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CLINICAL AND EPIDEMIOLOGICAL STUDY

Colonization of liver transplant recipients with KPC-producing *Klebsiella pneumoniae* is associated with high infection rates and excess mortality: a case–control analysis

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Abstract
Purpose From mid-2010 to early 2013 there was a large single-center (Leipzig University Hospital, Germany) outbreak of *Klebsiella pneumoniae* carbapenemase (KPC) type 2 producing *K. pneumoniae* (KPC-2-KP) involving a total of 103 patients. The aim of this study was to compare KPC-positive liver transplant recipients (LTR) and KPC-negative controls to determine both the relative risk of infection following colonization with KPC-2-KP and the case fatality rate associated with KPC-2-KP.
Methods The study cohort of this retrospective observational study comprised nine patients who had undergone orthotopic liver transplantation (LTx) (median age of 52 years, range 28–73 years) with confirmed evidence of colonization with KPC-2-KP. The data from these nine LTR were matched to 18 LTR (1:2) in whom carbapenem-resistant pathogens were not present and compared for clinical outcomes.
Results Of these nine cases, eight (89 %) progressed to infection due to KPC-2-KP, and five (56 %) were confirmed to have bloodstream infection with KPC-2-KP. Matched-pair analysis of KPC-positive LTR and KPC-negative controls revealed a substantially increased relative risk of 7.0 (95 % confidence interval 1.8–27.1) for fatal infection with KPC-2-producing *K. pneumoniae* after transplantation with a mortality rate of 78 % (vs. 11 %, $p = 0.001$).
Conclusions Colonization with KPC-2-KP in LTR leads to high infection rates and excess mortality. Therefore, frequent screening for carbapenem-resistant bacteria in patients on LTx waiting lists appears to be mandatory in an outbreak setting. Patients with evidence of persistent colonization with KPC-producing pathogens should be evaluated with extreme caution for LTx.

Keywords *Klebsiella pneumoniae* carbapenemase · KPC-producing *Klebsiella pneumoniae* · Carbapenem resistance · Liver transplant recipients · Mortality

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Introduction

The Gram-negative bacterium *Klebsiella pneumoniae* (KP) is a major cause of nosocomial infections, primarily among debilitated patients [1, 2, 6]. The emergence of strains resistant to carbapenems has left only limited treatment options which are mainly restricted to tigecycline, colistin and gentamicin [1, 11, 17]. Solid organ transplant recipients are especially at risk for infection by multidrug-resistant bacteria. To date, however, little is known about the specific impact of *K. pneumoniae* carbapenemase

(KPC)-producing *Enterobacteriaceae* in this setting [3–7, 9, 14].

From mid-2010 to early 2013 the Leipzig University Hospital, a 1,300-bed referral center, experienced the largest outbreak owing to KPC-2-producing KP (KPC-2-KP) observed in Germany up to that time [8, 17, 18]. This outbreak followed the transfer of a single patient from a hospital in Rhodes, Greece, an area known for endemic occurrence of KPC-producing pathogens [9, 17]. After the index case was detected in July 2010, despite implementation of barrier measures and subsequent establishment of PCR-based screening procedures, until October 2012 an additional 89 patients became either colonized (58 %) or infected (42 %), among them nine liver transplant recipients (LTR). The epidemic curve showed two peaks. The initial peak occurred between July 2010 and May 2011 during which time 42 patients with KPC-2-KP were identified. A high mortality rate of 52 % was observed for these patients, with those patients who were already critically ill being especially susceptible. The second peak occurred between August 2011 and October 2012, during which time 48 patients were affected. No transmissions were detected in June and July of 2011 [16].

Successful containment of the outbreak, defined by the absence of new KPC-positive cases for at least 2 months in the presence of systematic screening measures, was related to the implementation of an overarching concept of infection control. This approach included (1) systematic PCR-based screening for carbapenem-resistant *Enterobacteriaceae* (established in May 2012) upon patient admission, (2) repeated screening during hospital stay, (3) cohorting of KPC-positive patients in a separate hospital section as well as contacts in two specially designated isolation wards, (4) restriction of broad-spectrum antibiotics, especially carbapenems and (5) rigorously practiced barrier measures and hand hygiene [16]. The last case of the outbreak was detected in April 2013, resulting in a total of 103 KPC-2-KP-positive patients.

