MAJOR ARTICLE

Community-Associated Extended-Spectrum β-Lactamase–Producing *Escherichia coli* Infection in the United States

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(See the Editorial Commentary by Foxman on pages 649–51.)

Background. The occurrence of community-associated infections due to extended-spectrum β-lactamase (ESBL)–producing *Escherichia coli* has been recognized as a major clinical problem in Europe and other regions.

Methods. We conducted a prospective observational study to examine the occurrence of community-associated infections due to ESBL-producing *E. coli* at centers in the United States. Five academic and community hospitals and their affiliated clinics participated in this study in 2009 and 2010. Sites of acquisition of the organisms (community-associated or healthcare-associated), risk factors, and clinical outcome were investigated. Screening for the global epidemic sequence type (ST) 131 and determination of the ESBL types was conducted by polymerase chain reaction and sequencing.

Results. Of the 291 patients infected or colonized with ESBL-producing *E. coli* as outpatients or within 48 hours of hospitalization, 107 (36.8%) had community-associated infection (81.5% of which represented urinary tract infection), while the remainder had healthcare-associated infection. Independent risk factors for healthcare-associated infection over community-associated infection were the presence of cardiovascular disease, chronic renal failure, dementia, solid organ malignancy, and hospitalization within the previous 12 months. Of the community-associated infections, 54.2% were caused by the globally epidemic ST131 strain, and 91.3% of the isolates produced CTX-M–type ESBL.

Conclusions. A substantial portion of community-onset, ESBL-producing *E. coli* infections now occur among patients without discernible healthcare-associated risk factors in the United States. This epidemiologic shift has implications for the empiric management of community-associated infection when involvement of *E. coli* is suspected.

Keywords. extended-spectrum beta-lactamase (ESBL); *Escherichia coli*; community-associated infection.

Escherichia coli that produces extended-spectrum β-lactamase (ESBL) has become widespread in hospitals around the world since the late 1980s [1]. ESBLs refer to a group of β-lactamases that have acquired the capacity to hydrolyze penicillins, cephalosporins, and aztreonam [1, 2]. Organisms that produce ESBLs are thus resistant to most broad-spectrum β-lactams with the exception of carbapenems. The genes for these

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ESBLs are frequently encoded on transferable plasmids that also encode resistance genes for other classes of antimicrobials [3]. Acquisition of such plasmids can thus promptly render an organism multidrug-resistant [4]. In fact, it is commonly observed that ESBL-producing organisms are resistant to multiple classes of antimicrobials including β-lactams, fluoroquinolones, aminoglycosides, and sulfonamides [1].

The global spread of community-associated methicillin-resistant *Staphylococcus aureus* infections has emerged as a major public concern in recent years [5]. On the other hand, infections due to resistant gram-negative organisms have largely been regarded as a healthcare-associated phenomenon. However, emergence of community-associated infections caused by ESBL-producing *E. coli* has been reported in multiple countries since the mid-2000s [6–8]. In each of these instances, the ESBLs associated with community-associated infection have largely been the CTX-M type, specifically CTX-M-15, distinct from the TEM and SHV types that were historically common [2]. In addition, the majority of CTX-M–producing *E. coli* belong to a specific clone that is defined by phylogenetic group B2, serotype O25:H4, and multilocus sequence typing (MLST) profile ST131, including in the United States [9, 10]. However, the extent and significance of community-associated infections caused by ESBL-producing *E. coli* in the United States have not been elucidated.

The potential spread of ESBL-producing *E. coli* in the community poses a public health concern as well as a challenge to the management of community-associated infections, which are typically treated empirically with agents such as oral cephalosporins or fluoroquinolones without antimicrobial susceptibility testing. The main objective of this study was to describe the occurrence of ESBL-producing *E. coli* in the community, and to assess the clinical outcome of these patients at multiple hospitals and their affiliated clinics across the United States. We also sought to identify additional risk factors associated with healthcare-associated ESBL-producing *E. coli* cases in comparison with community-associated cases.

