An 11-year-old boy, suspected of a leg length discrepancy and a scoliosis, was referred to our pediatric outpatient department. His mother told us her son walked on tip-toes since the day he had learned to walk. The last month she also noticed an asymmetry of his spine. To improve his posture his general physician referred him to a physical therapist during 10 weeks without any satisfactory result. He experienced no other complaints, especially no pain or muscle weakness. Micturition and defecation were normal.

His medical history was uneventful; there was neither a history of perinatal complications nor of infection or trauma to the bones, joints or nervous system. The boy had achieved all milestones of psychomotor development within the normal age range. He attended the last class of primary school, which was appropriate for his age. His family history did not reveal any remarkable diseases, in particular no toe-walking, neurological diseases, scoliosis or leg length discrepancy.

On physical examination we saw a slightly obese, but otherwise healthy looking boy. Height was 145 cm (-1 SD) and weight was 45 kg (+2 SD). Vital signs were normal, as well as the results of examination of lungs, heart and abdomen.

His back showed an increased lumbar lordosis and a subtle lumbar scoliosis. There was no rib hump and no limitation of movements. He had no signs of spinal dysraphia. Leg length was measured between the anterior superior iliac spine and the medial malleolus and revealed a discrepancy of 1 cm. (left: 86 cm, right: 87 cm).

Observation of his gait pattern revealed that he walked, jumped and ran on his toes, that all movements were well coordinated and without loss of balance. We found a limitation of passive ankle dorsiflexion at both sides to a maximum of 5º of dorsiflexion. Neurological examination demonstrated a normal muscle bulk, tone, and strength, normal deep tendon reflexes and normal sensation.

Laboratory investigation showed a creatine kinase of 123 U/L (normal range: 5-200 U/L). On an X-ray of the spine a minor scoliosis of 3º was detected, without deformities of the vertebrae.

In conclusion, we saw an 11-year-old boy with toe-walking and a limitation in ankle dorsiflexion. As physical examination showed no other abnormalities, especially no neurological symptoms, we concluded that this was a case of idiopathic toe-walking. The leg length discrepancy was confirmed by physical examination and the X-ray result.
A discrepancy of 1 cm is clinically not relevant and the lumbar scoliosis is likely to be due to a bad posture secondary to his toe-walking. He was referred to an orthopaedic surgeon and received two sessions of lower-leg casting for 3 weeks. In addition, he performed daily stretching exercises under the supervision of a physical therapist. The combination of these therapies resulted in an improvement of ankle dorsiflexion and subsequently an almost normal gait.

**Comment**

Toe-walking is a common gait deviation in children with different underlying causes. The purpose of this case report is to illustrate the diagnostic process in idiopathic toe-walking, with emphasis on the differential diagnosis of several neurological, orthopedic or psychiatric causes. When children learn to walk a toe-to-toe gait pattern is considered part of the normal gait development. However if toe-walking persists after the age of 2 years a possible underlying disorder should be excluded. There are several neurological diseases associated with toe-walking including cerebral palsy, spinal dysraphia, neuropathy and myopathy (Figure 1). The diagnosis idiopathic toe-walking is one of exclusion. The exact incidence of (idiopathic) toe-walking is unknown, although most textbooks describe it as a “common” disorder in children.

A complete medical history and a careful physical examination are sufficient to differentiate between these neurological disorders and idiopathic toe-walking. To exclude cerebral palsy a detailed medical history should be taken, paying extra attention to the perinatal period and development. The history should be focused on signs of infection or hypoxia and the achieved milestones appropriate for age. In a case of spinal dysraphia one might experience faecal and urine incontinence, but the opposite, retention can also occur. Muscle strength and family history are important in all neurological disorders and especially in a case of neuropathy or myopathy.

