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ARTICLE

Use of linezolid in neonatal and pediatric inpatient facilities—results of a retrospective multicenter survey

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Abstract The purpose of this investigation was to describe the use of linezolid in pediatric inpatient facilities. A retrospective multicenter survey including data from nine participating tertiary care pediatric inpatient facilities in Germany and Austria was undertaken. Data on 126 off-label linezolid treatment courses administered to 108 patients were documented. The survey comprises linezolid treatment in a broad spectrum of clinical indications to children of all age groups; the median age was 6.8 years (interquartile range 0.6–15.5 years; range 0.1–21.2 years; ten patients were older than 18 years of age but were treated in pediatric inpatient units). Of the 126 treatment courses, 27 (21%) were administered to preterm infants, 64 (51%) to pediatric oncology patients, and 5% to patients soon after liver transplantation. In 25%, the infection was related to a medical device. Linezolid iv treatment was started after

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intensive pre-treatment (up to 11 other antibiotics for a median duration of 14 days) and changed to enteral administration in only 4% of all iv courses. In 39 (53%) of 74 courses administered to children older than 1 week and younger than 12 years of age, the dose was not adjusted to age-related pharmacokinetic parameters. In only 17 courses (13%) was a pediatric infectious disease consultant involved in the clinical decision algorithm. Linezolid seemed to have contributed to a favorable outcome in 70% of all treatment courses in this survey. Although retrospective, this survey generates interesting data on the off-label use of linezolid and highlights several important clinical aspects in which the use of this rescue antibiotic in children might be improved.

Abbreviations

caMRSA	Community-acquired MRSA
CNS	Central nervous system
EMEA	European Medicines Evaluation Agency
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRCoNS	Methicillin-resistant coagulase-negative *Staphylococcus* spp.
NICU	Neonatal intensive care unit
PICU	Pediatric intensive care unit
PIDC	Pediatric infectious disease consultant
PRSP	Penicillin-resistant *Streptococcus pneumoniae*
VRE	Vancomycin-resistant *Enterococcus* spp.

Introduction

During the last decade, the prevalence of infections due to multidrug-resistant Gram-positive pathogens has been increasing not only among adult but also among pediatric inpatients [1–4]. In addition to new challenges concerning the treatment of community-acquired pneumonia (community-acquired methicillin-resistant *Staphylococcus aureus*, caMRSA; penicillin-resistant *Streptococcus pneumoniae*, PRSP) [5], skin/soft tissue infections (caMRSA) [6], and osteoarticular infections (caMRSA) [7], the emergence of resistant isolates interferes significantly with the clinical management of healthcare-related infections (e.g., to hospital-acquired methicillin-resistant *S. aureus*, haMRSA; methicillin-resistant coagulase-negative staphylococci, MRCoNS; and vancomycin-resistant *Enterococcus* spp., VRE) in high-risk pediatric patients [8–12].

The oxazolidinone antibiotic linezolid [13] displays proven efficacy against infections caused by multidrug-resistant Gram-positive pathogens [14]. Scientific evidence for the use of linezolid in children of all age groups has been derived from prospective studies and a growing number of case reports and case series [15–17].

In contrast to the United States of America, where linezolid has been licensed for certain indications in pediatric patients [18], there is still no regulatory approval for the clinical use of linezolid in children in Europe [15]. Nonetheless, a recent study, including data from the UK, Italy, and Greece, identified significant off-label use of linezolid in European pediatric inpatient care facilities [19]. The aim of the present study was to investigate the use of linezolid in the participating tertiary-care pediatric treatment centers (mainly located in Germany and one in Austria) in a retrospective survey.

Materials and methods

This study was a priori designed as a retrospective multicenter survey. The retrospective approach was chosen in order to avoid the decision for any off-label treatment of a pediatric patient with linezolid as a result of participation of the attending physician in this survey. The final study protocol and the concept of data management was evaluated and approved by the executive committee of the German Society of Pediatric Infectious Diseases (DGPI). Eligible centers were contacted by written information (providing details of the planned investigation) released via e-mail to all registered members of the DGPI. All centers interested in participation were recruited after telephone contact to the principal investigator (A.S.).