METHODS

Design and Setting

We conducted a prospective, multicenter, observational study of consecutive, sequentially encountered patients with nonhospital-acquired infection, both inpatients and outpatients, due to ESBL-producing *E. coli* at hospitals and their affiliated clinics in 5 locations in the United States (New York City, New York; Pittsburgh, Pennsylvania; Detroit, Michigan; San Antonio, Texas; and Iowa City, Iowa) between 1 September 2009 and 31 August 2010. Only those cases with community-onset episodes, that is, those who were either outpatients or within 48 hours of admission when bacterial cultures were growing ESBL-producing *E. coli* [11], were collected and included. Patients were followed for 28 days after the onset of infection to assess clinical outcome. If the same patient had >1 episode with ESBL-producing *E. coli* during the study period, only the first episode was included. The study was observational in that administration of antimicrobial agents and other therapeutic management was controlled by the patient's physician rather than the investigators. The study was approved by institutional review boards as required by local hospital policy at the time of the study.

Definitions

All study definitions were established before data analysis. By study design, hospital-acquired infection was excluded. Healthcare-associated infection was defined as meeting one of the following criteria as proposed for bacteremia by Friedman et al [12]: (1) received intravenous therapy at home; received wound care or specialized nursing care through a healthcare agency, family, or friends; or had self-administered intravenous medical therapy in the 30 days before the infection; (2) attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the 30 days before the infection; (3) was hospitalized in an acute care hospital for 2 or more days in the 90 days before the infection; or (4) resided in a nursing home or long-term care facility. These definitions were used for classification of all episodes and not only for bacteremia. Infection not meeting the definitions of healthcare-associated infection was defined as community-associated infection.

Site of infection was determined to be pneumonia, urinary tract infection, surgical site infection, intra-abdominal infection, line-related infection, and otherwise according to Centers for Disease Control and Prevention definitions [13]. Clinical cure was defined as the resolution of signs, symptoms, and laboratory parameters that defined infection for each patient. Previous antimicrobial therapy was recorded for those with activity against gram-negative organisms given for at least 2 days within the 30 days before an episode with ESBL-producing *E. coli*. Antimicrobial therapy for the episode of *E. coli* infection was also recorded when given for at least 2 days within 14 days of collection of the first positive culture. Mortality was death from any cause within 14 days from the date of the first positive culture for ESBL-producing *E. coli*.

Microbiological Analysis

Escherichia coli was identified by manual or automated biochemical testing, and production of ESBL was determined by broth dilution or disk testing in the clinical microbiology laboratories according to the Clinical and Laboratory Standards Institute (CLSI) performance standards [14]. The isolates from community-associated episodes were then forwarded to the research laboratory for further testing. The minimum inhibitory

concentrations of antimicrobial agents commonly used in the treatment of infection due to *E. coli*, including those producing ESBL, were determined with the broth microdilution method using preformulated 96-well plates (Sensititre GN4F, Trek Diagnostics) and interpreted using the CLSI breakpoints [14]. Genes responsible for the ESBL phenotype were determined by polymerase chain reaction (PCR) analysis followed by nucleotide sequencing [15]. Sequence type (ST) 131 strains were identified using a published PCR protocol [16], followed by confirmation with full MLST for representative isolates [17].

Statistical Analysis

SAS software, version 9.2 was used for the analysis (SAS Institute, Cary, North Carolina). Univariate analyses were performed separately for each of the variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for binomial variables. *P* values were calculated by the use of the χ^2 test and median unbiased estimate for categorical variables. All variables with *P* values of <.2 in the univariate model were eligible for inclusion in the multivariable model. The analysis was a logistic regression model that was performed in a stepwise manner with a stay criterion of $P < .05$. Upon the determination of the initial model, variables that were not significant were removed from eligibility and the stepwise model was run again to determine a final model. All tests were 2-tailed.