On physical examination extra attention should be given to signs of spinal dysraphia, like lipoma, hypervascularisation and hair growth in the lumbar region. The most important part is the neurological examination; the muscle bulk, tone, and strength, the deep tendon reflexes and the sensation should all be normal in a case of idiopathic toe-walking. In addition, observation of the child during walking, running and jumping may be helpful. In idiopathic toe-walking the child is often able to walk normally (heel to toe) when cued, but returns to toe-walking when distracted. A more or less pronounced tightness of the calf muscles and the heel cord (but no fixed planter flexion contracture) often illustrated by the child’s lack of ability to squat while having the entire sole of the foot on the floor is typical in idiopathic toe-walking. Children with idiopathic toe-walking typically walk on their toes ever since they learned to walk.

Several theories have been proposed to explain idiopathic toe-walking. One theory is that toe-walking is a normal variant of the gait pattern, a habitual way of walking. Secondly, children could walk on their toes secondary to a congenital short tendo calcaneus. Thirdly, a genetic predisposition could be a possible cause, since a positive family history is found in 20 to 40% of the idiopathic toe-walkers. A fourth explanation for toe-walking could be that it is not an isolated problem, but part of a more complex disorder, since idiopathic toe-walking is associated with autism, learning disorders, language disorders and delay in gross and fine motor development. The goal of the treatment is a normal heel to toe gait. This requires 10 degrees of ankle dorsiflexion. Idiopathic toe-walking is expected to resolve without specific intervention if the child has normal passive ankle dorsiflexion and can walk heel to toe when cued. There are different treatment modalities for children with idiopathic toe-walking and limitation in the ankle dorsiflexion. The simplest intervention consists of achilles tendon stretching exercises under the supervision of a physical therapist.

### Table: Possible Investigations

<table>
<thead>
<tr>
<th>Neurological</th>
<th>Possible Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Palsy</td>
<td>Ultrasound, CT, MRI, Metabolic investigation</td>
</tr>
<tr>
<td>Spinal dysraphia</td>
<td>X-spine, Ultrasound, MRI</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Creatine kinase, Muscle biopsy</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>EMG</td>
</tr>
<tr>
<td>Idiopathic toe-walking</td>
<td>Diagnosis per exclusion</td>
</tr>
</tbody>
</table>

**Figure 1. Toe-walking: Differential diagnosis and additional diagnostic tests.**
physical therapist. The next step is serial casting therapy. In this therapy the ankle is casted between the point at which initial resistance to passive stretch is felt and the point at which no further stretch is possible. After 1 or 2 weeks, the cast is removed and a new cast is applied. The total casting period ranges from 3 to 6 weeks. The final possibility is open or percutaneous surgical tendon Achilles lengthening. There is still considerable debate in the literature on the effect of the different treatment modalities for idiopathic toe-walking. Some authors think it is questionable whether treatment alters the natural course of the disease, or conclude that non-surgical interventions have no lasting effect, while others recommend interventions in order to prevent the development of ankle equinus. Surgical intervention is usually reserved for the few cases with fixed ankle joint contracture or functional impairment.

In conclusion: The diagnosis idiopathic toe-walking is one of exclusion. A careful history and physical examination will usually be sufficient to establish the diagnosis without the necessity of further investigations.

A case of hereditary pancreatitis

P. van Warmerdam¹ and L. de Ridder³

Case report

A 17-year-old boy presented at the emergency department with complaints of acute abdominal pain in epigastrio, nausea and vomiting since one day. The abdominal pain had started acutely on the morning of presentation and had a paroxysmal character. The patient didn’t have the urge to move; sitting bended forward was the most comfortable position. There was no fever; defecation and diuresis were both normal. He did not use any medication.

His medical history revealed that he had had recurrent attacks of abdominal pain during a period of six months at the age of fifteen, initially diagnosed as constipation. A pancreatic cyst with a diameter of approximately nine centimetres was found by ultrasound a few months later and was marsupialised. The inheritance is autosomally dominant with a penetrance of about 80%. The patient’s great-aunt were known to have chronic pancreatitis. Secretions form due to impairment of the digestive enzymes. Autodigestion of this organ. Three different gene mutations have been described in hereditary pancreatitis: mutations in cationic trypsinogen, CFTR mutations and mutations in the cystic fibrosis transmembrane receptor (CFTR) have been associated with chronic pancreatitis. Secretions form due to impairment of inflammatory cytokines.