Eligible patients and data management

All linezolid treatment courses in pediatric patients were eligible for this survey stipulating the following prerequisites: the off-label treatment with linezolid had to be finished before the date of the first contact to the participating centers. Our main interest was to describe the use of linezolid in patients younger than 18 years old without age restrictions considering the use of linezolid in neonates or premature infants. The protocol allowed for the inclusion of patients older than 18 years if they were treated in a pediatric inpatient care facility (e.g., young adults with cystic fibrosis or relapsed malignancy of a pediatric malignancy). The treatment course with linezolid had to be scheduled for at least five days (with the exception of courses in which adverse events prompted a premature cessation of linezolid treatment).

The case report form (CRF) included basic patient data such as age (at onset of treatment), gender, underlying illness and comorbidities, prematurity (born before 36 completed weeks of gestation), and—in premature infants—birth weight and gestational age at birth. In addition, it comprised data about the clinical indication for linezolid, the type of infection, any relation of the infection to a

foreign body or medical device, previous and concomitant treatment with additional antibiotics, daily linezolid dose* per kg bodyweight, number of administrations*, the duration* of linezolid treatment (*all differentiated between intravenous and oral administration), adverse events attributed to linezolid by the attending physicians, and the outcome of the infection. If available, any results of microbiologic investigations related to the decision to use linezolid in the particular clinical situation were to be documented.

Any individual patient could be included into the survey for more than one linezolid treatment course if the infection treated with linezolid was diagnosed at least 4 weeks apart and was considered as a separate event by the attending physicians.

After the release of a specific drug alert by the U.S. Food and Drug Administration (FDA) in 2007 [20], the manufacturer changed the content of the package insert of Zyvox® (Zyvoxid® in Europe), which requested the clinicians to consider the possibility of a co-infection (mixed infection) with Gram-negative organisms in any case of bacteremia or skin/soft tissue infection. In addition, the new package insert postulates the timely consultation of an infectious disease specialist when treatment with linezolid is initiated. In this regard, the CRF in this study asked for any consultation of a certified pediatric infectious disease consultant (PIDC) before treatment with linezolid was initiated.

Ethical considerations

According to good clinical practice guidelines and European legal regulations, any off-label treatment with a drug not licensed for clinical use in children requires informed consent from at least one parent/legal representative of the child. This issue was not influenced by the retrospective survey, but was the responsibility of the attending physicians, following the decision to treat the patient with linezolid. The protocol of the study was evaluated and approved by the Ethical Committee of the Medical Faculty, University of Bonn, Germany (no. 189/08).

Statistics

Since this survey was retrospective in nature and not a comparative study, the presentation of the data is descriptive. In addition, associations of institutions and of outcome with clinically relevant variables were assessed by the exact versions of Fisher's, Fisher–Freeman–Halton, Kruskal–Wallis, and Wilcoxon–Mann–Whitney tests, where applicable. Two-sided tests were used throughout, and p-values < 0.050 were considered to be significant. StatXact 9.0 (Cytel Inc., Cambridge, MA, USA) was used for exact tests.

Results

In total, nine tertiary care pediatric inpatient facilities participated in the survey and contributed complete datasets of 126 linezolid treatment courses (median 13 per center; range 5–23) (Fig.1). All patients were treated in highly specialized units, such as pediatric oncology (including units for allogeneic hematopoietic stem cell transplantation), neonatal and pediatric intensive care, and pediatric organ transplantation.

The 126 treatment courses were administered to 108 patients (median 13 per center, range 5–18 patients), of whom 63 (58%) were males and 45 (42%) were females. The median age at onset of the linezolid treatment was 6.8 years (interquartile range 0.6–15.5 years; range 0.1–21.2 years; ten patients older than 18 years but treated in pediatric inpatient units). Among the 126 treatment courses, 27 (21%) were administered to 24 preterm infants (median gestational age at birth 26.5 months; range, 22–36 weeks; median birth weight, 650 g; range, 320–2,800 g), 64 (51%) to pediatric oncology patients, 6 (5%) to patients early after liver transplantation, and the remaining 31 (25%) to patients with other underlying

