subject of debate. In some studies, mainly case reports, it has been shown to be effective. A meta-analysis on using diet to treat EGID showed no efficacy in the majority of cases (21). In infants, EGID is part of the food protein-induced enterocolitis spectrum and is treated with an elimination diet. In older children and adults, EGID is typically unresponsive to diet and responsive to steroid treatment (13).

**Medical treatment**

In patients with moderate to severe LC or EGID, treatment with budesonide or prednisolone was effective in inducing and maintaining clinical remission. All medically treated patients showed good tolerance to medication and weaning off without adverse effects. The specific treatments that have been documented for LC and microscopic colitis are budesonide or prednisolone, 5-ASA and a bile-acid binding agent, cholestyramine (16). Of these therapies, there is only strong evidence for budesonide, which should be the first-line treatment for patients with moderate to severe symptoms (16,22).

Steroid therapy has been the mainstay of therapy for EGID, when there is no response to dietary elimination therapy. Treatment is complicated, due to a high rate of relapse. The infant subtype of EGID can be self-limiting, while the adult variety often requires medical intervention (10,16). Ten of the 16 patients with LC or EGID were treated with proton pump inhibitors because of

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gastro-oesophageal reflux disorder symptoms. However, the presence of eosinophils in the upper gastrointestinal tract can be due to gastro-oesophageal reflux disorder or proton pump inhibitor responsive oesophageal eosinophilia. The presenting features are almost identical to those of gastro-oesophageal reflux disorder. An endoscopy with mucosa biopsies or proper treatment with a proton pump inhibitor (1 mg per kg twice a day) in children for 8-12 weeks will clarify these diagnoses (13).

Limitations and strengths
Our study population consisted of 381 patients referred to a paediatric clinic for evaluation of RAP by their general practitioners (23). Thus, it was a selected study population. Although our study group was quite small, 16 patients met the diagnostic criteria for LC or EGID. Awareness was high, which may be one possible reason for a higher prevalence than previously reported. This was also a strength due to a possibly higher detection rate and more thorough investigation.

The diagnostic process was structured, and endoscopies were performed with biopsies despite normal mucosa. This was a strength and could have led to a higher detection rate among children with severe symptoms, with histopathologically confirmed diagnoses, which may otherwise have been considered functionally originating symptomatology.

During the study period, new diagnostic guidelines about performing endoscopies with biopsies in children were published. These suggested routinely random biopsies despite a normal mucosal appearance and preparing biopsies for enzyme testing in every case. This allow clinicians to detect lactase deficiency, which is not detectable using routine blood sample screening methods.

CONCLUSION
When children have LC and, or, EGID, the only symptom may be severe RAP. To a smaller extent, this may be accompanied by diarrhoea and, or, gastroesophageal reflux disorder. Biochemical markers provide no diagnostic value for LC and EGID. Biopsies with histopathological examination are crucial for the diagnosis, even in case of macroscopically normal bowel mucosa. Enzyme activity testing can

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be used to reveal insufficient lactase production. Medical treatment of LC and, or, EGID is tolerated and generally effective in inducing and maintaining clinical remission.

As a result of our findings, we recommend that LC and EGID should be considered in children when they have chronic RAP that compromises daily life and other organic or functional disorders have been ruled out or treated without success. If so, endoscopy should be performed, including biopsies for histopathological assessment and enzyme activity testing. Furthermore, we suggest that treatment is given according to the type and localisation of the inflammation to relieve symptoms. However, we hope that larger prospective studies will help to ease the dilemma concerning functional disorders, with regard to not testing for rare but treatable organic disorders of the gastrointestinal tract.

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FINANCE
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CONFLICTS OF INTEREST
The authors have no conflicts of interest to declare.
REFERENCES


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### Table 1 – Diagnostic process prior to endoscopy

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<th>Procedure</th>
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<tr>
<td>Semi-structured interview</td>
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<tr>
<td>Clinical examination</td>
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<tr>
<td>Transabdominal ultrasound regarding rectal diameter</td>
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<tr>
<td>Helicobacter pylori breath test</td>
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<tr>
<td>Blood test</td>
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<tr>
<td>Fecal sample</td>
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<tr>
<td>Evaluation of psychosomatic factors</td>
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<td>Abdominal ultrasound</td>
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Table 2

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<tr>
<th>Diagnosis</th>
<th>Male/female</th>
<th>Age</th>
<th>Location of inflammation</th>
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<tbody>
<tr>
<td>LC n=6</td>
<td>4 / 2</td>
<td>5.4 – 14.7</td>
<td>Colon and Coecum (n=6)</td>
</tr>
<tr>
<td>EGID n=11</td>
<td>7 / 4</td>
<td>2.1 – 13.9</td>
<td>Colon and/or Coecum (n=10)</td>
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<td></td>
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<td>Oesophagus and/or ventrikels (n=4)</td>
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<td>Rectum (n=2)</td>
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LC: Lymphocytic colitis  
EGID: Eosinophilic gastrointestinal disease  
Age: at first consultation in the pediatric clinic  
N=16: one patient suffered from first EGID and later LC

Figure 1 - Symptoms at referral, N=16