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Multicenter study to assess the use of BL-DetecTool for the detection of CTX-M-type ESBLs and carbapenemases directly from clinical specimens

Mariana Fernandez-Pittol,[1,2] Jordi Bosch,[1,2] Clara Ballesté-Delpierre,[3] Camille Gonzalez,[4] Alexandra Vasilakopoulou,[5] Dàmaris Berbel,[6] Eleonora Riccobono,[7,8] Sören Gatermann,[9] Katalin Kamotsay,[10] Sophie Reissier,[11] Dora Szabo,[12] Albert Zoltan Aszalos,[13] Laura Francius,[14] Hervé Volland,[15] Milovan Stankov-Pugès,[14] Magda Rosenmöller,[16] Thierry Naas,[4] Jordi Vila[17,18,19,20]

AUTHOR AFFILIATIONS See affiliation list on p. 7.

ABSTRACT Antimicrobial resistance (AMR) is one of the major public health problems worldwide. Multiple strategies have been put in place to address this problem. One of them is the rapid detection of the mechanisms of resistance, such as extended-spectrum beta-lactamases (ESBLs) and/or carbapenemases. We conducted a multicenter study that included nine European centers for the assessment of prototypes of a novel lateral flow immunoassay-based device (BL-DetecTool) for a rapid detection of ESBL (NG-Test CTX-M-MULTI DetecTool) and/or carbapenemases (NG-Test CARBA 5 DetecTool) from *Enterobacterales* and *Pseudomonas aeruginosa* in positive urine, positive blood cultures, and rectal swabs. We performed a prospective analysis between January 2021 and June 2022, including overall 22,010 samples. Based on each hospital information, the sensitivity to detect CTX-M was 84%–100%, 90.9%–100%, and 75%–100% for urine, positive blood cultures, and enriched rectal swabs, respectively. On the other hand, the sensitivity to detect carbapenemases was 42.8%–100%, 75%–100%, and 66.6%–100% for urine, positive blood cultures, and enriched rectal swab, respectively. BL-DetecTool allows a rapid and reliable detection of ESBL and carbapenemases directly from urine, positive blood cultures, or enriched rectal swabs, being an easy technique to implement in the workflow of clinical microbiology laboratories.

IMPORTANCE The assessed rapid assay to detect CTX-M beta-lactamases and carbapenemases directly from clinical samples can favor in the rapid detection of these mechanisms of resistance and hence the administration of a more adequate antimicrobial treatment.

KEYWORDS antibiotic resistance, carbapenemases, ESBL, rapid test, lateal flow immunoassay, direct sample

Antimicrobial resistance (AMR) is one of the major public health problems of the last years with an important clinical and economic impact (1). The World Health Organization recognized in 2015 the need to contain AMR and generated a series of recommendation to reduce the emergence and spread of these microorganisms (2, 3). In Europe, a consensus report was also released in 2021 by the European Centre for Disease Prevention and Control that included the analysis of 29 countries and described not only the public health implications but also the need of a common effort to increase surveillance networks that allow prevent and detect resistance. Moreover, there is a need of investment for strengthening the health system and preparedness (4). The report showed an overall increase in the population-weighted percentage of carbapenem resistance for both *Escherichia coli* and *Klebsiella pneumoniae* during 2017–2021. This

Editor Erin McElvania, Department of Pathology and Laboratory Medicine, NorthShore University HealthSystem, USA

Address correspondence to Jordi Vila, Jvila@clinic.cat.

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increase was also observed in *Acinetobacter* spp. and *Pseudomonas aeruginosa*. In Spain, the rates of AMR also increased as the rest of Europe and a significant decreased of the percentage of resistant isolates was reported only for methicillin-resistant *Staphylococcus aureus* (4).

Given the problems of resistance, different strategic actions are targeted at development of pathogen-specific drugs, improvement diagnostics, and immunotherapy (5). In general, the resistance phenomenon not only included the infection control, but it is also related with environmental factors and geographical movement of humans and animals. The One Health perspective has allowed a better understanding of the AMR problem and to initiate a new perspective to fight against it, considering that it cannot be solved focusing exclusively on humans (6). Without any doubt, an active work of different professionals is needed to tackle this problem. The development and evaluation of diagnostic test and reagents for recognizing resistant organism is very important in that respect (7).

One intervention is the development of rapid test for the detection of the mechanisms related to antibiotic resistance, such as extended-spectrum beta-lactamases (ESBLs) and/or carbapenemases in *Enterobacterales*. The lines of enlargement of these rapid diagnostic techniques include tests based on molecular biology, immunology, and biochemistry (8). Lateral flow immunoassays (LFIAs) have been shown to be sensitive, rapid, low cost, user-friendly, and easily implemented in clinical microbiology laboratories to detect CTX-Ms, the five main carbapenemases (OXA-48, KPC, NDM, VIM, and IMP), MCR-1/2, VREs, and GES enzymes (9–14) from bacterial cultures on agar plates.