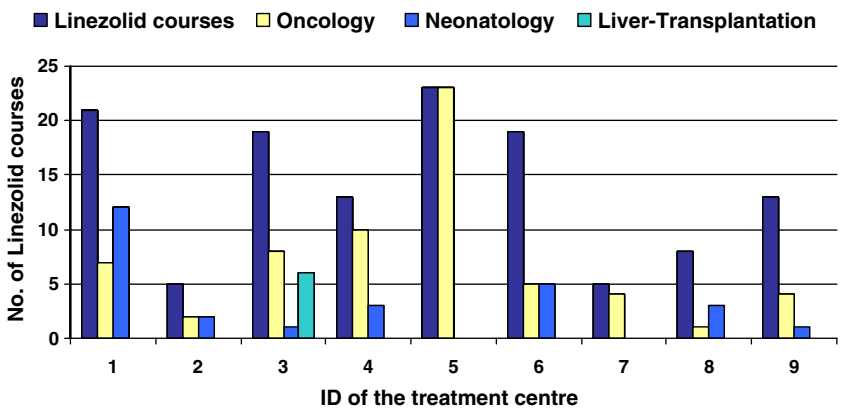

Fig. 1 Distribution of the linezolid treatment courses

diseases/diagnoses. Table 1 shows the number and proportions of chronic underlying diseases and comorbidities.

Tables 2 and 3 display the microbiological and clinical indications for the use of linezolid, respectively. Only 30 (24%) of the 126 treatment courses were related to MRSA or VRE, either as targeted treatment (23) or as empirical treatment in a patient previously colonized (7). Linezolid was used to treat a very broad spectrum of infections (Table 3). In 31 courses (25%), the infection was related to a foreign body or medical device (non-tunneled central venous catheters, Hickman/Broviac or Port-A-Cath long-term intravascular devices, intraperitoneal Tenckhoff catheter, bile duct catheter after liver transplantation, ventriculo-peritoneal shunt, Rickham reservoir, cardiac pacemaker, urinary tract catheter, Quinton dialysis catheter, tibia endoprosthesis after bone tumor resection).

In 104 (83%) of all linezolid courses, the patients had been treated before with up to 11 other intravenous antibiotics (median 3) for a median time of 14 days (interquartile range 8–26 days). In 69 (55%), the previous treatment had included a glycopeptide (vancomycin 35%, teicoplanin 20%), in 48% a carbapenem had been used (meropenem 42%, imipenem–cilastatin 6%). In only five courses (4%), the previous treatment had included fosfomycin.

In only 17 (13%) of linezolid treatment courses applied in only 4 of 9 centers was the consultation of a PIDC documented in the CRF ("timely before or after linezolid treatment started"). The proportion of courses with PIDC consultation increased significantly during the time period studied, from 7% initially to 21% in the last two years ($p=0.043$).

Linezolid was administered intravenously (iv) in 86% of all courses and orally (po) in 10%; in 4%, treatment was started iv and was subsequently switched to po administration. Details considering the daily dose of linezolid were available for 115 of the 126 treatment courses (91%). The iv dose ranged from 10 to 42 mg/kg/day (median 22; interquartile range 20–30 mg/kg/day) and the po dose from 15 to 38 mg/kg/day (median 22; interquartile range 17–30 mg/kg/day). In 35 (47%) of the 74 linezolid courses administered to patients older than 1 week and younger than 12 years of age, the recommended daily dose of 3×10 mg/kg was given; most patients received only 2×10 mg/kg/day. The duration of treatment was 2–56 days

Table 1 Underlying diseases and comorbidities in 126 linezolid treatment courses administered to 108 patients

Underlying disease/comorbidities	No. of courses	Proportion[a] (%)
Oncology	64	50.8
Prematurity	27	21.4
Gastrointestinal disease	8	6.3
Pulmonary disease	8	6.3
Urogenital disease	6	4.8
Hematology	9	7.1
Cardiology	2	1.6
Central nervous system	8	6.3
Hepatic/bile duct	5	4.0
Down syndrome	5	4.0
Cystic fibrosis	4	3.2
Myelodysplastic syndrome	3	2.4
Hemolytic uremic syndrome	2	1.6
Septic granulomatosis	1	0.8
Hemophagocytic lymphohistiocytosis	1	0.8
Myotonic dystrophy Curschmann–Steinert	1	0.8
VACTERL association[b]	1	0.8
Multidrug-resistant tuberculosis	1	0.8
Mitochondrial myopathy	1	0.8