The patient was admitted to the hospital because of progressive vomiting and to monitor his hydration state. Therapy consisted of refraining from enteral feeding, acetaminophen and a gastric tube. The day after admission the patient improved: he was able to eat and drink normally, and the gastric tube could be removed. In addition serum amylase and lipase decreased. Three days after admission he was discharged. Follow-up was performed one month after admission. Serum levels of amylase and lipase had decreased to 300 µ/L and 93 µ/L, respectively. Half a year later at his last appointment with the pediatrician he did not mention any complaints, besides some abdominal ache every now and then, which was relieved by resting. Because of his age further follow up was managed by the department of gastroenterology.

Comment

Hereditary pancreatitis is a rare cause of acute and chronic pancreatitis. It accounts for approximately 2% of the pediatric cases of acute pancreatitis. The inheritance is autosomally dominant with a penetrance of about 80%. It is unknown why 20% of the population with a mutation in chromosome 7 do not develop pancreatitis.

Three different gene mutations have been described in hereditary pancreatitis: mutations in cationic trypsinogen, CFTR mutations and mutations in a serine protease inhibitor. Due to a mutation in the cationic trypsinogen gene on chromosome 7, the inactive pro-enzyme trypsinogen is transformed into the active trypsin inside the pancreas instead of in the intestine. A cascade of enzyme reactions in the pancreas follows, leading to autodigestion of this organ. Inflammatory reactions occur regionally in the pancreas but also systemically, due to actions of inflammatory cytokines.

Mutations in the cystic fibrosis transmembrane receptor (CFTR) have been associated with chronic pancreatitis. Secretions form due to impairment of

References


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cyclic AMP regulated chloride channels which block ductal systems in various organs, leading to pancreatitis. The production of serine protease inhibitor Kazal type 1 (SPINK1 or pancreatic secretory trypsin inhibitor [PSTI]) reversibly inhibits activated trypsin. SPINK1 mutations do not always cause pancreatitis and probably act as a disease modifier, rather than being the primary cause of pancreatitis. Hereditary pancreatitis usually begins with recurrent episodes of acute pancreatitis in childhood. In general the first episode occurs before the age of 20 although cases with an onset as late as at the age of 60 have been described. The symptomatology and therapy of hereditary pancreatitis are the same as pancreatitis of another aetiology. Upper abdominal pain and vomiting are characteristic symptoms. The severity and duration of abdominal pain can vary per person and per episode. It ranges from mild abdominal pain to multi-organ failure and occasionally even death. Therapy is conservative, focuses on relief of the symptoms and includes intravenous rehydration, refraining from enteral feeding to avoid pancreatic stimulation, a gastric tube to treat intestinal ileus if any, and adequate analgesia.

Serum levels of amylase and lipase are usually increased in acute pancreatitis, although they may be completely normal, which can cause diagnostic delay. An ultrasound or CT-scan may show oedema, fibrotic changes of ducts, calcifications or cysts. Complications of hereditary pancreatitis are the same as in acute and chronic pancreatitis with a different aetiology: cysts, abscesses, pancreatic necrosis with endocrine and exocrine insufficiency and pancreatic cancer. About 50% of the patients with hereditary pancreatitis will develop chronic pancreatitis with permanent damage of the function and structure of the pancreas. The pathogenesis of this progression to chronic pancreatitis is poorly understood, although several hypothetical theories have been proposed. The chance of developing pancreatic cancer in a person with hereditary pancreatitis is 50 to 60 times higher compared to individuals without this disease. At the age of 70 years 40% of the individuals with hereditary pancreatitis have developed pancreatic cancer. Smoking increases this risk and decreases the age of onset by approximately 20 years. It is important for patients with hereditary pancreatitis to avoid smoking and to avoid alcohol, as this is a known risk factor for pancreatitis in general. Our patient had recurrent episodes of abdominal pain at 15 years of age. At first this was diagnosed as constipation, but these attacks may have been caused by recurrent acute pancreatitis. The pancreatic cyst that was diagnosed a few months after the first attack of abdominal pain supports this hypothesis. Research into the exact gene mutation that causes the pancreatitis in this family has been performed. Although no mutation was found in the cationic trypsinogen gene or the SPINK1 gene, it is still likely that he and his family members are suffering from hereditary pancreatitis, with unknown mutation.

