Background: Patients with hematologic diseases are at high risk of bloodstream infections (BSIs). This study aimed to analyze clinical features and distributions of microorganisms in patients with hematologic diseases presenting at a tertiary care university-affiliated hospital in Korea.

Materials and Methods: We retrospectively reviewed all BSI episodes recorded in patient medical records at two hematologic wards of the Catholic Hematology Hospital from January to December 2020. Our aim was to analyze demographic and clinical characteristics relevant to BSIs. We also described the antimicrobial resistance patterns of the major pathogens identified in this study, and evaluated risk factors for extended-spectrum beta-lactamase (ESBL) production in Enterobacteriaceae isolates and for vancomycin resistance in enterococcal isolates.

Results: A total of 380 BSI episodes were identified in 334 patients over the course of 1 year (monomicrobial BSI episodes, 86.1%; polymicrobial BSI episodes, 13.9%). Gram-negative bacteria accounted for 242 isolates (54.8%). The most frequently isolated Gram-negative bacteria isolates were Escherichia coli (107 [24.2%]) followed by Klebsiella spp. (72 [16.3%]), Pseudomonas spp. (21 [4.8%]), and Enterobacter spp. (12 [2.7%]). The most commonly identified Gram-positive bacteria were Enterococcus spp. (72 [16.3%]) followed by viridans streptococci (54 [12.2%]), coagulase-negative staphylococci (CoNS) (22 [5.0%]), and Corynebacterium spp. (22 [5.0%]). ESBL-producing Enterobacteriaceae accounted for 25.1% of the total distribution. Among 54 Enterococcus faecium isolates, 100.0% were resistant to ampicillin and 55.6% showed resistance to vancomycin, while 100.0% (n = 12) of Enterococcus faecalis isolates were susceptible to ampicillin and vancomycin, respectively. Use of ciprofloxacin prophylaxis (odds ratio: 5.20; 95% confidence interval: 1.11 - 24.34; P = 0.04) was an independent risk factor for ESBL production in Enterobacteriaceae BSIs.

Conclusion: Compared with the results of a previous study conducted at the same institution, our findings demonstrated that Gram-negative bacteria remained dominant pathogens in BSIs occurring in patients with hematologic diseases. Our findings also demonstrated a comparatively decreased prevalence of ESBL-producing Enterobacteriaceae in the evaluated BSIs. However, the prevalence of enterococcal BSIs had not decreased, and the proportion of vancomycin-resistant Enterococcus isolates from E. faecium BSIs had increased. In addition, we found that ciprofloxacin prophylaxis was statistically significantly associated with ESBL production in Enterobacteriaceae BSIs. We conclude that, in order to avoid critical
complications and to reduce the burden of antimicrobial-resistant organisms in patients with hematologic diseases, it is necessary to conduct periodic examinations evaluating changes in BSI epidemiology within a single medical center.

**Keywords:** Antimicrobial stewardship; Bacteremia; Drug resistance, Bacterial; Hematologic diseases

## INTRODUCTION

Bloodstream infections (BSI) are critical complications that commonly occur in immunocompromised patients with hematologic diseases, especially in those undergoing intensive chemotherapy or hematopoietic stem cell transplantation. BSI leads to increased patient mortality, delays the timing of treatment, and prolongs hospitalization, thereby leading to a poor prognosis [1]. Among various causative organisms, Gram-negative bacteria and Gram-positive bacteria are common pathogens leading to BSI in patients with hematologic diseases [1-3]. As is well known, most patients are neutropenic at the onset of BSI, and neutropenia is a risk factor for BSI development in immunocompromised hosts [4-6].

Pathogens underlying bacteremia have been changing over time, as have antimicrobial resistance patterns. For example, several studies from Europe and the United States have demonstrated a gradual increase in the prevalence of Gram-positive bacteria isolated from BSIs [7]. This may be due to the increased use of indwelling catheters as well as to more frequent exposure to antimicrobials in the general population [8]. We note that mucosal barrier injury is another common complication occurring in patients with hematologic diseases that can lead to BSIs. In addition, the use of antimicrobial prophylaxis and the administration of empirical broad-spectrum antimicrobials each contribute to transitions in antimicrobial susceptibility trends [7, 9, 10]. However, many recent studies performed in Korea show that Gram-negative bacteria are still the dominant causative pathogens for BSIs [11, 12].