RESULTS

Characteristics of Community- and Healthcare-Associated ESBL-Producing *E. coli* Episodes

During the study period, a total of 13 279 unique *E. coli* isolates were identified across the 5 participating hospitals. Of them, 523 (3.9%) were identified as ESBL-producing *E. coli*. The rates of ESBL producers were 6.7% in Detroit, 5.7% in New York City, 4.0% in Pittsburgh, 2.0% in San Antonio, and 1.8% in Iowa City. Overall, 292 community-onset episodes due to ESBL-producing *E. coli* occurred. The location of acquisition could not be determined for one episode. Of the remainder, 107 episodes (36.8%) were community-associated and 184 episodes (63.2%) were healthcare-associated. The former included 46 episodes from New York City, 32 from Detroit, 11 from Pittsburgh, 11 from Iowa City, and 7 from San Antonio. Table 1 shows the types of infection associated with ESBL-producing *E. coli*. Community-associated episodes were significantly more likely to represent symptomatic infection over colonization when compared with healthcare-associated episodes ($P < .0001$). As for the locations where the episodes were identified, 49.5% and 33.6% of the community-associated episodes occurred in the emergency rooms and outpatient clinics, compared with 48.4% and 22.8% of the healthcare-associated episodes, respectively. Urinary tract infection (cystitis and pyelonephritis) accounted for the majority of both community- and healthcare-associated infections. However, there were 12 (13.0%) and 22 (18.8%) episodes of bacteremia in these groups, most of which were secondary to urinary tract infection.

Table 1. Types of Infection Observed for Community- and Healthcare-Associated Extended-Spectrum β-Lactamase–Producing *Escherichia coli* Episodes (n = 291)

Infection Status	Healthcare-Associated	Community-Associated	*P* Value
Infection	117 (63.6%)	92 (86.0%)	<.0001
Colonization	59 (32.1%)	10 (9.3%)	
Indeterminate	8 (4.3%)	5 (4.7%)	
Total	184 (100%)	107 (100%)	
Type of infection			
Bacteremia	22 (18.8%)	12 (13.0%)	
Pyelonephritis	26 (22.2%)	13 (14.1%)	
Cystitis	57 (48.7%)	62 (67.4%)	
Cholecystitis	1 (0.9%)	0 (0%)	
Abscess/wound	5 (4.3%)	2 (2.2%)	
Others	6 (5.1%)	3 (3.3%)	

Characteristics associated with healthcare-associated episodes over community-associated ones were male sex, age 65 or older, white race, hospitalization within 1 year, receipt of antimicrobial agents with gram-negative activity within 30 days, and the presence of underlying conditions including chronic obstructive pulmonary disease, cardiovascular diseases, chronic renal failure, dementia, and malignancy on bivariate analysis (Supplementary Table 1). Independent risk factors for healthcare-associated episodes on multivariate analysis included the presence of cardiovascular disease (OR, 3.0; 95% CI, 1.1–7.9), chronic renal failure (OR, 5.6; 95% CI, 1.4–21.8), dementia (OR, 18.3; 95% CI, 2.2–154.2), solid organ malignancy (OR, 8.8; 95% CI, 1.8–43.3), and hospitalization within the previous 12 months (OR, 12.8; 95% CI, 6.6–24.7) (Supplementary Table 1).

Clinical Outcome

Only patients with infection were included in the clinical outcome analysis. Patients with community-associated infection were more likely than those with healthcare-associated infection to be discharged home (93.5% vs 71.1%; $P < .0001$). Information on clinical cure after 96 hours was available for 58.9% of the patients with infection. For those for whom this information was available, the clinical cure rates were 59.0% and 66.7% for community- and healthcare-associated infection, respectively (*P* = not significant). Fourteen-day mortality data were available for 81.8% of the patients. The mortality

rates were extremely low, with 100% and 98.0% of the patients alive after 14 days for community- and healthcare-associated episodes, respectively (P = not significant).

Table 2 highlights the features of all 12 community-associated bacteremia episodes. Eight were secondary to urinary tract infection, and 3 were secondary to intra-abdominal infection. Of the former, 3 patients had documented underlying urological abnormalities. The most common regimens for empiric therapy were cefepime, piperacillin-tazobactam, and ciprofloxacin, which were changed to carbapenems for the definitive therapy in all except 1 patient. While 5 of the patients were discharged to long-term rehabilitation facilities to complete intravenous carbapenem therapy, all patients were alive at 14 days after the onset of bacteremia, and all 10 patients for whom the information was available were alive at 28 days as well.