References:

Oligoarthritis associated with acute Epstein-Barr infection

Jansen NJ¹, Van Litsenburg RRL², Sanders MK³ and Langius FAA⁴

Case report
A 14-month-old girl with no relevant history, presented at our emergency department after waking up with a painful right knee. Except for cough and rhinitis, she did not have any complaints. In particular she had not been ill, there had not been any evident trauma, or sore throat, neither had there been any fever, pharyngitis or tick bite. The radiograph of the right knee showed no abnormalities. At that moment the patient was diagnosed as having a contusion of the knee. Although no clear signs were present yet, reactive arthritis/arthralgia were considered as differential diagnoses because of the cough and rhinitis. Three weeks later she was seen at the outpatient clinic. By then the right knee was painful, swollen and warm. Extension of the knee was limited; she refused to stand on it and kept in flexed position. There was no involvement of other joints. Further physical examination showed enlarged red tonsils and fever up to 39.1°C; no other abnormalities were found. Ultrasound of the right knee revealed hydrarthrosis, particularly in the suprapatellar bursa. She was admitted to our paediatric ward because of concomitant fever and general malaise.

Laboratory investigation on admission (see Table 1) showed C-reactive protein (CRP) 56 mg/mL and a slightly elevated white blood cell count (WBC) (13.9 x 10⁹/L) with lymphocytosis (9.9 x 10⁹/L), including atypical lymphocytes. Leukocytes (112 x 10⁹/L) were found in the synovial fluid: 97% neutrophils, 2% lymphocytes and 1% monocytes. The Gram stain was negative. Culture of the synovial fluid was polymicrobial; Enterococcus faecium and two different types of coagulase negative staphylococci (CNS) were isolated. Although Enterococcus and CNS have been described as a cause of arthritis, these pathogens were considered to be a result of procedural contamination because of the polymicrobial nature. The anti-streptolysin titre (AST) was negative, as was the Mantoux. In order to

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discriminate between arthritis and osteomyelitis a skeletal scintigraphy was performed. The scintigraphy showed oligoarthritis, since not only the right knee but also the right ankle and hip appeared to be involved. It did not reveal any signs of osteomyelitis.

Except for EBV all other potential causes of this oligoarthritis, including bacterial enteric infections and viral infections known to cause postinfectious or reactive arthritis, Lyme disease and autoimmune disorders, were excluded (see Table 1). The Monosticon was negative, which is common in young children, but the specific antibodies were indicative of an acute infection, with elevated IgM specific (>160 U/mL) and IgG specific (93 U/mL) antibody titre to viral capsid antigen (VCA), and low total antibody titre (4 U/mL) to nuclear antigen (EBNA1). Analysis of EBV presence in the synovial fluid was not performed.

The girl was treated with NSAIDs for 6 weeks. Two months after the onset of the first symptoms, signs of arthritis had almost disappeared. Additional treatment with antibiotics was performed for 6 weeks because of the destructive nature of native-joint E. faecium arthritis.