Emerging antimicrobial-resistant organisms adversely affect clinical outcomes in patients with hematologic diseases, due to unexpected delays in administering appropriate antimicrobials and prolonged hospitalizations [11, 13]. Given that the treatment of infections due to multidrug-resistant Gram-negative bacteria has presented a clinical challenge, the recently detected increase in antimicrobial-resistant Gram-negative bacterial infections is of great concern [14].

Hence, this study aimed to examine the clinical characteristics of recent BSI episodes at our medical center, to identify the causative microorganisms leading to these BSIs, and to identify antimicrobial resistance patterns in patients with hematologic diseases presenting at a single hematology hospital. We also aimed to evaluate risk factors for extended-spectrum beta-lactamase (ESBL) production in *Enterobacteriaceae* BSIs and for vancomycin resistance in enterococcal BSIs.

## MATERIALS AND METHODS

### 1. Data collection

We retrospectively reviewed medical records for all BSI episodes in adult patients with hematologic diseases that occurred between January and December 2020 at the Catholic
Hematology Hospital (Seoul, Korea). Patients older than 19 years of age with hematologic diseases were included in this study.

The clinical and demographic data collected for each patient included age, sex, underlying hematologic diseases, treatment for underlying diseases, disease status, absolute neutrophil counts (ANC) at the onset of BSI, C-reactive protein (CRP) levels, comorbidities, organisms isolated from blood samples, and the antimicrobial susceptibility of the detected organisms.

Two sets of blood samples were obtained from each patient. One set was obtained from a peripheral vein puncture and another set was simultaneously obtained from a central venous catheter. In patients in which central venous catheters were absent, two sets of blood samples were collected 30 minutes apart from two different peripheral venipuncture sites. Blood culture results were obtained using an automated blood culture system (BACTEC FX, Becton Dickinson, Sparks, MD, USA). The positive blood culture bottle was sent to Vitek MS (bioMérieux, Marcy L’Etoile, France) and Vitek 2 (bioMérieux, Hazelwood, MO, USA) for direct identification and antimicrobial susceptibility testing. The resulting minimum inhibitory concentration values were classified according to the guidelines set forth by the Clinical and Laboratory Standards Institute [15-17].

2. Ethics statement
The research protocol was approved by the Institutional Review Board of Seoul St. Mary’s Hospital (KC22RISI0001). The requirement for informed consent was waived due to the retrospective study design.

3. Definitions
Neutropenia was defined as an ANC of <500 cells/mm³ or an ANC of <1,000 cells/mm³ that was expected to fall to <500 cells/mm³ within the next 48 hours [3, 18]. Bacteremia was defined according to the isolation of the same bacterial species or pathogen in at least one blood culture examination [19]. If the blood samples yielded potential skin contaminant isolates, these isolates were considered true pathogens only if antimicrobial treatment was initiated under the supervision of infectious disease specialists and if the patient presented with clinical signs and symptoms consistent with infection [20].

BSI was considered polymicrobial if two or more organisms were isolated from a single blood culture sample simultaneously or from separate blood cultures obtained within a span of <48 hours [1, 12]. Consecutive positive blood cultures detecting the same microorganism during the same antimicrobial treatment period were considered indicative of a single BSI episode. Different organisms isolated from a single patient ≥48 hours apart were considered separate bacteremia episodes.

In addition, patients’ highest CRP level was obtained within five days from the culture-positive day, in accordance with previous methodologic study findings [21, 22]. Pathogens presenting with intermediate antimicrobial susceptibility were considered antimicrobial-resistant [11].

4. Prophylaxis, antimicrobial strategies, and antimicrobial stewardship interventions
At our institution, infectious disease specialists are responsible for administering strategies addressing prophylaxis, empirical antimicrobial therapy, and antimicrobial stewardship programs (ASPs). Before October 2016, oral ciprofloxacin (500 mg every 12 hours [q12h]) had
been used as routine antibacterial prophylaxis during any chemotherapy regimen as well as in the course hematopoietic stem cell transplantation until the recovery of the patient’s ANC to >500/mm³ or the first febrile episode. At this time, the initial empirical antimicrobials for neutropenic fever were anti-pseudomonal cephalosporins, cefepime, or ceftazidime (2 g q12h given intravenously [IV]) with aminoglycoside, isepamicin (400 mg q24h by IV), or amikacin (7 – 10 mg/kg q24h by IV). Carbapenems were selected as second-line antimicrobials.