Very recently, the BL-DetecTool, a rapid, cheap, and simple LFIA-based diagnostic test, has shown promising results, for the detection CTX-M-like enzymes and five main carbapenemases from biological samples 15–17). The BL-DetecTool is a LFIA that integrates an easy sample preparation device named SPID, which allows simple steps to perform, sampling, processing, incubation, and detection directly from clinical samples (18). The hands-on time for the processing of the samples, either urine or positive blood culture, is circa 2–5 min with a reading at 15 min after migration started, although a second reading at 30 min is recommended for the negative results at 15 min. Therefore, the total turnaround time is 35 min. We conducted a multicenter study that included nine European centers for the assessment of the BL-DetecTool for a rapid detection of ESBL and/or carbapenemases producing *Enterobacterales* within the laboratory's workflow directly from positive blood cultures, urine samples, and rectal swabs, in this later case performed directly or after enrichment.

MATERIALS AND METHODS

We performed a prospective analysis between January 2021 and June 2022. The participating centers were from nine different European countries: Hospital Clínic of Barcelona (Barcelona, Spain), Assistance Publique Hôpitaux of Paris (Paris, France), Semmelweis University (Budapest, Hungary), Attikon University Hospital (Athens, Greece), Hospital of Bellvitge (Barcelona, Spain), Florence University Hospital (Florence, Italy), Laboratorium Diagnosik Bochum (Bochum, Germany), Saint Laszlo Hospital (Budapest, Hungary), and Centre Hospitalier Amiens (Amiens, France). The ESBL and carbapenemase detections were performed using the BL-DetecTool that is a SPID device containing the LFIA strips of the NG-Test CTX-M-MULTI and NG-Test CARBA 5, which detect CTX-M enzymes belonging to the five sub-families (1, 2, 8, 9, and 25) and the five main carbapenemases (OXA-48, KPC, VIM, IMP, and NDM), respectively (NG Biotech, Guipry, France). These tests were applied if a reliable identification of *E. coli*, *K. pneumoniae* complex (including *K. pneumoniae*, *Klebsiella quasipneumoniae*, and *Klebsiella variicola* species),*Enterobacter cloacae* complex (including *Enterobacter asburiae*, *E. cloacae*, *Enterobacter hormaechei*, *Enterobacter kobei*, and *Enterobacter ludwigii*), and other *Enterobacterales* by direct matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) from blood cultures and urines. The processing time was 5 min, and the results were read after 15 min.

The number of urines, positive blood cultures, and rectal swab (direct or after enrichment) for each center during the analysis period are described in Table 1. Sample processing followed the protocols described in a previous study for both devices (16).

Blood cultures

Positive blood cultures in which Gram stain showed Gram-negative bacteria were selected. Direct identification was performed in these samples using MALDI-TOF-MS and confirmed with the subculture on appropriate solid culture media.

Urine

The process of urine selection varied depending on the participating center and was conducted by employing different methods, including bacterial identification through Gram staining, by flow cytometry-based automated bacterial analyzer, or direct selection of positive urines by targeting *Enterobacterales* (16). Direct identification with MALDI-TOF-MS was performed if Gram stain showed Gram-negative bacteria or ≥5,000 bacteria/µL, a bacterial counting using flow cytometer (Sysmex, Kobe, Japan), was obtained. This cut-off was used based on a previous report (19). The identification was confirmed with the subculture on appropriated solid culture media.

Rectal swabs

For direct testing of these samples, 500 µL of the transport medium was placed on the device following the indication of the BL-DetecTool protocol and, in some cases, enrichment culture was used. In these cases, 400 µL of transport medium was transferred into 4 mL of brain heart infusion (BHI) broth (bioMérieux, Marcy l'Etoile, France) supplemented with either a 5 µg cefotaxime disc for the detection of CTX-M or half of 10 µg ertapenem disc (BioRad, Marnes-la-Coquette, France) for the detection of carbapenemases at 37°C for 24 h (16). For the analyses, the samples were classified in two groups: rectal swab without (direct sample) or with enrichment (in BHI). Bacterial identification was confirmed with the subculture on ChromID ESBL and ChromID Carba (bioMérieux, Madrid, Spain).