Prolonged person-to-person transmission (probably via the hands of the healthcare personnel, boosted by contaminated surfaces) was considered to be the most likely cause of the outbreak, possibly with the contribution of undetected KPC-2-KP cases prior to establishment of systematic screening procedures. There was no evidence that the outbreak was caused by a single point source or that staff members colonized by KPC-2-KP served as an unrecognized reservoir.

Methods

Study design and study population

In this retrospective observational single-center study we included nine patients (six males and three females with a median age of 52 years; range 28–73 years), who had undergone orthotopic liver transplantation (LTx) between 15 September 2010 and 14 September 2011. All patients had confirmed evidence of KPC-2-KP in rectal swabs and/or blood cultures, urine cultures, bile cultures, tracheal cultures, peritoneal swabs or wound swabs (Table 1). The presence of KPC-2-KP was confirmed by culture, and molecular typing was performed using pulsed-field gel electrophoresis (PFGE) [21]. During the study period, screening measures for carbapenem-resistant pathogens had not yet been systematically implemented. Contact isolation was required for all patients who were colonized or infected with KPC-2-KP.

The data from these nine LTR were matched to 18 LTR (1:2) in whom carbapenemase-producing pathogens had not been detected (Table 2) and who were transplanted during the same study period. Groups were matched for age, sex, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Model for End-stage Liver Disease (Lab MELD) score directly prior to transplantation and at admission to the intensive care unit (ICU), respectively, and compared for clinical outcomes. All patients were followed up to 31 December 2011.

Microbiological susceptibility testing

Minimum inhibitory concentrations (MICs) of KP isolates were established according to ISO 20776-1 [20] using the microbroth dilution method, and susceptibilities were assessed employing European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints published online in 2012 (i.e., imipenem: $S \leq 2$ mg/L, $R > 8$ mg/L; meropenem: $S \leq 2$ mg/L, $R > 8$ mg/L; ertapenem: $S \leq 0.5$ mg/L, $R > 1$ mg/L; tigecycline: $S \leq 1$ mg/L, $R > 2$ mg/L; gentamicin: $S \leq 2$ mg/L, $R > 4$ mg/L; colistin: $S \leq 2$ mg/L, $R > 2$ mg/L) [19]. When appropriate, results were confirmed by the *E* test (bioMérieux, Marcy l'Etoile, France).

Data collection

Clinical and microbiological data were retrieved using the hospital's patient data management system. The database used by the authors was created in Microsoft Excel for Windows (Excel 2010; Microsoft, Redmond, WA).

Statistical analysis

Statistical analysis was performed using SPSS for Windows (SPSS version 20.0; IBM Corp, Armonk, NY). Numerical variables are summarized as the median, and categorical variables are given as frequencies or

Table 1 Clinical data on liver transplant recipients detected to be infected with *Klebsiella pneumoniae* carbapenemase type 2-producing *K. pneumoniae* (KPC-2-KP) ($n = 9$)

Patient ID	Underlying disease	Gender	Age (years)	Date of LTx (day/month/year)	Date of retransplantation (day/month/year)	Lab MELD	Exceptional MELD	APACHE II score	SOFA score
1	LC CHILD C	Female	50	15/09/2010	N/A	38	No	29	11
2	LC CHILD C	Male	52	25/09/2010	16/10/2011	39	No	22	14
3	LC CHILD C	Male	57	23/09/2010	N/A	13[a]	No	22	8
4	LC CHILD C	Male	47	25/10/2010	N/A	24	No	29	15
5	PSC	Female	27	01/03/2011	N/A	25	31	10	8
6	LC CHILD C	Male	48	30/07/2011	N/A	30	No	31	11
7	HCC	Male	73	30/07/2011	N/A	12	33	14	5
8	LC CHILD B	Male	54	04/05/2011	09/09/2011	8[a]	No	24	8
9	Acute liver failure	Female	63	10/09/2011	13/09/2011	33	No	18	12

