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ORIGINAL ARTICLE

Analyzing candidemia guideline adherence identifies opportunities for antifungal stewardship

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Abstract

Candidemia epidemiology varies significantly by region; thus, local data are essential for evidence-based decision-making in prophylaxis and treatment. Current management strategies are derived from large randomized controlled trials mostly executed in large high-volume tertiary care centers. Results may not be entirely transferable to smaller hospitals. This study investigates epidemiology, diagnosis, and treatment standards in six hospitals in the Cologne metropolitan area (number of inhabitants approx. one million). We assessed adherence to the current guideline of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA) using the EQUAL Candida Score of the European Confederation of Medical Mycology (ECMM). Data were documented by trained medical students as part of an integrated research and teaching concept at the University of Cologne. Between January 2014 and June 2017, 77 patients had candidemia, corresponding to an incidence of 0.2 cases/1000 admissions. While 55 patients were enrolled, 22 patients were excluded due to incompletely retrievable health records. Fluconazole monotherapy was the preferred first-line treatment in cases with *Candida albicans* infection (21/29). A central vascular catheter was present in 40 patients and was removed in 17 (43%) during treatment. Overall mortality at 30 days was 44%. Patients reached a mean EQUAL Candida Score of 9.9 (range 8–14), which was well below the maximum score of 22 for perfect guideline adherence. In summary, management of candidemia differed from current European recommendations. It remains unclear to what extent enhanced adherence would improve patient outcome. Larger prospective studies need to answer that question.

Keywords Invasive Candida infection · Invasive fungal disease · Blood culture · EQUAL Candida Score

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Introduction

Blood stream infections due to *Candida* species cause substantial morbidity and mortality [10, 17, 30, 40]. Candidemia is frequently associated with delayed or missed diagnosis, worsening outcome in severely ill patients. In particular, immunocompromised and critical care patients are affected [34, 41]. In Europe, at least 15 pathogenic *Candida* species are found in humans, but most *Candida* blood stream infections are caused by *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. Epidemiology varies significantly in different parts of the world, so that local data are of major importance for evidence-based treatment decisions [13, 24].

Known significant risk factors for candidemia are the use of broad-spectrum antibiotics, immunosuppression, central vascular catheters (CVC), hemodialysis, mechanical ventilation, and surgery [1, 6, 26, 39]. National and international recommendations offer guidance on candidemia management [8, 9, 19, 30, 32], but high mortality rates suggest the best treatment strategy is yet to be found [15, 16, 20].

Present treatments are derived from large randomized controlled trials (RCT), but individual management elements, e.g., central venous catheter removal, treatment duration, mandatory ophthalmoscopy, or indications for echocardiography, were not primary endpoints in randomized trials. Moreover, large RCT are mostly performed in large tertiary care centers and results may not be entirely apply to smaller hospitals.

Data from patients with candidemia were systematically documented by trained medical students as part of an integrated teaching and research concept at the University of Cologne. An important goal was to educate students in the practicalities of evidence-based medicine by acquainting them with all steps from source data retrieval to literature search and manuscript drafting.

This study investigated epidemiology, diagnosis, and treatment standards in six hospitals in the Cologne metropolitan area. We assessed adherence to the current guidelines of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) as well of the Infectious Diseases Society of America (IDSA) and the potential impact on outcomes using the EQUAL Candida Score of the European Confederation of Medical Mycology (ECMM) [23].

Patients and methods

Study design and setting

An audit of diagnostic and treatment decisions in patients with candidemia was conducted at six Cologne hospitals (214 to 420 beds) between August and October 2017. Five of the six participating hospitals are academic teaching hospitals associated with the University of Cologne. Medical students (FBC, LK CK, CK, SK, HM, JHN, AR, and JR) were trained for documentation of source data, i.e., health records, and then performed retrospective chart reviews of patients who had at least one documented episode of candidemia between January 1, 2014, and July 1, 2017. Data were collected from electronic and paper-based health records. Incomplete records that did not yield the minimum documentation requirements of first-line antifungal choice and treatment duration were excluded.