TABLE 1 Distribution of biological samples included in the study for the nine participating centers

Hospital	Urine		Blood culture		Rectal swap with/without enrichment	
	CTX-M-MULTI[a]	CARBA 5[a]	CTX-M-MULTI	CARBA 5	CTX-M-MULTI	CARBA 5
Assistance Publique Hôpitaux de Paris (Paris, France)	200	200	200	200	0/200	0/200
Semmelweis University (Budapest, Hungary)	553	557	352	352	0/500	0/508
Hospital Clínic (Barcelona, Spain)	502	504	494	495	202/150	357/150
Attikon University Hospital (Athens, Greece)	401	401	401	401	0/400	0/400
Hospital de Bellvitge (Barcelona, Spain)	400	400	400	400	400/400	400/400
Florence University Hospital (Florence, Italy)	357	337	375	374	0/398	0/398
Laboratorium Diagnosik Bochum (Bochum, Germany)	400	400	400	400	400/400	400/400
Saint Laszlo Hospital (Budapest, Hungary)	400	400	400	400	168/234	168/234
Centre Hospitalier Amiens (Amiens, France)	404	404	215	215	0/224	0/225
Total of samples	3,617	3,603	3,237	3,237	1,170/2,906	1,325/2,915

[a]Rapid detection of ESBL (NG-test CTX-M-multi DetecTool) and/or carbapenemases (NG-test CARBA 5 DetecTool).

Discrepant results, thus growth of colonies in agar media with an ESBL or carbapenemase phenotype, but negative for BL-DetecTool, were further analyzed either by repeating the CTX-M or CARBA 5 detection from the isolated colonies, susceptibility testing also monitored by synergy image testing, or by specific in-house PCR to detect genes encoding CTX-M or carbapenemases. The presence or absence of CTX-M or carbapenemase genes was carried out by whole genome sequencing in some specific cases, such as those colonies showing resistance to third generation cephalosporins but negative for CTX-M.

Statistical analysis

The prevalence of these antibiotic resistance mechanisms, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the accuracy of each device was calculated for every site using the MedCalc online software.

RESULTS

A total of 22,010 samples were tested among which urines (total, 7,220; CTX-M detection = 3,617 and CARBA-detection = 3,603) and blood cultures (total 6,474; with 3,237 for detection of CTX-M and for CARBA detection). All hospital involved in the study performed a direct detection from CTX-M and CARBA from rectal swab and only four, in addition, performed detection after enrichment. The figures of rectal swab were direct (total 2,495; with 1,170 for CTX-M detection and 1,325 for CARBA detection) or after enrichment (total 5,821; with 2,906 for CTX-M detection and 2,915 for CARBA detection) (Table 1). The prevalence of CTX-M producing *Enterobacterales* in our cohort was between 5.96% and 28.5% and that for carbapenemases was between 0% and 19.6%, depending on the hospital.

The identification of microorganisms carrying CTX-M or any type of the carbapenemases detected by BL-DetecTool from the different source is shown in Table S1. CTX-M producing *E. coli* and *K. pneumoniae* were the most frequent microorganism isolated in urine, positive blood cultures, and rectal swabs, either direct or after enrichment. However, *K. pneumoniae* either producing KPC, OXA-48, or NDM were the microorganism carrying carbapenemases most frequently found in all three samples.

The overall results related to sensitivity, specificity, PPV, NPV, and the accuracy of both tests in blood cultures, urines, and rectal swab (direct or after enrichment) are summarized in Table 2. However, the stratified results related to number of samples, type of samples, resistant determinant, and hospital are shown in Tables S2 to S7. The total of samples for the detection of CTX-M from urine was 3,617 and the sensitivity ranged from 84% to 100%; however, if we excluded the hospital (Saint Lazlo Hospital Budapest, Hungary) with 84%, the remaining hospitals showed a sensitivity higher than 94% (Table 2). The lower sensitivity of this hospital was due to eight urine samples that gave false negative results (seven samples with CTX-M producing *E. coli* and one with CTX-M producing *K. pneumoniae* (Table S2). Overall, discrepancies among the 3,617 urine samples analyzed were 23 false negative results, mainly *E. coli* and *K. pneumoniae,* and eight false positive results, three of which were associated with polymicrobial results. All hospitals showed a sensitivity higher than 90% to detect CTX-M from positive blood culture. The overall discrepancy among the 3,603 positive blood samples analyzed was 10 false negative results directly from sample, five associated with *K. pneumoniae* and five with *E. coli*. Concerning the detection of CTX-M in rectal swabs, the sensitivity of the direct detection went from only 3.4% to 100% (eight hospitals); however, after enrichment, the sensitivity increased and was from 75.8% to 100%. Again, most of the discrepancies were due to *E. coli* and *K. pneumoniae*. The prevalence, as expected, of carbapenemase producing bacteria was lower than for CTX-M producing bacteria. In fact, four hospitals reported prevalences <0.5% and, among these, three did not detect any carbapenemase in the analyzed urine samples. The sensitivity in the five remaining hospitals went from 42.8% to 100%. The hospital which showed a sensitivity of 42.8% presented a low prevalence (1.9%) and four false negative samples with *K. pneumoniae*