### Investigations

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>CRP 56 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBC 13.9 x 10^9/L with 9.9 X10^9/L lymphocytes.</td>
</tr>
<tr>
<td></td>
<td>Hb 6.7 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Platelets 533 x 10^9/L</td>
</tr>
<tr>
<td></td>
<td>ANA negative</td>
</tr>
<tr>
<td></td>
<td>C3/C4 normal</td>
</tr>
<tr>
<td></td>
<td>AST 3 IU/mL</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>Leukocytes 112 x 10^9/L with 97% neutrophils, 2% lymphocytes and 1% monocytes.</td>
</tr>
<tr>
<td></td>
<td>Gram stain: negative</td>
</tr>
<tr>
<td></td>
<td>Culture: Enterococcus faecium, two different coagulase-negative staphylococci (CNS)</td>
</tr>
<tr>
<td>Blood culture</td>
<td>No growth</td>
</tr>
<tr>
<td>Faecal cultures</td>
<td>Salmonella/Shigella/Yersinia/ Campylobacter: negative</td>
</tr>
<tr>
<td>Serology</td>
<td>Yersinia IgG: negative</td>
</tr>
<tr>
<td></td>
<td>Borrelia burgdorferi IgG: negative</td>
</tr>
<tr>
<td></td>
<td>Parvovirus: IgG/IgM: negative</td>
</tr>
<tr>
<td></td>
<td>CMV: IgG 3.5 U/mL, IgM &lt; 8.0 U/mL (prior infection)</td>
</tr>
<tr>
<td></td>
<td>EBV: Monosticon: negative, IgG anti-VCA 93 U/mL, IgM anti-VCA &gt; 160 U/mL, EBNA1 IgG 4 U/mL (acute infection)</td>
</tr>
<tr>
<td>Mantoux</td>
<td>Negative</td>
</tr>
<tr>
<td>Radiograph right knee</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>Ultrasound right knee</td>
<td>Fluid accumulation mostly in suprapatellar bursa. Indicative of arthritis.</td>
</tr>
<tr>
<td>Skeletal scintigraphy</td>
<td>Involvement of the right knee and to a lesser extent, the right ankle and hip.</td>
</tr>
</tbody>
</table>

Well-known viral infections causing arthritis are Rubella, Hepatitis B virus, Parvovirus B19, Varicella-Zoster virus and Mumps virus. Only few cases of arthritis associated with EBV have been described. Sero-epidemiological studies indicate that the great majority of adults have antibodies to EBV. Up to 50% of adolescents with serologically confirmed primary infections develop clinical symptoms of infectious mononucleosis such as headache, pharyngitis, lymphadenopathy and general malaise. Primary infection in infancy almost always appears to be asymptomatic. Characteristic laboratory findings are lymphocytosis and the presence of atypical lymphocytes. Suspected diagnosis of EBV infection is confirmed by the presence of heterophil antibodies or EBV-specific antibodies.

Literature on acute EBV-arthritis mostly comprises case reports. Arthritis in these cases is usually polyarticular, sometimes monoarticular but only seldom oligoarticular. EBV-arthritis without any of the classic symptoms of infectious mononucleosis has been described. Contrary to our case, most authors report adult or adolescent cases. Only a few children have been described; the youngest one being 4 years of age. Diagnoses have been confirmed by the presence of specific antibodies, sometimes in combination with heterophil antibodies. Isolation of the virus in the synovial fluid has rarely been performed. High synovial fluid white cell count, as found in our case, seems indicative for bacterial arthritis. However, it can also occur in reactive arthritis. Viral arthritides are self-limiting within 3 months and only supportive therapy is necessary.

The oligoarthritis in this case was considered to be the result of an active EBV infection; diagnosis was confirmed by the presence of specific antibodies. The bacteria cultured from the synovial fluid were taken into account as a possible cause, although a procedural
Identifying children with sickle cell disease in a non-endemic country: Age at presentation and presenting symptoms

X.W. van den Tweel\textsuperscript{1,}, H. Heijboer, K. Fijnvandraat\textsuperscript{2} and M. Peters\textsuperscript{1}

Introduction
Sickle cell disease is an autosomal recessive inheritable disorder that mainly affects the black population. As a result of a mutation in the \(\beta\)-globin gene, the red blood cell changes from a biconcave shape into the shape of a sickle in the presence of deoxygenation. Symptoms of sickle cell disease are chronic haemolytic anaemia, vaso-occlusion and increased susceptibility to infections.

Over the past decade the prevalence of haemoglobinopathies in Europe has increased due to immigration and family expansion of the black population living in Europe.

