diac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA*. 2003;289(20):2685-2694.
10. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol*. 2003;42(8):1454-1459.
11. Abraham WT, Young JB, León AR, et al; Multicenter InSync ICD II Study Group. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation*. 2004;110(18):2864-2868.
12. Bristow MR, Saxon LA, Boehmer J, et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350(21):2140-2150.
13. Cleland JG, Daubert JC, Erdmann E, et al; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352(15):1539-1549.
14. Beshai JF, Grimm RA, Nagueh SF, et al; RethinQ Study Investigators. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med*. 2007;357(24):2461-2471.
15. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C; REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. 2008;52(23):1834-1843.
16. Moss AJ, Hall WJ, Cannom DS, et al; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361(14):1329-1338.
17. Tang ASL, Wells GA, Talajic M, et al; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363(25):2385-2395.

Etiology of Febrile Episodes in Patients With Acute Myeloid Leukemia: Results From the Hema e-Chart Registry

Several studies have attempted to analyze the epidemiologic patterns of infectious complications in patients with acute myeloid leukemia (AML), although the power of these studies was frequently limited by their retrospective design.[1,2]

A lively debate currently focuses on the potential of Internet-based software and associated technologies, such as electronic medical records, to simplify reporting, to improve database content, and to optimize the timing of interventions.[3,4] Because a well-designed surveillance system is essential for the systematic collection, analysis, and dissemination of data, we designed an electronic medical record system.

Methods. From March 2007 to March 2009, all newly diagnosed AML candidates for conventional chemotherapy from 17 hematology units in Italy were enrolled in the Hema e-Chart and followed-up prospectively to assess the incidence of febrile events (FEs). Data were entered prospectively into electronic case report forms using previously described methods.[5] Enrolling a patient in the Hema e-Chart registry had no impact on the standard clinical practice of each hematology unit.

Results. In the 747 adults with AML treated with conventional chemotherapy, 528 FEs were registered: 208 of them (39.3%) were classified as fever of unidentified origin (FUO), while there were 21 (3.9%) disease/treatment-related fevers (DTRF). The remaining 299 FEs (56.6%) were associated with infections.

Table. Distribution of FEs Among 747 Patients With AML

Event	FE, No. (%)	AMR, No. (%)
FUO	208 (39.4)	10 (4.8)
DTRF	21 (4.0)	0
Bacterial	203 (38.4)	10 (4.9)
Fungal	73 (13.8)	11 (15.1)
Viral	2 (0.4)	0
Mixed	21 (4.0)	3 (14.3)
Fungal and bacterial	19	
Bacterial and viral	1	
Fungal and viral	1	

Abbreviations: AMR, attributable mortality rate; DTRF, disease/treatment-related fever; FE, febrile events; FUO, fever of unidentified origin.

Bacterial infections were identified in 223 cases. After we excluded 20 cases of mixed infections, 203 patients had a bacterial infection only. Thirty-one patients had possible bacterial pneumonia (ie, no etiological agents were isolated and the patients were successfully treated with antibiotic therapy only). Overall, 192 patients had a microbiologically proven bacterial infection, and in 20 of them, 1 or more other agent was identified as a concomitant cause of fever. Among the 192 FEs with an identified bacterial agent, 147 infections were caused by a single agent (83 from gram-positive [56.5%] and 64 from gram-negative [43.5%] bacteria). Two or more bacterial agents were associated in 45 episodes.

Of 528 patients, 93 invasive fungal diseases (IFDs) were identified (17.6%), with an incidence of 12.4% in the examined population. Molds and yeasts were detected in 80 (86%) and 12 (13%) cases, respectively. Invasive fungal diseases were proven in 24 cases (25.7%), probable in 20 cases (21.6%), and possible in 49 cases (52.7%). In all cases of possible IFD, the suspected etiological agent was a mold. Proven or probable cases comprised 12 yeast (all *Candida* spp), 31 mold (all *Aspergillus* spp), and 1 dimorphic fungus (*Histoplasma capsulatum*) infection. In 73 of 93 IFDs, a single fungal infection was detected; in the remaining 20 cases, a mixed infection was diagnosed.