Microbiological Analysis

Isolates for 3 episodes could not be confirmed as ESBL producers in the research laboratory, likely due to the loss of plasmids encoding the ESBL genes. These isolates were excluded from susceptibility testing and ESBL gene analysis but included in the testing for ST131. The antimicrobial susceptibility of the isolates associated with community-associated episodes is shown in Table 3. Activity of cephalosporins, in particular ceftriaxone, was suboptimal due to the production of ESBL. The agents retaining >90% activity included piperacillin-tazobactam, all of the carbapenems tested (ertapenem, imipenem, meropenem, and doripenem), amikacin, tigecycline, and nitrofurantoin. In addition, minocycline was active against 84.6% of isolates. In contrast, activity of the most commonly used oral regimens for cystitis, fluoroquinolones and trimethoprim-sulfamethoxazole, was severely compromised with just 11.5% and 31.7% of isolates susceptible, respectively. In composite, 64.4% were resistant to both fluoroquinolones and trimethoprim-sulfamethoxazole. For the 17 patients who had received a fluoroquinolone in the prior month, all isolates were nonsusceptible to ciprofloxacin. For the 8 patients who had received trimethoprim-sulfamethoxazole in the prior month, all isolates but 1 were nonsusceptible to this agent.

The types of ESBLs identified are shown in Table 4. The vast majority (95 isolates; 91.3%) had CTX-M–type ESBL. Of those, 75 isolates produced CTX-M-15, which is now the most common ESBL globally. Only 8 isolates (7.7%) had SHV-type ESBLs, and none had TEM-type ESBLs. One isolate produced CMY-2, which is an AmpC-type β-lactamase that confers resistance to cephalosporins like ESBLs. False-positive ESBL test results in *E. coli* isolates producing CMY-2 are known to occur on rare occasions [18, 19]. Of all 107 isolates, 58 (54.2%) were identified as ST131 by PCR. Forty-eight of them (82.8%) produced CTX-M-15. The remainder produced CTX-M-14 (n = 3), CTX-M-22 (n = 1), CTX-M-27 (n = 2), CTX-M-57 (n = 1), or CMY-2 (n = 1), while the ESBL could not be determined for 2. CTX-M-15-producing ST131 strains were observed across the study isolates, but were particularly dominant in New York City and Detroit, accounting for 48.9% (22/45) and 63.3% (19/30) of the community-associated cases, respectively. When 5 isolates (one from each participating site) were subjected to full MLST, 4 had ST131, whereas the other had ST705, a previously reported single-locus variant of ST131 [20].

DISCUSSION

Here we report that more than one-third of community-onset ESBL-producing *E. coli* infection seen at hospitals and their affiliated clinics across the United States are now epidemiologically defined as community-associated, having occurred among patients with no discernible healthcare-associated risk factors. *Escherichia coli* strains that produce ESBL are widespread in healthcare settings, accounting for 9.8% of *E. coli* in US hospitals in 2009 in one study, representing a rapid increase from 5.1% in 2005 [21]. Infections due to ESBL-producing *E. coli* have largely been regarded as a healthcare-associatedphenomenon. However, reports of community-associated infections caused by ESBL-producing *E. coli* started to emerge in the mid-2000s, mostly from Europe and Canada [7, 8, 22]. They have since been observed in other regions of the world including Oceania, East Asia, and South America [23–28]. We reported the first 2 cases of community-associated urinary tract infection due to ESBL-producing *E. coli* in the United States in 2007 [29]. Subsequently, a study from community hospitals in North Carolina reported 27.2% of the ESBL-producing *E. coli* infections observed between 2005 and 2008 to be community-associated [30]. This study was limited to a single state and did not accompany microbiologic analysis. Although comparative historic data are otherwise not available regarding the acquisition location of ESBL-producing *E. coli*, our findings suggest that this organism is already established in communities across the United States.