[a] Referring to 126 linezolid treatment courses

[b] Vertebral anomalies, anal atresia, congenital heart disease, trache-oesophageal fistula or esophageal atresia, reno-urinary abnormalities, and radial limb defects

Table 2 Microbiological indications for linezolid treatment (126 treatment courses)

Microbiological indication	No.	Proportion (%)
MRSA infection	7	5.6
Severe infection in a patient previously colonized with MRSA	1	0.8
VRE infection	16	12.7
Severe infection in a patient previously colonized with VRE	6	4.8
Other[a]	96	76.2

[a] For example, sepsis not responding to conventional treatment, severe systemic or local infection due to MRCoNS, sepsis due to viridans streptococci, linezolid instead of vancomycin in patients with sepsis and severe renal impairment, multidrug-resistant tuberculosis ($n=1$)

Table 3 Clinical indications for linezolid treatment (126 treatment courses)

Type of infection	No.	Proportion (%)
Pneumonia	12	9.5
Bloodstream infection	60	47.6
Skin/soft tissue infection	6	4.8
CNS infection	9	7.1
Other[a]	49	38.9

[a] For example, infection of a ventricular-peritoneal shunt device, urinary tract infection exit site/tunnel infection of a long-term central venous catheter, chronic infection related to prosthetic implant after bone tumor resection, severe gastrointestinal infection (gut perforation, peritonitis, necrotizing enterocolitis, cholangitis after liver transplantation)

(median 12; interquartile range 7–17) in the iv courses and 3–730 days (median 14; interquartile range 13–40) in the po courses. In 8 (7%) of 114 iv treatment courses and in 5 (29%) of 17 po treatment courses, linezolid was administered for more than 28 days (the upper time limit of the FDA approval for the duration of treatment).

In 111 (88%) treatment courses, linezolid was administered in combination with other antibiotics; combination treatment contained a carbapenem in 64 courses (51%) and a glycopeptide (vancomycin) in 10 courses (8%). In only 15 (12%) of the 126 courses was linezolid given as monotherapy.

Table 4 illustrates the distribution of the four different categories which had been offered to the participating physicians in the CRF to describe the outcome of the infection treated with linezolid. In the majority of all cases, the infection was cured (52%) or the patient at least experienced a significant overall improvement during linezolid treatment (18%). Eventually, 18 deaths were observed (mortality, 16.7% referring to 108 patients and 14.3% referring to 126 documented treatment courses). In nine cases, the death of the patient was definitely or probably related to the infection (lethality, 7.1% referring to 126 infections).

Irrespective of any causal relationship, a significant proportion of the patients (21%) experienced severe adverse events during linezolid treatment. The most common of these adverse events were thrombocytopenia (nine courses, always reversible), neutropenia (only in oncology patients, always reversible), transiently elevated liver enzymes (five courses; one patient with concomitant adenovirus infection), and one case of pancreatitis. Arterial hypertension was observed in a 2.8-year-old toddler who developed a mean blood pressure of 132 mmHg and had to receive antihypertensive medication; no information on possible drug interactions was available in this case. Linezolid was chosen as a 'nephroprotective' alternative to vancomycin in eight courses (6%) involving patients with severely impaired renal function.

Table 4 Outcome of 126 infections treated with linezolid (in 88% in combination with other antibiotics)

Outcome	No.	Proportion (%)
Complete recovery from the infection	65	51.6
At least a significant improvement of clinical status	22	17.5
No improvement, change of treatment	18	14.3
Linezolid treatment prematurely stopped because of an SAE	3	2.4
Death of the patient	18	14.3

SAE serious adverse event

In only three courses (2.4%) was the administration of linezolid prematurely stopped due to severe adverse events allocated to linezolid by the attending physicians. Severe skin reactions (drug exanthema, eosinophilia, and itching) led to the cessation of linezolid. Neuropathic adverse events related to linezolid treatment were not observed in this survey. The duration of treatment did not correlate with adverse effects allocated to linezolid by the attending physicians (data not shown).