Patient ID	Date of earliest KPC-2-KP isolation (day/month/year)	Days from admission to KPC-2-KP colonization	Infection due to KPC-2-KP	Detection of KPC-2-KP bloodstream infection (day/month/year)	Detection of other MDR pathogens	Antibiotic therapy for KPC-2-KP infection	Clinical outcome	Date of death (day/month/year)	LOS (days)
1	10/10/2010	30	Peritonitis	10/10/2010	*Enterococcus faecium* (urine)[b]	Tigecycline, gentamicin	Died (hemorrhagic shock)	03/11/2010	54
2	11/10/2010	25	Pneumonia	06/11/2010	*Enterococcus faecium* (BAL)[b]	Tigecycline, colistin, gentamicin	Alive	N/A	120
3	03/12/2010	72	Pneumonia, UTI	N/A	ESBL (*Enterobacter cloacae*) (UTI)	Tigecycline, colistin, gentamicin	Died (sepsis/MOF due to KPC-2-KP)	14/01/2011	114
4	15/11/2010	24	Surgical site infection, UTI	N/A	*Enterococcus faecium* (UTI)	Tigecycline, colistin	Alive	N/A	150
5	29/11/2010	13	Cholangitis, peritonitis	N/A	ESBL (*Escherichia coli*) (peritonitis)	Tigecycline, colistin, gentamicin	Died (sepsis/MOF due to KPC-2-KP)	26/03/2011	130
6	14/09/2011	50	Surgical site infection	21/09/2011	*Stenotrophomonas maltophilia* (BAL)[b]	Tigecycline, gentamicin	Died (right heart failure)	24/09/2011	60
7	08/09/2011	41	Pneumonia	15/09/2011	*Enterococcus faecium* (BAL)[b]	Tigecycline, colistin	Died (sepsis/MOF due to KPC-2-KP)	18/09/2011	51
8	16/10/2011	39	No (colonization only)	N/A	ESBL (*Klebsiella oxytoca*) (BAL)[b]	No	Died (sepsis/MOF)	19/10/2011	42
9	16/09/2011	8	Pneumonia	19/09/2011	*Enterococcus faecium* (BAL)[b]	Tigecycline, colistin, gentamicin	Died (sepsis/MOF due to KPC-2-KP)	25/09/2011	17

APACHE II Acute Physiology and Chronic Health Evaluation II (severity-of-disease classification system), *BAL* bronchoalveolar lavage, *ESBL* extended-spectrum beta-lactamase, *HCC* hepatocellular carcinoma, *KPC-2-KP Klebsiella pneumoniae* carbapenemase type 2-producing *K. pneumoniae*, *LC* liver cirrhosis, *LOS* length of hospital stay, *LTx* liver transplant recipients, *MDR* multidrug-resistant, *MELD* Model of End-stage Liver Disease, *MOF* multiple organ failure, *N/A* not applicable, *PSC* primary sclerosing cholangitis, *SOFA score* Sequential Organ Failure Assessment score, *UTI* urinary tract infection

[a] Transplanted on the center list

[b] Colonization only

Table 2 Clinical data of matched controls ($n = 18$)