Most general practitioners, pediatricians and other healthcare workers are not familiar with the presenting symptoms of this disease. Early diagnosis of sickle cell disease is important because pneumococcal infections can be prevented by the institution of penicillin prophylaxis and parental education may add to timely recognition and treatment of complications.\textsuperscript{1}

The main objective of this study was to document the age and type of symptoms at diagnosis in children with sickle cell disease, in a population not subject to neonatal screening. The second objective of this study was to compare age and type of presenting symptoms in HbSS/ HbS-\(\beta\)\textsuperscript{0}-thalassemia and HbSC/ HbS-\(\beta\)\textsuperscript{+}-thalassemia. The results of this study may add to rapid recognition of this disease. Moreover, the results of this study may be used for evaluation of the effectiveness of future neonatal screening programmes.

Methods
Children from the sickle cell clinic of the Emma Children’s Hospital, Amsterdam were included consecutively in this study if they were born and diagnosed with sickle cell disease in the Netherlands between 1979 and 2005. The study population was classified according to severity into two groups: HbSS/ HbS-\(\beta\)\textsuperscript{0}-thalassemia and HbSC/ HbS-\(\beta\)\textsuperscript{+}-thalassemia.

Presenting symptoms were classified as sickle cell disease specific symptoms or non-specific symptoms.
Specific symptoms were defined as those that were attributable to sickle cell disease and consisted of haemolytic anaemia, jaundice, a vaso-occlusive crisis (acute pain in the extremities, back or abdomen), sickle cell disease related infections (pneumococcal meningitis/septicaemia or pneumococcal pneumonia), acute splenic sequestration, aplastic crisis, cerebral vascular accident and acute chest syndrome. Non-specific symptoms were defined as symptoms not necessarily attributable to sickle cell disease. The diagnosis of sickle cell disease was made during the process of clinical work-up for these symptoms. Descriptive statistics are presented as median, minimum, maximum and percentages. The Mann-Whitney U test was used to compare groups because there was a skewed distribution. A p value of 0.05 or less was considered statistically significant. SPSS statistical software version 11.5 was used for all statistical computations.

Results
Eighty-eight children were included in the study, 67 were diagnosed with HbSS/ HbS-β0-thalassemia and 21 with HbSC/ HbS-β+-thalassemia. The majority of these children (72%) were detected because they presented with symptoms specific for sickle cell disease. Painful crisis was the most common presenting symptom. In 4 patients the presenting symptom was a pneumococcal infection.

Of the non-specific symptoms, infections were most frequent. The median age at diagnosis in the total patient group was 25 months. As expected, there was no age difference between the two groups at diagnosis with regard to non-specific symptoms. However, in the group of children who had been diagnosed by specific symptoms, those with HbSS/ HbS-β0-thalassemia were diagnosed at a younger age (24 months) than those with HbSC/ HbS-β+-thalassemia (45 months) (P=0.07). The youngest age at diagnosis by specific symptoms was 7 months. In two cases (HbSC and HbSS) the diagnosis had not been made until the age of 13 and 14 years, respectively.

Discussion
In this study we evaluated the age at diagnosis and the presenting symptoms in 88 children with sickle cell disease who were born and diagnosed in the Netherlands. We observed a broad age range at diagnosis. This can be explained by several factors. There is a large interindividual variation in clinical severity of children with SS disease, due to modifying factors such as deletion(s) in the α-gene cluster (favourable effect) and different β-gene haplotypes. Infections or other environmental factors and doctor’s delay also influence the age at diagnosis.

Painful crisis was the presenting specific symptom in 42% of the HbSS/ HbS-β0-thalassemia and in 47% of the HbSC/ HbS-β+-thalassemia children. In studies of a neonatally screened population, painful crisis was reported to occur more frequently as the presenting specific symptom, 66% to 91% in HbSS and HbSC respectively7, or even up to 98.3% for both HbSS and HbSC disease. Since these patients were diagnosed shortly after birth, acute bone or abdominal pains were attributed to sickle cell disease at their first occurrence. In our patient group these symptoms may have occurred without being recognised as symptoms of sickle cell disease. In two children an acute splenic sequestration was the first clinical manifestation, which has also been described by others.8-14

In 28 percent of our patients the diagnosis of sickle cell disease was made when medical attention was sought for symptoms not necessarily caused by sickle cell disease. The ethnic background of the patient prompted laboratory testing for sickle cell disease. The proportion of children diagnosed by these non-specific symptoms depends to a large extent on the diagnostic suspicion of the physician in charge which is influenced by ethnic background of the patient population. Recognition by healthcare workers of signs and symptoms of sickle cell disease is very important and will minimize doctor’s delay. Children may present with a first manifestation of the disease up to the age of at least 14 years.

