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Clinical Infectious Diseases 2007; 45:400–1
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DOI: 10.1086/521125

Direct Susceptibility Testing of Respiratory Samples

To the Editor—Bouza et al. [1] report the clinical impact of direct susceptibility testing of respiratory secretions using the E-test method. Direct susceptibility testing of blood culture isolates is being used in most microbiology laboratories in Germany (and, I would claim, in most laboratories worldwide); however, I am not aware of any prospective study on the clinical impact of obtaining early results. In our laboratory (University of Frankfurt, Frankfurt am Main, Germany), it has been customary since the 1960s to directly streak an aliquot of any gram-positive blood culture sample on agar plates, place up to 18 antibiotic disks, and interpret the inhibition zone after 6–8 h of incubation (at the end of the day shift, which, in most cases, is approximately 4:30 p.m. on weekdays). On Saturdays, Sundays, and public holidays, the reading is performed on the next regular work day. Many laboratories work discontinuously [2]. Recently, we prospectively evaluated the time required to provide the clinician with a tentative categorization (TC) result (either susceptible, intermediate, or resistant) and to detect any deviation from the final definitive categorization (FC) obtained with use of the E-test method. The results were presented at the 25th International Congress of Chemotherapy and 17th European Congress of Clinical Microbiology and Infectious Diseases in Munich, Germany [3].

The time required to inform the ward of the TC result was as short as 5.1 h and as long as 97.8 h (mean TC time, 22.5 h). A longer time was required because of a slow-growing organism (e.g., Peptococcus species) or because the blood culture result was determined to be positive on a Saturday. Very major errors (TC result of susceptible and FC result of resistant), major errors (TC result of intermediate and FC result of resistant), and minor errors (TC result of resistant and FC result of susceptible) were seen in 0.35%, 0.16%, and 1.06% of cases, respectively. The disk diffusion technique is cheaper and delivers reliable early susceptibility results. We have not evaluated the impact of the disk diffusion technique on patient care; however, >90% of patients were receiving appropriate antimicrobial treatment when the TC result was reported. Testing blood culture isolates is easier than testing respiratory samples, because the former generally involves a single pathogen, whereas respiratory samples regularly yield >1 pathogen.

Bouza et al. [1] report that, in the control group, the percentage of patients who received an adequate defined daily dose of therapy was smaller (68.3%) than in the E-test group (91.28%), a fact that could be attributed to inappropriate initial therapy in this group (which I presume Kollef [4] is referring to in his editorial). This high rate needs to be further elucidated. In a publication from Spain [5], only 8 patients with hospital-acquired pneumonia received inappropriate therapy; 152 were receiving appropriate therapy.

Acknowledgments

Potential conflicts of interest. P.M.S.: no conflicts.

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Clinical Infectious Diseases 2007; 45:401
© 2007 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2007/4503-0025$15.00
DOI: 10.1086/521125

Reply to Shah

To the Editor—The first part of Dr. Shah’s letter [1], in which he discusses direct antibiograms in blood cultures, has no immediate connection with our work. Direct antibiogram of positive blood cultures with antibiotic-impregnated disks is performed in many European hospitals, including ours (Hospital General Universitario Gregorio Marañón, Madrid, Spain). The technique was reported to be a practical approach many years ago [2,3], but it is not recommended by the American Society of Microbiology, because the inocula has never been properly standardized [4]. We do not doubt that providing clinicians with early microbiological information, although imperfect, is beneficial [5].

Data obtained using the direct E-test method for blood culture isolates have also been reported [6–9]. They show the reliability of the procedure and a good correlation with standard antimicrobial-susceptibility testing.

In response to the last paragraph of Dr. Shah’s letter [1], in which he alludes to our work regarding ventilator-associated pneumonia (VAP), we would like to comment that, before performing our study of the clinical impact of the direct E-test method on lower respiratory tract secretions [10], we demonstrated a high correlation (96.1%) between direct E-test susceptibility testing and the standard an-
tibiogram on isolated bacteria [11]. We chose the E-test, because it is an inocula-independent technique [12–14].

We do not agree with Dr. Shah’s comment that “respiratory samples regularly yield ≥1 pathogen” [1, p. 401]. VAP is mainly a monomicrobial disease, and polymicrobial results occur in no more than 30% of patients with VAP [10].

The main point of Dr. Shah’s letter [1], which is also mentioned in Dr. Kollef’s editorial [15], is that the purportedly high rate of inadequate treatment in our control group could proportionally magnify the impact of our intervention. The adequacy or inadequacy of antimicrobial therapy in the medical literature has to be carefully defined. Very often, inadequate therapy refers to inefficacious empirical treatment or incomplete adherence to well-accepted treatment guidelines [16]. We were much more exhaustive in evaluating the adequacy of antimicrobial therapy in our cohorts. On a daily basis, we assessed the adequacy of antimicrobial therapy for the patient’s causative pathogen and, at the same time, the need for every single antibiotic dose (i.e., the defined daily dose). Studies of inadequate treatment in patients with VAP have estimated that the rate of inadequate treatment is 20%–60%, and it is well recognized that inadequate treatment constitutes the main therapeutic problem in VAP [17–25]. This point is also frequently stated in many of Dr. Kollef’s publications [17, 18, 26]. It is obvious that the possibility of adequate therapy, particularly during the empirical phase of treatment, clearly depends on the drug-resistance rates of the causative bacteria in different geographic areas.

Shah [1] refers to a study by Sopena et al. [27, 28]. This study included only patients with nosocomial pneumonia that was not acquired during receipt of mechanical ventilation. In this case series, 65% of the cases did not have an etiological diagnosis, meaning that it would be impossible to evaluate the adequacy or inadequacy of therapy using the criteria applied in our article.

We are grateful to Dr. Shah [1] for sharing his views with us and for the opportunity that his letter provides to clarify the issue of adequacy and inadequacy of therapy in the treatment of VAP.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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Clinical Infectious Diseases 2007;45:401–3 © 2007 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2007/4503-0027$15.00 DOI: 10.1086/521125

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]. Polymicrobial 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.

Acknowledgments

Financial support. Associazione Italiana contro le Leucemie (Salerno and Benevento sections).

Potential conflicts of interest. All authors: no conflicts.

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