Among the community-onset episodes surveyed in our study, cardiovascular disease, chronic renal failure, dementia, solid organ malignancy, and hospitalization within the previous 12 months were independent risk factors for healthcare-associated as opposed to community-associated episodes. Although these variables are not included in the generally accepted definitions of the location of acquisition of infection proposed by Friedman et al [12], these are debilitating conditions that would likely require ongoing medical care at least on an outpatient basis. The above-mentioned definitions do not consider outpatient care outside the context of hospital or hemodialysis clinic as a healthcare-associated factor, which

Table 2. Features of 12 Community-Associated Bacteremia Episodes

Age	Sex	Underlying Condition(s)	Admitted From	Source of Bacteremia	Empiric Therapy	Empiric Therapy Appropriate	Definitive Therapy	14-Day Outcome	Discharged To	ST131	ESBL Type
73	M	Congestive heart failure Peripheral vascular disease	Home	Urine	Ciprofloxacin Cefepime	Yes	Imipenem Ertapenem	Survived	LTRF	Yes	CTX-M-14
50	F	Hypertension	Home	Urine	Cefepime	No	Ertapenem	Survived	Home	Yes	CTX-M-15
71	M	Alcohol abuse	Home	Urine	Cefepime	Yes	Ertapenem	Survived	LTRF	Yes	CTX-M-15
76	F	Diabetes	Home	Urine	Cefepime	No	Imipenem Ertapenem	Survived	LTRF	Yes	CTX-M-15
67	M	Diabetes Chronic prostatitis	Home	Urine	Cefepime Gentamicin	Yes	Ertapenem Meropenem	Survived	Home	Yes	CTX-M-15
25	F	Nephrolithiasis	Home	Urine	Ampicillin-sulbactam Gentamicin	Yes	Cefoxitin Amoxicillin-clavulanate	Survived	Home	Yes	CTX-M-15
63	F	Kidney transplant	Home	Urine	Cefepime	Yes	Imipenem Meropenem	Survived	Home	No	SHV-5
63	F	Diabetes Gastric bypass	Home	Abdominal wound	Ciprofloxacin Piperacillin-tazobactam	Yes	Meropenem	Survived	LTRF	No	SHV-7
57	M	Prostate cancer	Home	Urine	Ciprofloxacin Gentamicin	No	Ertapenem	Survived	Home	No	CTX-M-15
73	M	Diabetes	Home	Liver abscess	Cefepime	Yes	Imipenem	Survived	LTRF	Yes	CTX-M-15
35	M	HIV infection	Home	Unknown	Piperacillin-tazobactam	Yes	Meropenem	Survived	Home	No	CTX-M-14
68	M	Kidney transplant	Home	Bile	Piperacillin-tazobactam	Yes	Imipenem	Survived	Home	Yes	Unknown

Abbreviations: ESBL, extended-spectrum β-lactamase; HIV, human immunodeficiency virus; LTRF, long-term rehabilitation facility.

Table 3. Antimicrobial Susceptibility of the Community-Associated Extended-Spectrum β-Lactamase–Producing *Escherichia coli* Isolates (n = 104)

Agent	Susceptible (%)	Intermediate (%)	Resistant (%)
Ampicillin-sulbactam	30.8	54.8	14.4
Ticarcillin-clavulanate	64.4	33.7	1.9
Piperacillin-tazobactam	100.0	0	0
Ceftriaxone	1.9	3.8	94.2
Ceftazidime	57.7	18.3	24.0
Cefepime	72.1	15.4	12.5
Aztreonam	30.8	8.7	60.6
Ertapenem	99.0	1.0	0
Imipenem	100.0	0	0
Meropenem	100.0	0	0
Doripenem	100.0	0	0
Gentamicin	59.6	1.0	39.4
Tobramycin	44.2	8.7	47.1
Amikacin	98.1	1.0	1.0
Tigecycline	100.0	0	0
Levofloxacin	11.5	1.0	87.5
Ciprofloxacin	11.5	1.0	87.5
Trimethoprim-sulfamethoxazole	31.7	0	68.3
Tetracycline	26.0	1.0	73.1
Minocycline	84.6	11.5	3.8
Nitrofurantoin	98.1	1.9	0

may lead to underestimation of healthcare-associated episodes. However, whether routine office visits themselves actually expose patients at risk for acquisition of this organism may be questioned. Alternatively, undocumented antimicrobial use may be more frequent in those with ongoing office visits. Reevaluation of these definitions would require determining the size of the population at risk [31], which could not be done in this study due to its study design.