Data collection

The electronic case report form (eCRF) ECMM Candida Registry-CandiReg (CandiReg) (ClinicalTrials.gov Identifier: NCT03450005) used for documentation of all cases was designed in EFS Leadership 7.0 Version 1.2 (Questback, Cologne, Germany), accessible through www.clinicalsurveys.net. It contained data items for the assessment of quality in candidemia treatment. Quality indicators were defined as diagnostic (blood cultures, species identification, echocardiography, ophthalmoscopy) and treatment procedures (echinocandin use, transition to fluconazole after susceptibility testing, CVC removal) according to the EQUAL Candida Score (Table 1) [20, 23]. The maximum EQUAL Candida Score counts 22 points for CVC carriers, while 19 for patients without a CVC.

Cases were initially identified from the laboratory database using the Hybase® software. After medical students received training on the hospital information system by infection control personnel at each hospital, they documented cases autonomously. To achieve standardized reporting by students, all eCRF records were double-checked by an infectious disease physician for missing values or inconsistency, and queries were issued until resolved.

Teaching

The evaluation of results as well as the concept of the paper was part of a new teaching concept on scientific writing at the University of Cologne embedded into the Medical School Research Track. This part of the Cologne University curriculum provides interested students insights into biomedical and clinical research by a panel of elective courses. As a requirement, only students who had completed obligatory courses on clinical trials as well as evidence-based medicine and a seminar on candidemia could participate. Nine students participated in this pilot project. After documentation of candidemia cases, a 1-day course trained students in drafting an original manuscript on the basis of STROBE [37]. Sections of this draft were divided among students for further elaboration and OAC and SCM merged revised drafts thereafter.

Table 1 EQUAL Candida Score [23]

Quality indicator	ESCMID/IDSA guidance		Score	
	Strength of recommendation	Level of evidence	Patients with CVC	Patients without CVC
Initial blood culture (40 mL) [12, 30]	Essential	n/a	3	3
Species identification [12, 30]	Essential	n/a	3	3
Susceptibility testing [12, 30]	Recommended	I [12]/III [30]	2	2
Echocardiography [9, 30]	B	II	1	1
Ophthalmoscopy [9, 28]	B	II [9]/III [30]	1	1
Echinocandin treatment [9, 30]	A	I	3	3
Step down to fluconazole depending on susceptibility result [9, 30]	B	II	2	2
Treatment for 14 days after first negative follow-up culture [9, 30]	A [30]/B [9]	II	2	2
CVC removal [2, 9, 30]	A	II		n/a
≤ 24 h from diagnosis			3	
> 24 < 72 h from diagnosis			2	
Follow-up blood culture (at least one per day until negative) [9, 30]	B	III	2	2
Maximum score			22	19

A—strong recommendation; B—moderate recommendation. I—evidence from at least one properly designed randomized controlled trial; II—evidence from at least one well-designed clinical trial, without randomization, from cohort or case-control analytic studies, from multiple time series, or from dramatic results of uncontrolled experiments; III—evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

Microbiology

Candida spp. were isolated from blood using the BactAlert3D™ (BioMérieux, Marcy l'Etoile, France) and the BD BACTEC™ FX (BectonDickinson, Sparks, MD, USA) systems. The isolates were identified to species level using morphology on chromogenic agar plates (BioMérieux, Marcy l'Etoile, France) or the VITEK TWO System (BioMérieux, Marcy l'Etoile, France) and were confirmed by MALDI-TOF mass spectrometry (MALDI-Biotyper™, BrukerDaltonik GmbH, Bremen, Germany). Susceptibility to antifungal agents was determined using the VITEK TWO System (BioMérieux, Marcy l'Etoile, France).

Statistical analyses

To calculate and analyze the incidence of candidemia, numbers of candidemia episodes in each hospital between January 1, 2014, and July 1, 2017, were retrieved by the microbiology laboratories using Hybase®, while admission numbers were obtained from the administrative databases of the respective hospitals.

Categorical variables are presented as numbers and percentages; they were compared using X^2 or Fisher's exact test as appropriate. Continuous variables are presented as mean ± SD or median and range; they were compared using Student's *t* test, Mann-Whitney test, or Kruskal-Wallis test, depending on normality assumption. A two-tailed p value < 0.05 was defined as statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 24.0, IBM SPSS Inc., Chicago, USA).

Results

Patients

Seventy-seven patients with candidemia were identified, corresponding to an incidence of 0.2 cases/1000 admissions. In 22 patients, incompletely retrievable files prohibited documentation. The following results refer to the 55 eligible patients (Fig. 1).