References
Severity of enterocolitis predicted by IL-8 in pediatric oncology patients

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Abstract
Enterocolitis in oncology patients remains an important complication with poor insight in microbial, pathological and inflammatory aspects. Pediatric oncology patients admitted with neutropenic fever, who developed abdominal pain and diarrhea, were monitored with rectal biopsies, cultures, and inflammatory markers. Twenty-five patients were included (mean age 7.1 years). Eight patients (32%) needed intensive care treatment, 3 (12%) patients died. Gram-positive bacteraemia was diagnosed in 4 patients (16%). Most patients had negative blood and stool cultures. Predictors of a severe clinical course of the enterocolitis were an increased serum IL-8 (>100 pg/mL) and an increased serum CRP (>150 mg/L), both measured on the first day of clinical illness. Relative risks for admission to ICU were 11.3 (95% CI 1.6 to 77.9) for elevated IL-8 and 6.4 (95% CI 0.92 to 45.1) for increased CRP. Rectal biopsies and pathology could not predict outcome (p=0.22). IL-8 analysis at the onset of enterocolitis symptoms can identify high-risk patients, which might be used clinically to design future intervention trials.

Introduction
Neutropenic enterocolitis represents a complex spectrum of inflammatory processes of the colon seen in immunocompromised hosts after intensive chemotherapy for malignancies. It ranges from pseudo-membranous colitis caused by Clostridium difficile to typhilitis.1 The clinical picture ranges from mild infection to severe transmural colitis with a high mortality-rate (50-100%).2 The pathogenesis of this disorder is thought to be due to a multifactorial disruption of the mucosal barrier, in which the bacterial flora, neutropenia and cytotoxic therapy play a role. Prognostic inflammatory markers in neutropenic enterocolitis have not been defined to date. In neutropenic enterocolitis both toxic and ischemic bowel injury may play an important role. The response of the inflammatory cascade to pathogens attacking the gastro-intestinal mucosa involves mainly the cytokines IL-6, IL-8, IL-10 and TNF-α. The role of these cytokines may be important in the pathophysiology of the inflammatory responses in neutropenic enterocolitis in children.3

Therefore a prospective single unit study was started to identify the incidence of enterocolitis in a paediatric oncology unit, to gain insight in the pathogenetic mechanisms, and to identify clinical and inflammatory prognostic markers.

Methods
Entry criteria were neutropenic pediatric oncology patients who had abdominal pain, diarrhea and fever for more than 24 hours. Neutropenia was defined as <500/μL absolute neutrophils. Diarrhoea was defined as having at least grade 2 diarrhoea (4-6 times in 24 hours correlating to the CTC toxicity criteria). Fever was defined as a temperature >38.5°C. All types of malignancies were included. On the first day of the study the following were performed: 1) history and clinical checklist 2) physical stool examination 3) stool cultures 4) rectal biopsy 5) blood investigations and 6) serum levels of inflammatory markers.

On day 3 and day 7 above investigations were repeated. The rectal biopsy was repeated if findings on day 1 were abnormal. The next course of chemotherapy started when all abnormal findings had normalized. The study was performed in a single pediatric oncology unit. Approval from the medical ethics committee was obtained. Informed consent was obtained from the parents and from the child if >12 years of age.

Statistics
To examine the prognostic value of elevated inflammatory markers we used both cut-offs mentioned in the literature (for IL-8 above 1000 pg/mL, CRP above 150 mg/L) and optimal cut-offs from the data were calculated using the Youden index (sensitivity + specificity -1) as criterion. To estimate the predictive value of increased inflammatory parameters we calculated relative risks with 95% confidence intervals (CI). All reported p-values are two-sided.