After October 2016 (i.e., following the modification of our ASP), the use of routine ciprofloxacin antibacterial prophylaxis was interrupted. Instead, we started selectively authorizing remission induction or re-induction chemotherapy for patients with acute leukemia as well as in those undergoing cord blood transplantation. Monotherapy with cefepime (2 g q8h by IV) was selected as the first-line empirical antimicrobial, piperacillin/tazobactam (4.5 g q8h by IV) was selected as the second-line antimicrobials, and carbapenems were chosen as the third-line treatment for use in empirical therapy. Empirical glycopeptides were allowed only with evidence of severe mucositis (grade ≥3), combined skin and soft tissue infections, catheter-related infections, Gram-positive bacteremia, or hemodynamically unstable states, with the consultation of infectious disease specialists. Infectious disease specialists changed empirical antimicrobials depending on the confirmed pathogens, findings of antimicrobial susceptibility, and recovery from neutropenia or a febrile state. Antimicrobials were discontinued if a sufficient duration of recovery had been achieved. Patients were followed up at our outpatient clinic if antimicrobial therapy had to be continued.

5. Statistical analyses
The clinical characteristics of the BSIs are presented using counts and percentages for categorical variables and using medians and ranges for continuous variables. Univariate and multivariate logistic regression models were implemented to analyze risk factors for ESBL-producing *Enterobacteriaceae* and vancomycin-resistant *Enterococcus* (VRE). A two-sided *P*-value of <0.05 was considered the threshold for statistical significance. All statistical analyses were performed using SPSS statistical software (version 25.0; SPSS Inc., Chicago, IL, USA).

RESULTS
1. Clinical characteristics of the BSI episodes
The clinical characteristics of the evaluated BSI episodes are described in Table 1. A total of 380 BSI episodes were identified, 48.4% of which occurred in men, and the median age of the presenting patients was 53 years. Patients with acute myeloid leukemia (AML) accounted for 62.6% of these cases, followed by patients with acute lymphoblastic leukemia (ALL; 25.5%), multiple myeloma (MM; 4.5%), and lymphoma (2.6%).

In sorting the BSI episodes into treatment groups, we found that BSIs occurring in patients who underwent consolidation chemotherapy prior to the BSI episode accounted for 50.8% of the evaluated episodes, BSIs associated with remission induction chemotherapy or re-induction chemotherapy accounted for 25.5% of the BSI episodes, and hematopoietic stem cell transplantation accounted for 23.4% of the episodes; there was only one BSI episode in the palliative care group (0.3%).

Regarding the disease status of patients experiencing BSI episodes, 64.2% of the episodes occurred in patients who were in complete remission (CR), 22.1% occurred in patients who
were in incomplete remission (IR), and 13.7% occurred in naïve cases. Moreover, 10.5% of the BSI episodes required intensive care unit (ICU) admission, and 9.5% required the use of vasopressors. A total of 18.7% of the BSI episodes had occurred following the use of ciprofloxacin prophylaxis, and 20% were associated with comorbidities (diabetes, 18.9%; chronic liver disease, 1.1%). A total of 86.1% of the BSI episodes were monomicrobial episodes, while 13.9% were polymicrobial BSI cases.

**2. Distribution of microorganisms**

A total of 442 microorganisms were identified in the 380 BSI episodes analyzed in the present study. Gram-negative bacteria accounted for 242 (54.8%) of the microorganisms, while Gram-positive bacteria accounted for 196 (44.3%). The most frequently isolated Gram-negative bacteria were *Escherichia coli* (107, 24.2%), followed by *Klebsiella* species (72, 16.3%), *Pseudomonas* species (21, 4.8%), and *Enterobacter* species (12, 2.7%).