Viral infections resulted to be the cause of fever in 4 cases only, with a very low incidence in the overall population (4 of 747 AML cases [0.5%]).

During the study period, only 34 FEs were recognized as the cause of death, with an overall incidence in AML cases of 6.4% (34 of 528). The highest attributable mortality rate (11 of 73 [15.1%]) was observed in the IFD group. Overall, 10 deaths were registered in the FUO group (4.8%), 10 in the bacterial group (4.9%), and 3 in the mixed-infection group (14.3%). No deaths were observed either in the viral infection or in the DTRF group. Of 21 patients with mixed infection, 3 patients died (attributable mortality rate [AMR], 14.3%) (**Table**).

Comment. Our study shows that FUO and fungal and bacterial infections were most frequently observed in AML cases. The etiology of FUO, detected in over 38% of episodes, remains unknown despite the use of currently avail-

able diagnostic tools, and FUO-AMR is as high as 5%. This result is important considering the potential progressive expansion of preemptive therapy use in routine practice.

Bacterial infections are the most frequent cause of infectious complications in cases of AML. In our survey, the ratio of gram-positive to gram-negative bacteria approached one. Strikingly, more than 25% of proven bacterial infections were polymicrobial and 9% were mixed infections, of which most were fungal and bacterial.

The incidence of IFDs observed confirmed a trend of increased frequency of mold infections relative to yeast infections; the ratio in our study was 5:1.[1] Considering the high number of observed FUO episodes, we cannot exclude that the incidence of IFDs might be higher. The AMR due to IFDs is decreasing, confirming recent data that report a similar trend.[6]

The incidence of FUO is still high and remains one of the most challenging issues faced by hematologists. Whether viral infections in AMLs are really rare or underestimated is yet to be verified.

Hema e-Chart allows the prospective collection and analysis of targeted high-quality data derived from clinical experience and provides information on the epidemiologic patterns of infectious complications in AMLs, which are rarely studied in prospective multicenter observational trials. Our registry appears to be very useful particularly in the early phases of AML, when infectious complications are more frequent and thus affect the schedule of chemotherapy.

Livo Pagano, MD
Morena Caira, MD
Annamaria Nosari, MD
Giuseppe Rossi, MD
Pierluigi Viale, MD
Franco Aversa, MD
Mario Tumbarello, MD
for the Hema e-Chart Group, Italy

AuthorAffiliations: Ematologia, Università Cattolica S. Cuore, Rome, Italy (Drs Pagano and Caira); Ematologia e Centro Trapianti Midollo, Ospedale Niguarda Ca' Granda, Milan, Italy (Dr Nosari); U. O. Ematologia, Spedali Civili, Brescia, Italy (Dr Rossi); Clinica di Malattie Infettive, Università di Bologna, Bologna, Italy (Dr Viale); Ematologia, Università di Perugia, Perugia, Italy (Dr Aversa); and Malattie Infettive Università Cattolica S. Cuore, Rome (Dr Tumbarello).
Correspondence: Dr Pagano, Istituto di Ematologia, Università Cattolica del Sacro Cuore, Largo Francesco Vito, 1, I-00168 Rome, Italia (lpagano@rm.unicatt.it).
Author Contributions: *Study concept and design:* Pagano, Nosari, Rossi, Viale, and Aversa. *Acquisition of data:* Caira and Aversa. *Analysis and interpretation of data:* Pagano, Caira, Nosari, Rossi, Viale, Aversa, and Tumbarello. *Drafting of the manuscript:* Pagano and Caira. *Critical revision of the manuscript for important intellectual content:* Pagano, Nosari, Rossi, Viale, Aversa, and Tumbarello. *Statistical analysis:* Tumbarello. *Study supervision:* Pagano, Nosari, Rossi, Viale, Aversa, and Tumbarello.