Table 4. Extended-Spectrum β-Lactamase (ESBL) Types of Community-Associated ESBL-Producing *Escherichia coli*

ESBL	No. of Isolates
CTX-M group	95 (91.3%)
CTX-M-15	78 (75.0%)
CTX-M-14	12 (11.5%)
CTX-M-27	3 (2.9%)
CTX-M-22	1 (1.0%)
CTX-M-57	1 (1.0%)
SHV group	8 (7.7%)
SHV-5	5 (4.8%)
SHV-2	1 (1.0%)
SHV-7	1 (1.0%)
SHV-12	1 (1.0%)
CMY-2	1 (1.0%)

Abbreviation: ESBL, extended-spectrum β-lactamase.

We found that the majority (54.2%) of ESBL-producing strains causing community-associated episodes belonged to ST131 or its related sequence types. Among these strains, all except one produced CTX-M–type ESBL, in particular CTX-M-15. Infections caused by *E. coli* ST131 producing CTX-M–type ESBLs are now commonly observed in US hospitals as well [15, 32]. However, these strains were mostly derived from hospital-acquired or healthcare-associated episodes. Our study thus demonstrates that community-associated ESBL-producing *E. coli* infections in the United States is driven in large part by clonal expansion of ST131 strains carrying CTX-M–type ESBL genes. Although most of the community-associated episodes represented urinary tract infection, in 12 of those (11.2%) bacteremia developed. Eight of the bacteremic cases were due to ST131 strains. All 8 cases survived these episodes, but prolonged carbapenem therapy was required for cure. Carbapenems must be used with caution in this scenario, however, especially in light of the recent acquisition of KPC-type carbapenemase genes by *E. coli* including the ST131 strain in the United States [33].

The risk factors for ESBL-producing *E. coli* in the community remain largely unclear. Evidence from outside the United States suggests that contaminated food sources and travel from a high-prevalence country may be some of them [10]. However, there are currently no data positively linking these sources with ESBL-producing *E. coli* in the community in the United States. Also yet to be elucidated is why ESBL-producing *E. coli* ST131 strains appear to be particularly successful in the community. Although ST131 has been previously considered highly virulent [34], recent data suggest that the virulence potential may vary substantially within ST131 [35–38]. As for antimicrobial resistance, the underlying fluoroquinolone resistance that appears to be present in the majority of ST131 strains would most likely provide them with survival advantage. The ESBL predominantly associated with this sequence type is CTX-M-15, as was observed in this study as well, but other ESBLs and broad-spectrum β-lactamases including CMY and KPC have also been found [10, 33]. Therefore, there does seem to be affinity between ST131 and plasmids encoding these β-lactamases, which may expedite its spread when exposed to selective pressure.

We acknowledge several limitations of our study. We were not able to assess the risk factors for infection with ESBL-producing isolates as opposed to non-ESBL-producing ones owing to the case-only study design. Also, we did not evaluate changes in the incidence of these infections over time. Finally, the scope of molecular epidemiological studies was limited. We plan to address these questions in future investigations.

In summary, community-associated ESBL-producing *E. coli* infections now occur across the United States. The advent of this resistant organism in the community has the potential to affect empiric management of community-associated infection where involvement of *E. coli* is suspected. Continued surveillance and investigation of their reservoirs and spread among healthy persons are needed to monitor the shifting epidemiology and prevent further spread in the community.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. Y. D. has previously received research funding from Merck and consulted for Pfizer. J. S. L. has served as a consultant for Astellas, Merck, Pfizer, and Forest. J. H. J. has received research support from bioMérieux and Merck, served on an advisory board for Becton Dickinson, and consulted for Merck. S. S. R. has served as a consultant for bioMérieux and has received research support from bioMérieux, Cerexa, and Nanosphere. D. L. P. has received research funding from Sanofi Pasteur, served as a consultant for Leo Pharmaceuticals, Novartis, Johnson & Johnson, Merck, AstraZeneca, Pfizer, Bayer/Trius, and Achaogen, and served on the speakers' bureau for AstraZeneca. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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