Patient ID	Underlying disease	Gender	Age (years)	Date of LTx (day/month/year)	Lab MELD	Exceptional MELD	APACHE II score	SOFA score	Earliest isolation of MDR pathogens after LTx (days)	Persistent colonization with MDR pathogens	Evidence of infection	Detection of BSI	Clinical outcome	LOS (days)
103	HCC	Male	61	13/09/2010	9	25	16	10	N/A	No	No	No	Alive	58
104	HCC	Female	47	24/10/2010	13	34	12	2	N/A	No	No	No	Alive	22
106	LC CHILD C	Female	43	17/12/2010	16[a]	No	18	3	6	ESBL (*E. coli*–urine)	No	No	Alive	47
109	SSC	Male	54	23/06/2010	17	28	28	9	N/A	No	No	No	Alive	23
120	LC CHILD C	Male	58	03/09/2010	26	No	13	13	N/A	No	Invasive candidiasis, candidemia	Yes	Died (sepsis/MOF)	25
122	HCC	Male	61	06/10/2010	17[a]	No	21	7	N/A	No	No	No	Alive	27
129	LC CHILD C	Male	49	12/01/2011	33	No	11	11	11	ESBL (*E. coli*–wound)	No	No	Alive	56
139	Polycystic liver disease	Female	49	21/01/2011	31	No	10	2	N/A	No	No	No	Alive	28
140	LC CHILD C	Male	66	23/11/2010	19[a]	No	18	9	8	ESBL (*E. coli*–urine)	Urinary tract infection (ESBL - *E. coli*)	No	Alive	98
151	HCC	Male	66	06/01/2011	31	No	30	11	N/A	No	No	No	Alive (re-LTx due to graft failure)	40
152	LC CHILD C	Male	50	25/01/2011	14	33	19	11	2	MRSA (nose and throat)	No	No	Alive	28
155	LC CHILD C	Male	50	29/01/2011	16[a]	No	4	7	15	MRSA (nose and throat)	No	No	Alive	31
159	LC CHILD C	Male	56	18/01/2011	16[a]	No	24	12	21	ESBL (*E. coli*–urine)	Sepsis (ESBL-*E. coli*)	Yes	Died (sepsis/MOF)	94
163	LC CHILD C	Male	65	15/02/2011	19[a]	No	14	9	N/A	No	No	No	Alive	16
167	LC CHILD C	Female	47	08/03/2011	39	No	28	11	N/A	No	Urinary tract infection (*E. faecium*)	No	Alive	38
171	LC CHILD C	Male	56	01/12/2010	34	No	25	6	42	ESBL (*E. coli*–urine)	No	No	Alive	41
173	PBC	Female	55	09/04/2011	22[a]	No	4	7	N/A	No	Urinary tract infection (*E. coli*)	No	Alive	66
180	LC CHILD C	Male	53	21/04/2011	29	No	13	6	1	MRSA (nose and throat)	No	No	Alive	30

BSI Bloodstream infection, *MRSA* Methicillin-resistant *Staphylococcus aureus*

[a] Transplanted on the center list

proportions. Categorical data were analyzed by the chi-square test or Fisher's exact test. The nonparametric Mann–Whitney *U* test was used to compare two independent groups. *P* values (2-tailed) of <0.05 were considered to be statistically significant.

Ethics approval

A corresponding approval from the University of Leipzig ethics committee was obtained before the beginning of the data evaluation. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Due to the retrospective nature of this study the need for informed consent was waived.

Results

KPC outbreak strain

For all 103 KPC-positive patients identified during the outbreak at least one microbiological specimen yielded a *K. pneumoniae* strain carrying the $bla_{\text{KPC-2}}$ gene. Of these 103 cases, 92 were confirmed by culture and 11 by at least two positive KPC-specific PCR results. PFGE patterns of all but two KPC-2-KP strains isolated during the outbreak were considered to be identical to the initial isolate recovered from the index patient transferred from Greece to our hospital for treatment of nosocomial pneumonia.

Liver transplant recipients

Of the nine LTR, two were colonized with KPC-2-KP at 92 and 351 days prior to transplantation, respectively. Seven patients admitted to the ICU after LTx were found to be colonized at a mean of 40 (interquartile range 19–58) days after admission. Three patients underwent retransplantation due to graft failure. Eight of the nine cases (89 %) progressed to infection, and in five of these nine (56 %) patients bloodstream infection with KPC-2-KP was confirmed. Primary infections were pneumonia (4/8 patients), tertiary peritonitis (2/8) and surgical site infections (2/8). All patients had received broad spectrum antibiotics within 30 days before colonization with KPC-2-KP, mainly piperacillin/tazobactam (6/9), third-generation cephalosporins (4/9) or carbapenems (4/9). Antimicrobial resistance tests showed susceptibility to tigecycline (MICs 0.5–2 mg/L, partially only intermediate), gentamicin (all MICs: 2 mg/L) and colistin (MICs: 0.25–1 mg/L). For clinical treatment, these antimicrobials were used in combination [tigecycline given intravenously (IV) 50–100 mg every 12 h; gentamicin given IV 5–7 mg/kg once daily; colistin methanesulfonate given IV 2–3 million IU every 8 h]. Of the nine LTR, four were treated with tigecycline/gentamicin/colistin, two with tigecycline/gentamicin and two with tigecycline/colistin. One LTR colonized with KPC-2-KP without evidence of infection did not receive antibiotic treatment. Antibiotic regimens were selected primarily on the individual decision of attending physicians. Combination therapy with carbapenems (i.e. prolonged high-dose meropenem administration) was discussed, albeit not considered reasonable taking into account that MICs for meropenem and imipenem were ≥16 mg/L in all KPC-2-KP isolates [23, 24].