Financial Disclosure: None reported.
Funding/Support: This project was supported by an unrestricted grant from Merck Sharp & Dohme, Italy.
Other Members of the Hema e-Chart Group, Italy: C. Cattaneo, U. O. Ematologia, Spedali Civili, Brescia; R. Fanci, Azienda Ospedaliera–Universitaria Careggi–Ematologia, Firenze; A. Bonini A, Ematologia, Arciospedale S. Maria Nuova, Reggio Emilia; N. Vianelli, Istituto Seragnoli–Università di Bologna, Bologna; M. Riva, Ematologia e Centro Trapianti Midollo, Ospedale Niguarda Ca' Granda, Milano; L. Beltrame, U. O. Ematologia Policlinico Universitario Tor Vergata, Roma; M. Musso, Emato-oncologia ed Unità, Trapianti Midollo Osseo, La Maddalena, Palermo; G. Rossi, Ematologia, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo; N. Filardi, Ematologia, Azienda Ospedaliera–S. Carlo, Potenza; A. Piccin, Ematologia, Ospedale Generale, Bolzano; A. Cuneo, Ematologia, Azienda Ospedaliera–Universitaria Arcispedale S. Anna, Ferrara; M. G. Garzia, Ematologia Azienda Ospedaliera S. Camillo Forlanini, Roma; S. Sannicolò, Ematologia, Umberto I, Mestre; M. Morselli, Ematologia, Policlinico Universitario di Modena e Reggio; U. Salvatori, Ematologia Ospedale Civile "Ca Foncello," Treviso; T. Aloisi, Ematologia, Università di Perugia.

1. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica.* 2006;91(8):1068-1075.
2. Nørgaard M, Larsson H, Pedersen G, Schønheyder HC, Sørensen HT. Risk of bacteraemia and mortality in patients with haematological malignancies. *Clin Microbiol Infect.* 2006;12(3):217-223.
3. Faensen D, Claus H, Benzler J, et al. SurvNet@RKI—a multistate electronic reporting system for communicable diseases. *Euro Surveill.* 2006;11(4):100-103.
4. Angelow A, Schmidt M, Weitmann K, et al; German Transregional Collaborative Research Centre on Molecular Pathogenesis and Therapy of Inflammatory Dilated Cardiomyopathy. Methods and implementation of a central biosample and data management in a three-centre clinical study. *Comput Methods Programs Biomed.* 2008;91(1):82-90.
5. Pagano L, Caira M, Nosari A, et al; Hema E-Chart Group Italy. Hema e-Chart: Italian Registry for prospective analysis of epidemiology, management and outcome of febrile events in patients with hematological malignancies. *J Chemother.* 2010;22(1):20-24.
6. Pagano L, Caira M, Picardi M, et al. Invasive Aspergillosis in patients with acute leukemia: update on morbidity and mortality—SEIFEM-C Report. *Clin Infect Dis.* 2007;44(11):1524-1525.

Pharmaceutical Fraud and Abuse in the United States, 1996-2010

Prescription drug spending totaled $234 billion in 2008 (up from $40 billion in 1990) and accounted for 10% of health care expenditures.[1] Pharmaceutical fraud may be an important component of health care costs. Between 1996 and 2005, $3.6 billion was recovered for 13 pharmaceutical fraud cases initiated by "whistle blowers" (termed *qui tam* relators). These recoveries, despite accounting for 3% of the number of federal fraud cases involving health care, accounted for 40% of federal fraud financial recoveries involving *qui tam* relators.[2] We report on pharmaceutical fraud investigations completed between 1996 and 2010 regardless of *qui tam* relator involvement status.

Methods. All cases involved pharmaceutical manufacturers and False Claims Act (FCA) violations (the most