The most commonly identified Gram-positive bacteria were *Enterococcus* species (72, 16.3%), followed by viridans streptococci (54, 12.2%), coagulase-negative staphylococci (CoNS; 24,

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**Table 1. Clinical and demographic characteristics of bloodstream infection episodes**

| Characteristics | Total (n = 380) |
|-----------------|----------------|
| Male sex        | 184 (48.4) |
| Age (years), median (range) | 53 (18 – 78) |
| Underlying hematologic diseases | |
| AML             | 238 (62.6) |
| ALL             | 97 (25.5)  |
| MM              | 17 (4.5)   |
| Lymphoma        | 10 (2.6)   |
| MDS             | 9 (2.4)    |
| AA              | 4 (1.1)    |
| Others*         | 5 (1.3)    |
| Disease status  | |
| Naïve           | 52 (13.7)  |
| Complete remission | 244 (64.2) |
| Incomplete remission | 84 (22.1) |
| Neutropenia at the onset of BSI (ANC <500/mm³) | 367 (96.6) |
| CRP (mg/dL), median (range) | 14.7 (0.83 – 45.17) |
| ICU admission   | 40 (10.5)  |
| Septic shock    | 36 (9.5)   |
| Use of prophylactic ciprofloxacin | 71 (18.7) |
| Comorbidities   | |
| None            | 304 (80.0) |
| Diabetes        | 72 (18.9)  |
| Chronic liver disease | 4 (1.1) |
| Type of BSI     | |
| Monomicrobial   | 327 (86.1) |
| Polymicrobial   | 53 (13.9)  |

*This category includes chronic myelogenous leukemia (n = 2) and hemophagocytic lymphohistiocytosis (n = 3). AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; MDS, myelodysplastic syndrome; AA, aplastic anemia; BSI, bloodstream infection; ANC, absolute neutrophil count; CRP, C-reactive protein; ICU, intensive care unit.*
5.4%), and Corynebacterium species (22, 5.0%). Of the 72 isolates of Enterococcus species detected in this study, 54 (12.2%) were Enterococcus faecium, 12 (2.7%) were Enterococcus faecalis, and other Enterococcus species such as Enterococcus gallinarum (n = 5) and Enterococcus avium (n = 1) accounted for six (1.4%) of the remaining isolates. Of the 22 Corynebacterium spp. isolates, most were Corynebacterium striatum (n = 21); there was one Corynebacterium jeikerei isolate (Table 2).

3. Pathogen antimicrobial resistance patterns
The antimicrobial resistance patterns of the identified Gram-negative and Gram-positive bacteria are described in Tables 3 and 4, respectively. Among the 107 E. coli isolates, 40 isolates (37.4%) were ESBL-producing E. coli, 67.3% were resistant to ciprofloxacin, and none showed resistance to carbapenems. Of the 72 Klebsiella spp. isolates, 6.9% were ESBL producers and 16.7% were resistant to ciprofloxacin, which added up to a total prevalence of 25.1% for ESBL-producing Enterobacteriaceae. Of the 21 Pseudomonas species isolates, 9.5% of were carbapenem-resistant, showing resistance to imipenem and meropenem. Among the four Acinetobacter baumannii isolates, 100.0% were multidrug-resistant organisms (MDROs). All Stenotrophomonas maltophilia isolates (n = 4) were found to be susceptible to trimethoprim-sulfamethoxazole (TMP/SMX).

Analyzing the antimicrobial resistance patterns of the detected Gram-positive bacteria, 100.0% (n = 54) of the E. faecium isolates showed resistance to ampicillin and 55.6% (n = 30)
showed resistance to vancomycin, while 100.0% (n = 12) of *E. faecalis* isolates were susceptible to both ampicillin and vancomycin. Among the other identified *Enterococcus* species, including *E. gallinarum* and *E. avium*, 83.3% of the isolates showed resistance to vancomycin, resulting in a prevalence of 48.6% of the VRE in total. Of the 54 viridans streptococci isolates, 9.3% were resistant to third-generation cephalosporins. Of the 24 CoNS isolates, 95.8% were methicillin-resistant CoNS (MRCNS). Finally, of the 11 *S. aureus* isolates, 27.3% were methicillin-resistant *S. aureus* (MRSA).