In one case with VRE sepsis after allogeneic stem cell transplantation, linezolid was changed to quinupristin/dalfopristin after the in vitro testing of the vancomycin-resistant *Enterococcus faecium* isolate derived from blood culture displayed only intermediate sensitivity to linezolid in vitro. In a second case, a linezolid-resistant (vancomycin-resistant) *E. faecium* isolate was intraoperatively sampled during hepatic transplantation from the bile duct of a patient who had been treated with linezolid preoperatively. The patient eventually recovered after a change of the antibiotic regimen to teicoplanin and later on to tigecycline.

The nine participating centers differed significantly regarding indications for linezolid use ($p<0.001$), the proportions of episodes of linezolid use with prior consultation of a PIDC ($p<0.001$), the median number of antimicrobials used before linezolid ($p<0.011$), and the outcome of the episodes ($p<0.001$).

Regarding outcome, complete recovery from infection was significantly more frequent in preterm children (74% vs. 45%, $p=0.010$) and in patients with "other diagnoses", i.e., not oncologic diagnoses and not after liver transplantation (72% vs. 35%, $p<0.001$). Outcome was not significantly associated with indication, kind of infection, or with PIDC consultation.

Discussion

To our knowledge, this study represents the first retrospective survey evaluating the off-label use of linezolid in pediatric inpatient facilities in Germany and Austria. Although, due to methodical limitations, the data yielded from this survey is not comparable to data derived from a prospective study, it documents a significant amount of off-label use in critically ill, high-risk patients among all pediatric age groups.

We believe that this survey provides a representative impression of the issue of interest. Although we are not aware of any definite data, it seems improbable that linezolid is used outside tertiary care centers in Germany, due to the concentration of high-risk patients in specialized units (e.g., oncology with stem cell transplantation, extremely low birth weight neonates, etc.) and due to the very high cost of linezolid compared to standard antibiotics used in children.

Whereas linezolid was administered to children of all age groups, a significant proportion of all patients (22%) were premature neonates treated in neonatal intensive care units. Kocher et al. [17] recently reviewed the available data on linezolid treatment in neonates and preterm infants and identified five studies and eight case reports including cases of endocarditis due to VRE [21] and to MRSA [22]. A dosage regimen of 10 mg/kg bodyweight given either orally or intravenously every 8 h in infants aged ≥1 week and the same dose given every 12 h in infants <1 week [23] was shown to be safe and effective, with a mean treatment duration of 10–28 days in the treatment of infections with multiresistant Gram-positive pathogens in preterm infants.

In 25% of all courses in this survey, the infection was related to a foreign body or medical device. There are many reports describing the successful treatment of central nervous system (CNS) infection due to multiresistant Gram-positive pathogens with linezolid in infants and children [15]; most of these events were related to a ventriculoperitoneal shunt [24, 25]. Pharmacokinetic studies revealed the sufficient penetration of linezolid from plasma into the CNS; inflammation of the meninges does not seem to influence the penetration of linezolid into the cerebrospinal fluid [26]. However, these positive reports of linezolid treatment in premature infants have to be interpreted cautiously. The distribution of linezolid into the cerebrospinal fluid of an individual patient may be highly variable [27]; the monitoring of linezolid concentrations through an external ventricular drain may be beneficial in these patients, but technical resources for the drug monitoring of linezolid are not available in most centers.

In addition, the introduction of a new antibiotic in clinical care may cause a publication bias; negative experiences with linezolid may be underreported [28]. Finally, the timely detection of toxic neuropathy [29] of the peripheral nervous system, including optic neuropathy or auditory nerve neuropathy, which have been described in a small number of children and adolescents [30–32], remains a significant challenge in premature infants. Neuropathic adverse events were not observed in this survey.

Eventually, this survey, which primarily included pediatric patients, comprises ten linezolid treatment courses in adults (>18 years of age). These adult patients have been treated in pediatric inpatient facilities (median age 19.0 years; range, 18.2–21.2 years). One was a young adult with cystic fibrosis (CF) and pulmonary exacerbation due to MRSA infection [33]. In Germany, young adults with CF often prefer to be treated in specialized pediatric units. All other patients were suffering from relapsed leukemia, lymphoma or relapsed solid tumors primarily diagnosed during adolescence, or from a congenital immunodeficiency syndrome. In four cases, the patient was cured; in two cases at least a significant improvement of the situation was observed; in two cases, treatment was changed; and two patients eventually died (in one case of central venous catheter sepsis in an oncology patient, death was probably related to the infection) [34].