The mean duration of hospitalization was 24.7 ± 28.2 days. Patients had a mean age of 66 years, and 52 (95%) patients had at least one comorbidity (Table 2). Most prevalent underlying diseases were hematologic or oncologic (42%), cardiovascular (38%), and diabetes mellitus (26%). Fifteen patients (27%) had extensive, mostly abdominal, surgery prior to candidemia. Mean time interval between surgery and candidemia was 40 days (range 0 to 120 days). Baseline patient characteristics did not differ between survivors and patients who died during the hospitalization.

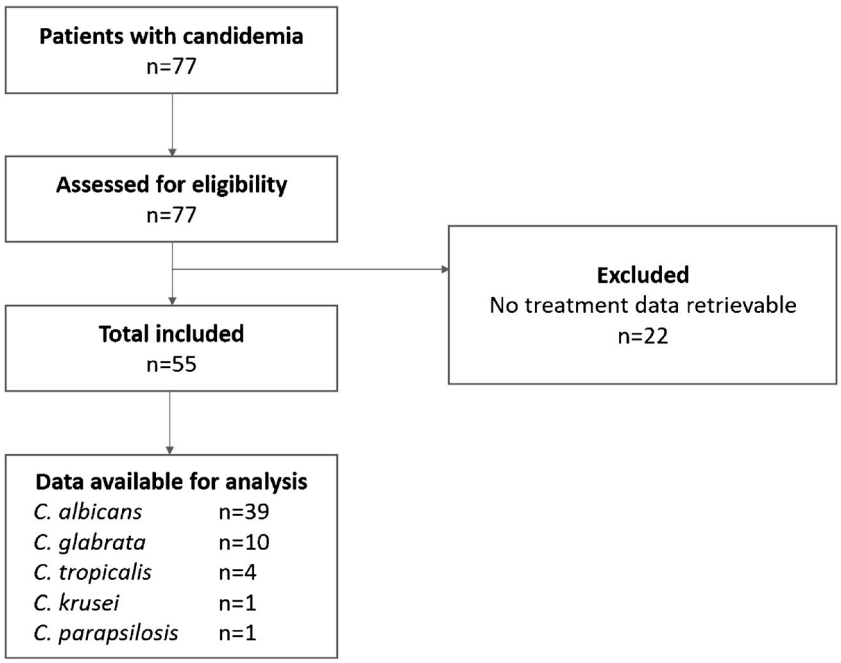

Fig. 1 Study flow chart

Indicators for candidemia guideline adherence

Diagnostic work-up In all cases, *Candida* were identified to species level. All isolates were tested for susceptibility. Echocardiography was performed in 33% and ophthalmoscopy in 2% of patients.

Treatment *Candida albicans* causes the blood stream infection in 77% of cases. Among those, fluconazole monotherapy was given in 72% of cases for an average treatment duration of 14 days (range 0 to 35 days). Table 3 lists targeted treatment. Nine patients who did not receive empirical nor targeted antifungal treatment died before or immediately after receipt of microbiological results. Five patients received combination or sequential therapy, mostly within the azole class, and infrequently by adding an echinocandin. *Candida glabrata* accounted for 18% of episode and was the second most common pathogen. These patients received fluconazole (2), voriconazole (2), caspofungin (2), or amphotericin B (1) monotherapy.

The majority of patients (73%, $n = 40$) had a CVC at candidemia diagnosis. In most patients ($n = 37$), the CVC was removed within 24 h of diagnosis. Among CVC carriers, 11 patients died within a mean of 13 days (range 0 to 70 days). Out of those, five patients died within 2 days of diagnosis of blood stream infection.

Follow-up Only two (3.6%) of the included patients had daily follow-up blood cultures until first negative result.

Patients in our study had a mean EQUAL Candida Score of 9.9 (range 8 to 14). Those without a central line reached a score of 8.9 (range 8 to 13). The mean score was higher in survivors (10.1, range 8 to 14) than in non-survivors (9.2, range 8 to 12) ($p = 0.059$, Mann-Whitney U Test) (Fig. 3).

Outcome

While 30 (54.5%) patients were alive at last contact, 25 (45.5%) patients died within 30 days after diagnosis of candidemia (43.6%) (Fig. 2). Treating physicians attributed six deaths (10.9%) to candidemia.