### 4. Risk factors of ESBL-producing *Enterobacteriaceae* and VRE

We performed univariate analyses for the 179 identified *Enterobacteriaceae* isolates. Five variables were identified as potential risk factors for ESBL production, including remission induction/re-induction chemotherapy (odds ratio [OR]: 4.10; 95% confidence interval [CI]: 1.80 - 9.34; *P* < 0.01), IR disease status (OR: 3.48; 95% CI: 1.49 - 8.14; *P* < 0.01), ICU admission (OR: 4.61; 95% CI: 1.51 - 14.14; *P* = 0.01), septic shock (OR: 3.34; 95% CI: 1.10 - 10.13; *P* = 0.03), and the use of prophylactic ciprofloxacin (OR: 5.64; 95% CI: 2.22 - 14.36; *P* < 0.01). Consolidation chemotherapy (OR: 0.17; 95% CI: 0.08 – 0.36; *P* < 0.01) and CR disease status (OR: 0.21; 95% CI: 0.10 – 0.44; *P* < 0.01) each showed an inverse relationship with ESBL production (Table 5). These variables were additionally evaluated using multivariate analysis, which demonstrated that ciprofloxacin prophylaxis was statistically significantly associated with ESBL production (OR: 5.20; 95% CI: 1.11 – 24.34; *P* = 0.04).

On univariate analysis, ALL (*i.e.*, an underlying hematologic disease) was identified as a risk factor for vancomycin resistance in 72 enterococcal isolates (OR: 6.29; 95% CI: 1.58 –24.94; *P* = 0.01), and AML was inversely associated with vancomycin resistance (OR: 0.17, 95% CI: 0.05 – 0.59; *P* = 0.01). However, additional multivariate analysis showed no statistically significant associations with vancomycin resistance (Table 6).
DISCUSSION

This retrospective study examined the clinical characteristics and distributions of microorganisms within 380 BSI episodes occurring in patients with hematologic diseases who presented at our medical center in the year 2020. In addition, antimicrobial resistance patterns for major pathogens were described in this work, which likewise addressed the associated risk factors for ESBL production in Enterobacteriaceae BSIs and for vancomycin resistance in enterococcal BSIs.
We found that the relative prevalence of underlying hematologic diseases in the patients enrolled in our study were somewhat similar to those of a study previously conducted at the same institution between June 2009 and May 2010 [12]. However, as the treatment paradigms for addressing the underlying hematologic diseases have since been revolutionized (for instance, with the use of venetoclax and hypomethylating agents in AML, as well as through the use of targeted immunotherapy agents such as blinatumomab and inotuzumab ozogamicin in ALL [23, 24]), the study populations are clearly distinguishable from each other. Therefore, periodic monitoring evaluating epidemiologic transitions in regard to BSI and changes in resistance patterns of the identified microorganisms at a single medical facility is critical with respect to effective infection prevention and control.

The distribution of the causative microorganisms underlying the BSIs evaluated in this study demonstrated the current persistent dominance of Gram-negative bacteria. *E. coli* was the most commonly identified pathogen, followed by *Klebsiella* spp., *Enterococcus* spp., viridans streptococci, CoNS, and *Corynebacterium* spp. (Table 2). We also found an unexpected result in that *Corynebacterium* spp. was the sixth most prevalent pathogen isolated from BSIs occurring in patients with hematologic diseases [11, 25]. We note that there was no *Corynebacterium* outbreak at our institution during the study period, and that none of the *Corynebacterium* BSI episodes were related to infective endocarditis.

Recently, the proportion of ESBL-producing *Enterobacteriaceae* BSIs in patients with hematologic diseases has increased, according to the results of several previous studies [13, 26, 27]; this trend was consistent within data from different countries [7, 28]. In addition, results from previous studies showed statistically significantly higher mortality due to BSIs caused by ESBL-producing pathogens compared with BSIs caused by non-ESBL-producing *Enterobacteriaceae*, implying an urgent need for an effort to reduce infections caused by MDROs [9, 13].

The most prominent finding in this study is the detected change in ESBL production in *Enterobacteriaceae* over time, compared with the data collected from our medical center from approximately 8 years ago. This previous study showed a prevalence of 43.7% for ESBL-producing *Enterobacteriaceae* BSIs, reflecting the 31.9% prevalence of ESBL-producing *E. coli* and the 71.0% prevalence of ESBL-producing *Klebsiella pneumoniae* [12]. In contrast, our data demonstrated a total prevalence of 25.1% for ESBL-producing *Enterobacteriaceae* within the evaluated BSI episodes, with a 37.4% prevalence of ESBL-producing *E. coli* and 6.9% prevalence of ESBL-producing *Klebsiella* spp.