The vast majority of all patients (83%) had been treated with numerous other antibiotics for a median time of 14 days, including glycopeptides and carbapenems, before linezolid treatment was initiated. Considering the overall ‘efficacy’ of linezolid treatment in this survey (limited by methodological aspects), the question arises as to whether it may have been beneficial to start linezolid earlier in the course of the infection. The off-label status of linezolid in children and the limited clinical experience with linezolid under these circumstances may represent serious obstacles responsible for a significant delay in initiating appropriate treatment. Fosfomycin, used only in 4% of all courses in this survey, may be a feasible alternative to or a reasonable combination partner with other systemic antibiotics in VRE infections [35].

One remarkable observation of this survey was that a significant proportion of all children younger than 12 years of age (57%) did not receive the correct age-adjusted dose of linezolid [36–38]. We can only speculate whether a lack of knowledge about age-related differences in linezolid pharmacokinetics might have caused this problem. This may be an issue of antibiotic stewardship programs and might have been detected by a PIDC during bedside consultation [39].

Another aspect of PIDC counseling would have been the transition from iv (86%) to po administration, taking into account the high bioavailability of po-administered linezolid. In this survey, sequential treatment (first iv, then po) is documented in only a small number of cases (4%). Sullivan and Tobias [40] reported preliminary retrospective data on the use of oral linezolid in infants admitted to a pediatric intensive care unit (n=7; age 6 weeks to 12 months) for the completion of antibiotic therapy in the outpatient setting. Primary infectious disease issues included endocarditis, tracheitis, pneumonia, or central line sepsis resulting from MRCoNS, MRSA, and enterococci. All patients were discharged home to complete their course of linezolid po (7 days to 6 weeks). No complications related to linezolid therapy and no rehospitalizations were noted. One important advantage of this approach is the avoidance of prolonged vascular access. Even in patients in whom outpatient treatment is not feasible, the change from iv to po may be of benefit from a pharmacoeconomic perspective [41].

The low proportion of cases in which a PIDC had been involved in the clinical decision process (13%; in only 4 of 9 centers) reflects the low availability of certified PIDCs even in specialized tertiary care centers in Germany.

Important interventions under the responsibility of a PIDC are to reduce uncontrolled patterns of antibiotic prescribing in clinical practice and to give advice to the attending physicians on the appropriate use of rarely indicated 'rescue antimicrobials' in particular cases. In case of an adverse outcome of the infection treated with linezolid, the missing documentation of a PIDC consultation may display a negative impact on the institution from a legal perspective. The increasing number of complicated infections in high-risk patients due to multiresistant pathogens underscores the critical need for PIDCs in German tertiary care treatment facilities [19].

Besides other indications, linezolid has been shown to be an efficacious treatment option in children with multidrug-resistant tuberculosis [42], including case reports from children [43]. One patient in this survey received linezolid for this indication po for 730 days without severe adverse effects. At the time of this writing, he is well and still cured of his infection.

The duration of treatment exceeded the time frame of linezolid treatment of the package insert (28 days) [18] in 7% of all iv and in 29% of all po treatment courses. Prolonged treatment may be associated with an increased risk of severe adverse events, including hematotoxicity, peripheral neuropathy [30–32], and lactate acidosis, since linezolid interferes with mitochondrial metabolic pathways [29, 44]. Thus, a prospective monitoring protocol for all patients receiving prolonged courses of linezolid, adjusted to the age of the patient, should be provided [45].

This survey documents only two cases in which linezolid was changed to other antibiotics as a result of in vitro sensitivity testing of the related pathogen (VRE). The single case with intraoperative sampling of a linezolid-resistant isolate after treatment with linezolid raises the suspicion of the emergence of resistance during linezolid therapy of an *E. faecium* infection [46]. Appropriate dosing schedules, reasonably limited treatment duration, and repeated in vitro testing of relevant microbiological samples are necessary in order to avoid the selection and to foster the timely detection of linezolid-resistant isolates [47, 48]. The nosocomial spread of linezolid-resistant multiresistant Gram-positive pathogens is a matter of concern and highlights the critical role of stringent hospital infection control policies [49, 50].

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