Discussion

In this retrospective study in six Cologne hospitals, overall candidemia incidence rate was 0.2/1000 admissions. This concurs with the reported general incidence of candidemia in Europe ranging from 0.2 to 0.8/1000 admissions [3, 5, 36], and incidence data from Germany of 0.07 per 1000 patient days during 2006 to 2011 [25]. Species distribution was as expected [7, 25].

While the majority of patients were alive at last contact, 25 (43.6%) patients died within 30 days after diagnosis of candidemia (Fig. 2). These findings are in line with prior reports on overall mortality of around 46% [3, 17, 40]. Treating physicians attributed death in 11% to *Candida* infection, while attributable mortality was described to be over 40% [17, 40].

Our cohort patients were much older than those in large RCT (mean age 69 versus 56 years) [4, 21, 27, 31]. These data support the assumption that not only the growing number of immunocompromised patients contributes to the increase of candidemia but also changing demography [3, 22].

While most published studies were performed at large centers [3, 4, 11, 21, 31], our patients differ in risk factors. We report less

Table 2 Patient characteristics

	All *N* = 55	Survivors *N* = 30	Deceased *N* = 25
Demographic			
Sex			
Female	52.7% (29)	60.0% (18)	44.0% (11)
Male	47.3% (26)	40.0% (12)	56.0% (14)
Age > 70 years	56.3% (31)	53.3% (16)	60.0% (15)
Time of hospitalization (days)	24.7 ± 28.2 (47/55)	29.3 ± 32.8 (27/30)	14.5 ± 3.6 (20/25)
ICU	35.2% (19/54)	34.5% (10/29)	36.0% (9)
Underlying disease			
Major surgery	27.3% (15)	30.0% (9)	24.0% (6)
Abdominal	11	8	3
Non-abdominal	4	1	3
Trauma	5.5% (3)	6.7% (2)	4.0% (1)
Hematology/oncology	41.8% (23)	36.7% (11)	48.0% (12)
Solid organ transplantation	1.8% (1)	3.3% (1)	(0)
Immunosuppression due to other disorder	3.6% (2)	3.3% (1)	4.0% (1)
Alcoholism/alcohol use disorder	5.5% (3)	6.7% (2)	4.0% (1)
Chronic cardiovascular disease	38.2% (21)	33.3% (10)	44.0% (11)
Chronic pulmonary disease	12.7% (7)	10.0% (3)	16.0% (4)
Chronic renal disease	9.1% (5)	3.3% (1)	16.0% (4)
Chronic liver disease	1.8% (1)	3.3% (1)	(0)
Diabetes mellitus	25.5%(14)	30.0% (9)	20.0% (5)
No risk factor identified	5.5% (3)	3.3% (1)	8.0% (2)
CVC information			
Patients with CVC	80.0% (40/50)	79.3% (23/29)	81.0% (17/21)
Removal after diagnosis	42.5% (17/40)	47.8% (11/23)	35.3% (6/17)
Diagnostic procedure bv			
Echocardiography	33.4% (18/54)	40.0% (12)	24.0% (6)
Ophthalmoscopy	1.9% (1/54)	3.3% (1)	(0)
Susceptibility testing	100% (55/55)	100% (30)	100% (25)
Follow-up blood cultures	3.6% (2/55)	6.7% (2)	(0)

immunocompromised (3.6% vs 53–55%), but more patients with hematologic or oncologic malignancies compared to other studies (41.8 vs 10%) [3, 4, 21, 31]. A third of our patients had undergone extensive, mostly abdominal surgery, and most patients had a CVC on the day of candidemia diagnosis.

Microbiological work-up closely followed current ESCMID recommendations including identification to species level and susceptibility testing.

ESCMID and IDSA moderately support a recommendation of echocardiography to exclude endocarditis [9], but only one third of our cohort underwent echocardiography. In Spain, a prospective cohort of 187 patients showed that at least 4.2% of all candidemia patients have *Candida* endocarditis. The latter is often clinically unanticipated and the authors highly recommend performance of echocardiography [14]. Certainly, this is advisable in persistently positive blood cultures or in the presence of peripheral artery embolism.

Currently, ophthalmoscopy is recommended in all candidemia patients, but in fact was done in a single patient only. Of note, none of our patients had clinical signs of eye involvement. Others have scrutinized the need for ophthalmoscopy [28, 38]. Low incidence, symptomatic nature, and favorable outcome of ocular involvement led to question the universal need for ophthalmoscopy in candidemia. Our data mirror that clinically driven approach.

