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Improved Management of Neutropenic Enterocolitis Using Early Ultrasound Scan and Vigorous Medical Treatment

To the Editor—Neutropenic enterocolitis is a life-threatening complication in hematological patients, with an associated mortality rate of 29.5%–50% [1, 2]. Polymicrobic infiltrates in the inflamed bowel wall with subsequent necrotizing perforations and systemic dissemination of infectious agents are the terminal events [1–4]. Bowel wall thickening, well detected by modern imaging techniques, is the true warning sign [1–7]. Data on the clinical impact of new strategies for early diagnosis of disease and for treatment of these patients are scanty [5]. We prospectively investigated whether ultrasound-driven vigorous medical treatment could improve outcome in patients with neutropenic enterocolitis.

Since 2000, we have systematically performed high-resolution ultrasound with dynamic tissue harmonic technology (EUB 6500; Hitachi) and a 2–5 MHz broad-band convex probe (EUB 514 C probe; Hitachi) at patients' bedsides to evaluate intestinal thickness within 12 h after the appearance of severe neutropenia, fever, and abdominal pain or diarrhea among 500 patients treated with intensive chemotherapy for hematological malignancies. Overall, 25 consecutive adult patients (5%; 10 male and 15 female patients; 20 with acute leukemia and 5 with lymphoma) with evidence by ultrasound of wall thickness ⩾5 mm (median wall thickness, 6 mm; range, 5–20 mm) in the small bowel (12 patients), the large bowel (7 patients), and both (6 patients) were diagnosed as having neutropenic enterocolitis. The patients promptly received ceftazidime (6 g/day), amikacin (1 g/day), teicoplanin (400 mg/day), metronidazole (0.5–1 g/day), amphotericin B (1–1.5 mg/kg/day intravenously), granulocyte colony-stimulating factor, and total parenteral nutrition for a median duration of 10 days (range, 7–15 days). In all 25 patients, the follow-up ultrasound demonstrated progressive reduction of intestinal mural thickening, along with symptom disappearance. Before 2000, in our institution, ultrasound was used only to document abnormal bowel wall thickening (median thickness, 11 mm; range, 6–20 mm) in 25 patients who had already received a clinical diagnosis of neutropenic enterocolitis (i.e., neutropenic fever; significant abdominal pain requiring analgesics, usually in the right lower quadrant; and ⩾3 bloody diarrhea stools daily). The median time between the appearance of fever and the diagnosis of neutropenic enterocolitis was 9 days (range, 5–11 days) before 2000 versus 3 days (range, 1–5 days) in 2000 and after, thus allowing earlier administration of antimicrobial therapy ($P = .01$, by Mann-Whitney U test). Consequently, 4 patients had invasive fungal infections (*Candida albicans* was found in blood samples from 2 patients by culture, and 2 patients had histological and microbiological evidence of *Aspergillus fumigatus* in bowel specimens available after surgical resection) before 2000, and no patient had fungal pathogen isolates in 2000 or after. Remarkably, 12 (48%) of 25 patients died of acute abdomen and/or shock due to severely necrotizing neutropenic enterocolitis before 2000. In contrast, none of the 25 patients in the systematic ultrasound era died until day 30 after chemotherapy ($P < .001$, by log-rank test).

Our study reveals that the systematic use of high-resolution ultrasound as part of the work-up of patients with neutropenic fever and cancer is particularly valuable to identify neutropenic enterocolitis at an early stage, when conservative treatment would be maximally effective [8]. A bowel wall thickness ⩾5 mm was the pragmatic criterion to start vigorous medical treatment. At this time, the administration of broad-spectrum antimicrobial therapy, in addition to granulocyte colony-stimulating factor and bowel rest, may significantly reduce neutropenic enterocolitis–related morbidity and mortality.

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Human Bocavirus in Children with Acute Asthma

To the Editor—Allander et al. [1] have reported their study of human bocavirus (HBoV) in children with acute wheezing. Other authors have also revealed that bocavirus is present in nasopharyngeal aspirate specimens from children with respiratory tract infection with or without wheezing. All authors have found a predominance of young infants, mainly <2 years of age, in their results [2–4]. The majority of the published studies are retrospective, based on specimens that were frozen after they were obtained from hospitalized infants, with a clinical heterogeneity among patients and a great number of virus in the youngest infants (an age group that is commonly hospitalized with acute respiratory tract infection).

For several years, we have checked for *Mycoplasma pneumoniae* and respiratory viruses in children hospitalized with acute asthma [5]. Because a real-time PCR is available in our virology unit, we investigated prospectively the presence of HBoV in nasopharyngeal aspirate specimens from children aged 2–15 years who were hospitalized with severe acute asthma from 1 October 2005 through 1 May 2006. All children were known to be asthmatic and were hospitalized after an observation period in the emergency unit because of failure of treatment with repeated inhaled bronchodilators and hypoxia, as previously described [5].

Nasopharyngeal aspirate specimens were tested for common viral respiratory pathogens by direct immunofluorescence assays with monoclonal antibodies to respiratory syncytial virus, influenza A and B viruses, adenovirus, and parainfluenza type 1, 2, and 3 viruses. Specimens were also inoculated into HUH7 and A549 cell monolayers for virus isolation. PCR for detection of *M. pneumoniae* and human metapneumovirus were also performed.

The first PCR for HBoV was a conventional PCR targeting the VP2 gene, using a forward primer with a sequence 5′-CAGTGGTACCAGACACCAGAAG and a reverse primer with a sequence 5′-GCCAGTTCTTTGTTGCGTATCT. The PCR products were analyzed by agarose gel electrophoresis. The second PCR assay was a real-time PCR assay that targets the HBoV NS1 gene. Specific primers and probe were defined from the reported sequences of the NS1 gene at positions 953–1029 of the HBoV strain st1 (GenBank accession no. DQ000495) and were obtained from bocavirus r-gene (Argene). A specimen was considered to contain HBoV only if the results of PCR were positive for both regions VP2 and NS1.

The results of PCR performed for 50 hospitalized children with acute asthma (29 male and 21 female children) are shown in table 1. The numbers of patients infected with *M. pneumoniae*, respiratory syncytial virus, and influenza viruses were expected because of previous studies in the same hospital unit [5]. Three of 50 children were infected with human metapneumovirus. HBoV was identified in nasopharyngeal aspirate specimens from 7 of 50 hospitalized children and was associated with respiratory syncytial virus in 1 patient and with human metapneumovirus in 1 patient. The median age of patients infected with HBoV was 3 years; 1 of 7 patients was >5 years of age, and 4 of 7 patients were male.

Table 1. Bocavirus and other pathogens isolated in nasopharyngeal aspirate specimens from 50 children (age, 2–15 years) hospitalized with severe acute asthma during the winter season 2005–2006.

Pathogen	No. of patients from whom the pathogen was isolated
Mycoplasma pneumoniae	7
Bocavirus[a]	7
Respiratory syncytial virus	5
Human metapneumovirus	3
Influenza A virus	3
Influenza B virus	1
Adenovirus	0
Parainfluenza viruses	0
No pathogen identified	24

[a] One case was associated with respiratory syncytial virus, and 1 case was associated with human metapneumovirus.

Our data reveal that HBoV is a common cause of severe exacerbation of asthma in children. The respiratory infection is not limited to young infants, and children aged >2 years are commonly infected.

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