Although this research did not aim to investigate the effects of the described ASP intervention, the ASP modification implemented during the intervening time period could comprise a possible explanation for the marked decrease in ESBL-producing *Enterobacteriaceae* BSI that was detected in this study. More specifically, we speculate that this finding could be due to an effort to reduce the use of quinolone prophylaxis at our hospital. In addition, multivariate analysis showed an association between ciprofloxacin prophylaxis and ESBL production in *Enterobacteriaceae* BSIs, corresponding to the findings of previous investigations [29, 30].

Our study findings demonstrated that the prevalence of ESBL-producing *E. coli* BSIs had declined, while quinolone-resistant *E. coli* continued to show a high prevalence. Moreover, although the number of identified cases was small, carbapenem-resistant *Enterobacteriaceae* were identified among the *Klebsiella* spp. BSIs detected in this study. In addition, even though
there were only a few confirmed *A. baumannii* isolates, all were carbapenem-resistant, which strongly suggests a research and clinical focus for future studies and intervention protocols.

We note that the prevalence of pseudomonal BSIs was not found to increase at our medical center compared with the evaluation conducted 8 years prior, even though the use of prophylactic ciprofloxacin was reduced. However, we stress that careful monitoring is required. Moreover, we found that quinolone-resistant and carbapenem-resistant *Pseudomonas* did not pose much of an issue at this time. Of the BSI episodes, only 11 (2.5%) were due to *S. aureus*, and the resistance rate to methicillin was less than that found in other studies conducted in Korea [31, 32]. The rate of enterococcal BSIs did not decrease even after implementing the ASP intervention, and no statistically significant independent risk factors for vancomycin resistance in enterococcal BSI were detected in the present study. However, the prevalence of VRE isolates from *E. faecium* BSIs increased compared with that in a previous study conducted at the same institution [33], and hence we conclude that a strenuous effort is required in order to effectively prevent VRE BSIs.

This study has several limitations. First, our findings are based on a single-center investigation with a retrospective study design, and possible missing data for some variables could have led to underestimation or overestimation of the detected associations. Second, some patient information could have overlapped due to the use of episode-based data. Third, a mortality analysis was omitted from this study. Lastly, a data gap exists between this research and the previous study conducted at the same institution, and as such, changes in BSI epidemiology could not be analyzed serially over time.

In addition to these potential limitations, we note several substantial strengths of our study. First, our presentation of subsequent findings from the same medical facility provides a better and more comprehensive understanding of recent trends, periodic transitions of BSI pathogens, and differences in resistance patterns that do standalone investigations conducted in different contexts. Also, the number of BSI episodes evaluated in this study was large compared with that of previous studies, even though the study period was short and the data were collected from a single medical center (likely because this research was conducted at a specialized center) [34, 35]. Future research endeavors as well as a systematic literature review are needed in order to build effective new ASP strategies with the goal of reducing BSIs caused by MDROs. Additional studies evaluating the clinical and molecular epidemiology of the detected increase in *Corynebacterium* BSIs are needed as well. In addition, the relationship between antimicrobial resistance and mortality needs to be addressed more comprehensively in future investigations.

In conclusion, the findings of this study demonstrated that Gram-negative bacteria remained the dominant pathogens detected in BSIs in patients with hematologic diseases, mirroring the results found in a previous study conducted at our medical institution. We also detected a decreased prevalence of ESBL-producing *Enterobacteriaceae* BSI. However, the prevalence of enterococcal BSIs had not decreased, and the prevalence of VRE isolates from *E. faecium* BSIs had increased. In addition, we found that the use of ciprofloxacin prophylaxis was statistically significantly associated with ESBL production in *Enterobacteriaceae* BSIs. We conclude that periodic examinations of changes in BSI epidemiology following alterations in prophylaxis and empirical antimicrobial strategies are needed in order to better avoid critical complications and to reduce the burden of antimicrobial-resistant organisms in patients with hematologic diseases. Moreover, we strongly recommend that future studies evaluate the
potential association between antimicrobial resistance and mortality in patients with BSIs and underlying hematologic diseases. Our findings thereby inform future research directions and directly guide clinical practice and health management at our institution, as well as providing a model for other health care institutions.

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