Fluconazole was the initial treatment of choice in most patients, which clearly contrasts with the ESCMID guideline [9]. Such treatment decision is in line though with the US American guideline accepting fluconazole as alternative for those not critically ill and without prior azole exposure. Of

Table 3 Treatment of patients with candidemia

Pathogen	Frequency *n* (%)	Duration of treatment (days)	Drug	Patient number
C. albicans	39 (70.9)	14.0 (0/35)	Monotherapy with	
			Fluconazole	21
			Voriconazole	2
			Caspofungin	1
			Combination* treatment	
			With echinocandin	1
			w/o echinocandin	4
C. glabrata	10 (18.2)	13.0 (1/24)	Monotherapy with	
			Fluconazole	2
			Voriconazole	2
			Caspofungin	2
			Amphotericin B	1
			Combination* treatment	
			With echinocandin	1
			Combination* treatment	
			w/o echinocandin	1
C. parapsilosis	1 (1.8)	8 (8/8)	Monotherapy with	
			Fluconazole	1
C. krusei	1 (1.8)	9 (9/9)	Combination* treatment	
			With echinocandin	1
All *Candida* spp.	55 (100)	13.3 (0/35)	Monotherapy with	
			Fluconazole	24
			Voriconazole	4
			Caspofungin	3
			Amphotericin B	1
			Combination* treatment	
			With echinocandin	2
			w/o echinocandin	5

*Either concomitant or sequential

note, this approach is graded as "weak recommendation" based on "low-quality evidence" [30].

An analysis of seven prospective randomized controlled trials for treatment of candidemia showed an association between CVC removal and decreased mortality [2]. Yet, only observational studies are available for the evaluation of the effects of CVC removal, and results are heterogeneous [18, 29, 33]. The ESCMID and IDSA guidelines, based on moderate evidence, strongly recommend removing indwelling lines [9]. In our patients, CVC removal rate was 43%. CVCs

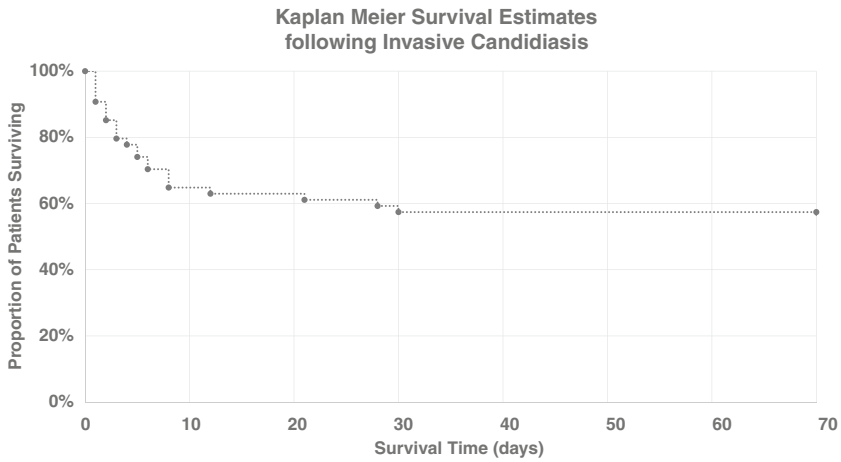

Fig. 2 Patient survival after onset of candidemia (Kaplan-Meier analysis)