In matched LTx controls, five cases were colonized with extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and three cases with methicillin-resistant *Staphylococcus aureus* (Table 2). Five infections occurred (5/18); these consisted of invasive candidiasis (1/18), urinary tract infections with *Enterococcus faecium* (1/18) and *Escherichia coli* (2/18), respectively, including an ESBL-producing strain, and bloodstream infection due to an ESBL-producing *E. coli* strain (1/18). One of the patients in this group underwent retransplantation due to graft failure.

Clinical outcomes

Hospital mortality in LTR with KPC-2-KP was 78 % (7/9), with five deaths (56 %) occurring due to sepsis and multiple organ failure with positive blood cultures for KPC-2-KP, and two deaths due to non-infectious complications (right heart failure and hemorrhagic shock, respectively). Among the matched LTx controls, there were two deaths due to invasive candidiasis and bloodstream infection with an ESBL-producing *E. coli* strain, respectively.

Univariate analysis of the matched-pairs showed a significant difference in hospital mortality [78 % (LTR with KPC-2-KP) vs. 11 % (controls); $p = 0.001$] and length of hospital stay (LOS) (60 vs. 32 days; $p = 0.035$). Risk evaluation for mortality revealed a relative risk of 7.0 (95 % confidence interval 1.8–27.1) for LTR with KPC-2-KP.

Discussion

During this single-center outbreak affecting a total of 103 patients, 14 of 42 cases (33 %) with evidence of nosocomial infection by KPC-2-KP occurred in solid organ transplant (SOT) recipients or stem cell transplant (SCT) recipients. This is in line with results from other clinical observational studies published recently demonstrating that up to 41 % of nosocomial infections by carbapenem-resistant *K. pneumoniae* (CRKP) occurred in SOT or SCT recipients [3, 5, 6, 9, 14].

The case–control analysis of LTx patients presented here revealed a very high infection rate of 89 % in LTR colonized with KPC-2-KP, suggesting that this patient group is particularly vulnerable to infections by carbapenem-resistant bacteria [13]. This increased susceptibility is probably related to previous antibiotic exposure, treatment with a complex surgical procedure, prolonged ICU stay, preexisting immunosuppression and the use of invasive devices [5].

In the only major cohort study published to date that focuses on the survival of LTR with infections by CRKP, Kalpoe et al. [14] reported infections due to CRKP ($n = 14$) being the only post-LTx clinical variable independently associated with mortality (hazard ratio 4.9, $p = 0.007$). The survival rate was significantly lower for patients with evidence of CRKP infection compared to patients without CRKP infection (29 vs. 86 %; $p < 0.001$). The poor outcome observed in our LTR cohort associated with KPC-2-KP infection [78 % (hospital mortality in LTR with KPC-2-KP) vs. 11 % (controls); $p = 0.001$] is consistent with data presented by Kalpoe et al. [14] as well as in other published reports [3–7, 9, 13]. Moreover, if one takes into account data provided by Ben-David et al. [10] on infection-related mortality of CRKP bloodstream infections compared to bloodstream infections by sensitive KP strains (CRKP, 48 %; ESBL-producing KP, 22 %; sensitive KP strains, 17 %; $p < 0.001$), the observed excess mortality has most likely to be attributed to carbapenem resistance.

During a 4-year observation period (from 2008 to 2011), we detected invasive infections due to carbapenem-susceptible *Klebsiella* spp. strains in 35 of 283 LTR (12 %) from our transplant center, with a high proportion of ESBL-producers (71 %). The hospital mortality rate in these patients was 30 % (sensitive *Klebsiella* strains) and 36 % (ESBL-producing *Klebsiella* strains), respectively, compared to 78 % in KPC-positive patients ($p = 0.027$).