Results
Over a 3-year-period (November 1998 until January 2002), 452 new patients with oncological disorders were admitted to the unit. Of these 25 patients fulfilled the entry criteria of the study and were included, 15 were male and 10 were female. The diagnoses at presentation showed 11 haematological disorders (ALL/ANLL), 4 B-cell lymphoma’s, 9 solid tumours and 1 haemophagocytic syndrome. The mean age at diagnosis was 7.1 years (range 1.0-17.1 years). Enterocolitis presented in most cases within the first 3 months after diagnosis and the start of chemotherapy. The vast majority of patients had signs of mucositis (92%), 40% of patients had less than 48 hours of fever and 60% had fever >48 hours. The stool pattern was recorded as “watery and frequent” in 60% of patients and in 28% of patients “bloody diarrhoea” was recorded. The abdominal pain was classified as “cramps” in 72% of patients, and 24% of patients had continuous pain. Histological examination of the rectal biopsies resulted in “no changes” in 12 patients (48%), “infiltrate only” without pseudomembranes in 9 patients (36%), “pseudomembranes” in 3 patients (12%) and 1 patient had “ulcerative changes” with fibrin exudates (4%). Only 2 patients had C. difficile in the stool culture and 1 of these patients had a positive blood culture with C. difficile (the same strain was found in the blood-culture as in the stool-culture). In 3 patients C. difficile toxin stool tests were positive. Of the 25 patients, 8 were admitted to the ICU due to cardiovascular

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3 Department of Medical Microbiology, AMC, Amsterdam.
symptoms for which inotropic support was indicated. Of these patients five did not have a proven bacteraemia. Three died following the enterocolitis episode. To identify possible factors predictive of the clinical course we used admittance to ICU with need for inotropic support during the enterocolitis episode as our primary endpoint.

Of the evaluated inflammatory serum markers CRP and IL-8 showed a significant difference between the 2 groups (Fig. 1 and 2). Using a cut-off value of 1000 pg/mL 6 out of 7 patients were found to have a high IL-8 in the ICU group compared to 2 out of 16 patients in the non-ICU group. The risk of ICU admittance was 11.3 times (95% CI 1.6-77.9) higher in the elevated IL-8 group than in the non-ICU group. All 3 patients who died had IL-8 >1000 pg/mL (table 1).

Discussion
The main aim of the study was to identify patients likely to develop a severe enterocolitis. The clinical symptoms diarrhea, abdominal pain and mucositis showed no significant difference between the ICU and the non-ICU group. The rectal biopsy findings did not contribute to treatment decisions, it was shown that the findings of pseudomembranes on rectal biopsy correlated fully with C. difficile toxin positivity or culture positivity. Routine laboratory investigations could not distinguish the severe cases from the less severe cases. The inflammatory parameters in the present study showed that CRP and IL-8 were of prognostic value. The extent and course of serum concentrations of IL-8 and IL-6 in the patients with colitis symptoms were significantly different from those seen in septic conditions in non-neutropenic children. In non-neutropenic patients concentrations of IL-8 are at least 10-100 fold higher. IL-8 used at a cut-off point of 1000 pg/mL, was found to be a strong prognostic factor. Although the chemotactic activity towards neutrophils is the most important function of IL-8, we know that in these patients neutrophils are missing and also absent in the extravascular tissues. Taken together, these data indicate that IL-8 in neutropenic patients is less likely derived from enterocytes and myeloid cells, but from tissue cells such as endothelial cells, and fibroblasts. The chronic low flow and hypoxia prone situation is not impossible as a contributing factor for endothelial cell-induced IL-8 generation. We hypothesize that the IL-8 increase seen in our patients reflects the extent of damage of the intestinal wall, and could therefore predict the severity of the disease. For the daily clinical practice, we would strongly advise to initiate early aggressive supportive care in neutropenic patients with abdominal cramps and diarrhea in whom IL-8 levels are elevated.

Chapter 4 of thesis: Prediction and prevention of infectious complications in children with cancer by M.D. van de Wetering
References