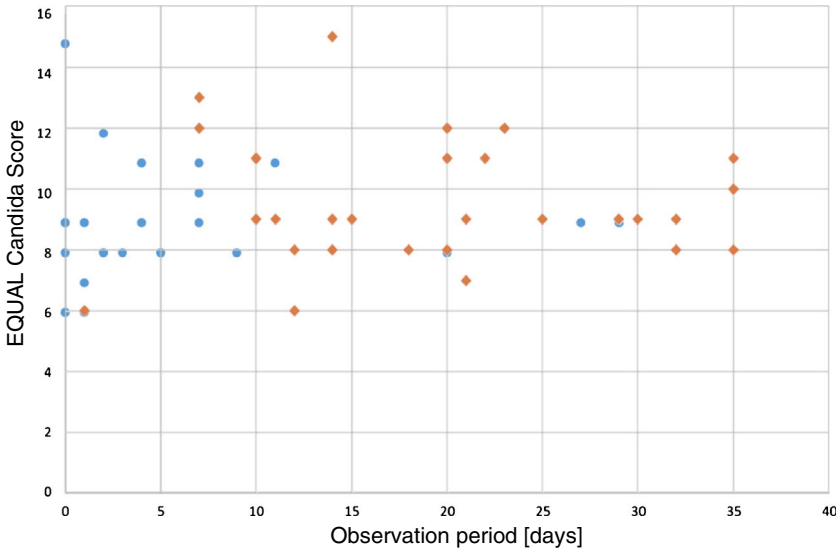

Fig. 3 EQUAL score in survivors (orange) and non-survivors (blue). Mean score was higher in survivors (10.1, range 8 to 14) than in non-survivors (9.2, range 8 to 12) ($p = 0.059$, Mann-Whitney U test)

were removed in survivors more frequently than in non-survivors. However, this difference was not statistically significant (47.8 vs 35.3%, $p = 0.525$). Among patients with retained CVC, five died within 2 days of candidemia diagnosis, two of these on the actual day of diagnosis, rendering it unlikely that CVC removal would have changed the course.

Along ESCMID and IDSA, follow-up blood cultures should be taken daily until negative to determine treatment duration. This was only performed in two patients. However, recommendation by both guidelines is moderate and based on expert opinion. Clinical routine differs from expert recommendation and necessity of daily blood cultures may be discussed.

Measured by EQUAL Candida Score guideline, adherence was higher in survivors compared to non-survivors (Fig. 3) [23]. This score is a tool for quick and simple evaluation of guideline adherence. It is only applicable to patients with the intention to cure, but not to best supportive care situations. The EQUAL Candida Score aggregates and weighs diagnostic as well as therapeutic elements recommended for optimal management of candidemia [2, 9, 12, 28, 30]. In a different invasive fungal disease, namely cryptococcosis, the impact of guideline adherence on mortality was recently shown [35].

Greater adherence to current guidelines is desirable. One approach to increase guideline adherence is infectious disease consultation. Now, this has been offered by infectious disease specialists of the central laboratory. Another approach is infectious disease internships offered by the University of Cologne.

Limitations of this study are its retrospective nature, the small number of patients, a heterogeneous patient population as well as varying follow-up time, and missing data. Non-retrievable files may confound with complex treatment courses. A further limitation is that there are no reference populations to compare our results to as adherence to current guidelines has not been assessed using the EQUAL Candida Score. Future studies with greater sample sizes are required to determine more reliably the association of the EQUAL Candida Score quantifying adherence to ESCMID guidance documents.

However, data collected in this study represent a real-life scenario of routine care and documentation. We combined our research goal with medical student education. By offering an active opportunity to practice clinical research and scientific writing. Ideally, the course will encourage participating students to use guidance documents when facing orphan diseases as practicing physicians.

We observed management of candidemia deviating from current ESCMID and IDSA guidelines, but it remains unclear to what extent enhanced adherence would improve patient outcome. Larger prospective studies were suitable to answer that question.

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Compliance with ethical standards

Conflict of interest OAC is supported by the German Federal Ministry of Research and Education and the European Commission and has received research grants from, is an advisor to, or received lecture honoraria from Actelion, Amplyx, Arsanis, Astellas, AstraZeneca, Basilea, Cidara, Da Volterra, Duke University (NIH UM1AI104681), F2G, Gilead, GSK, Janssen, Leeds University, Matinas, Medicines Company, MedPace, Menarini, Merck/MSD, Miltenyi, Paratek, Pfizer, PSI, Rempex, Roche, Sanofi Pasteur, Scynexis, Seres, Summit, Tetraphase, and Vical. FCK reports grants from the German Federal Ministry of Research and Education, and non-financial support from Miltenyi Biotec GmbH. PK reports non-financial support from Merck/MSD, non-financial support from MedImmune, and lecture honoraria from Astellas, outside the submitted work. HW has received research grants from, is an advisor to, or received lecture honoraria from the German Society for Hematology/Oncology, BeckmanCoulter, BrukerDaltonics, BioMérieux, Hologic, Siemens, BioMérieux, Cepheid, Hologic, iSense, r-biopharm, and SpecificTechnologies. All remaining authors have declared no conflicts of interest.

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