Nevertheless, controlled studies allowing better guidance of the clinical management of infections by CRKP and other multidrug-resistant bacteria are lacking, and prospective randomized controlled trials with currently available antibacterial agents effective against CRKP are likely not feasible [14]. Previous studies, however, have suggested that the efficacy of currently available antimicrobials is poor, but that the optimized adjunctive management of infectious foci, such as catheter removal, wound debridement and abscess drainage, is essential [10, 11]. Additionally, patients seem to benefit from combination therapy [11, 15, 23, 24].

As results from case–control studies have suggested that antimicrobial exposure is strongly associated with the acquisition of CRKP, cautious antimicrobial use remains extremely important in the prevention of multidrug-resistant bacterial infections [3, 13, 14]. Prolonged antibacterial treatment is not recommended in most clinical situations and does increase the risks of toxicity and development of secondary resistance [13, 14]. In accordance with these data, all LTR in our study had received broad-spectrum antibiotics within 30 days before the detection of colonization with KPC-2-KP.

In times of high failure rates of antimicrobial therapy, infection control strategies are essential for the prevention of bacterial infections [13, 14]. Notably, a supraregional outbreak of CRKP in Israel was not controlled by local measures and could only be contained after a centrally coordinated, nationwide intervention strategy was implemented [10, 14]. Also in our hospital, successful containment of the KPC-2-KP outbreak was related to the strict implementation of an overarching concept of infection control that included systematic screening for carbapenem-resistant *Enterobacteriaceae* [22], cohorting of KPC-positive patients in a separate hospital section as well as contacts in two specially designated isolation wards, restriction of broad-spectrum antibiotics, especially carbapenems, and rigorously practiced barrier measures and hand hygiene [16].

Only two patients in our study were known to be colonized with KPC-2-KP before LTx. However, surveillance was not performed throughout the entire study period, and it appears possible that other LTR in whom KPC-2-KP was detected were also colonized prior to LTx. Therefore, a classification bias between KPC-positive patients and controls cannot be completely excluded.

Active surveillance for the detection of rectal carriage of carbapenem-resistant *Enterobacteriaceae* is now routinely performed in high-prevalence countries, especially upon admission to ICUs [6, 10, 12, 14]. This approach has also been considered a useful means for hospitalized LTx candidates and LTR to allow immediate implementation of appropriate infection control measures to prevent horizontal transmission and to identify patients at risk for infection by carbapenem-resistant pathogens. Although active surveillance studies have demonstrated high infection rates among CRKP-colonized individuals that are associated with substantial mortality [2, 4–7, 14], colonization with CRKP is so far not considered to be a contraindication to LTx [14]. This position might need re-evaluation with respect to the fundamental difficulties of graft allocation due to severe organ shortage in countries such as Germany.

Perioperative antibacterial prophylaxis (i.e., for LTx, administration of cefuroxime + metronidazole) is adjusted at our hospital according to microbiological knowledge of the susceptibilities of the colonizing strains (routinely performed: urine and rectal cultures); therefore, we can potentially minimize the perioperative infection risk.

However, systematic data supporting this strategy are lacking, and prospective studies are needed to validate this approach and to further determine the significance of colonization with KPC-KP or other carbapenem-resistant *Enterobacteriaceae* in LTx candidates.

Our study has several limitations. First, it is possible that other unmeasured factors associated with the severity of disease and length of hospital stay may have contributed to the clinical outcomes observed in our study cohort. Secondly, the observed excess mortality could potentially be confounded by other complications that were present at the time of KPC-2-KP infection.

Conclusions

In conclusion, our observational study suggests that colonization with KPC-2 producing KP in LTx patients may lead to high infection rates and excess mortality and, therefore, frequent screening for KPC-KP and other carbapenem-resistant *Enterobacteriaceae* [22] in patients on LTx waiting lists appears to be mandatory in an outbreak setting.

Patients with evidence of persistent colonization with KPC-producing pathogens failing decolonization efforts [12, 16] should be considered with extreme caution for LTx.

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Conflict of interest All authors deny any potential conflicts of interest, including relevant financial interests, activities, relationships, and affiliations (other than those affiliations listed in the title page) relevant to the subject of this manuscript.

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