TABLE 2 Overall results of the analysis of both test CTX-M-MULTI and CARBA 5 from all participant centers in direct biological samples

Type of sample	Prevalence %	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %	Accuracy %
Urine - CTX-M	5.9–28.5	84.0–100[a]	98.7–100	92.9–100	97.1–100	96.6–100
Blood culture - CTX-M	7.2–28.5	90.9–100	99.6–100	98.2–100	99.1–100	99.0–100
Rectal swab - CTX-M (without enrichment)	6.4–28.5	3.4–100	99.7–100	50.5–100	88.0–100	89.4–100
Rectal swab - CTX-M (enrichment)	6.4–28.5	75.8–100	98.4–100	91.8–100	97.0–100	96.3–100
Urine - CARBA 5	0–19.6	42.8–100	99.4–100	61.0–100	97.4–100	97.8–100
Blood culture - CARBA 5	0.1–19.6	75.0–100	100	100	97.7–100	98.1–100
Rectal swab - CARBA 5 (without enrichment)	0.1–19.6	26.1–100	99.2–100	85.2–100	94.6–100	95.4–100
Rectal swab - CARBA 5 (enrichment)	0.1–19.6	66.6–100	100	100	99.2–100	99.2–100

[a]Minimal value and maximal value observed in different hospitals.

(two positives for KPC and two positives for NDM) (Table S5). For CARBA 5 detection in positive blood cultures, only one hospital (Laboratorium Diagnosik Bochum, Germany) did not report any positive sample in the remaining. The sensitivity was 75%–100%. The specificity of CARBA 5 was 100% in all hospitals. Finally, the detection of carbapenemases in rectal swab was as heterogeneous as we found for detection of CTX-M. The sensitivity from a direct detection in rectal swabs in all hospitals went from 26.1% to 100%, whereas after enrichment (four hospitals), it went from 66.6% to 100%.

DISCUSSION

In general, every year, a significant increase in multidrug-resistant (MDR) microorganism especially of *Enterobacterales* is observed (4). Different efforts have been made to try to manage this worldwide situation. Early detection of the main resistance mechanism is one of the actions to a better control of patients with active infection, identification of carriers of MDR bacteria, and prevention of further spread of MDR strains (20). One promising test in the field of rapid diagnostic is the LFIA. These tests can be developed either because of the interaction of antigen-antibody (immunoassays) or DNA-DNA hybridization (nucleic acid lateral immunoassay). The advantages of LFIA include its low cost, easy sampling manipulation, no temperature-depending storage, and short time for results (18). The second generation of these tests is capable of directly detecting enzymatic activity responsible of the resistance. NG-Test CTX-M-MULTI and NG-Test CARBA 5 are two of the developed devices and both tests have been developed to target enzyme-mediated resistance for the most important clinically *Enterobacterales* (18). The main advantage of using the BL-DetecTool device is the direct processing of positive urines, blood cultures, and rectal swab without pre-treatment steps. The use of these BL-DetecTool allows, as showed in this study, a rapid and reliable detection of ESBL and carbapenemases directly from urine, positive blood cultures, or rectal swabs. In contrast to previous studies, the number of samples included in our cohort was much higher and a slight decrease in the sensitivity was observed. In the cases of urine, previous studies report a sensitivity of 100% for CTX-M detection, and in our study, the sensitivity was around 84%–100% depending on the center, whereas for the detection of CTX-M in positive blood culture, the sensitivity for almost all hospitals was higher than 96%. For CARBA 5 in urine, the results were similar to previous report (87.5%–100%), with the exception of one hospital in which the sensitivity was of 42.8% likely associated with the low prevalence of carbapenemases in this. Hospital (1.9%) and four false negative

samples related to the low inoculum of the bacteria in urine; in exceptional cases, this false negative result could also be attributed to the low volume (<5 mL) of urine used. The sensitivity of the detection of carbapenemases directly from positive blood culture was also very good with figures above 88% with the exception of one hospital. In rectal swabs, differences were observed between samples with a previous enrichment protocol and direct samples. It is worthy of mention that the wide range of sensitivity in rectal swabs performed directly in the different hospital which goes from 3.4% to 100% to detect CTX-M and from 26.1% to 100% to detect carbapenemases. The main reasons for these extremely different results could be either the low inoculum of bacteria in the rectal swab, the heterogeneity of the sample, or the transport media either solid or liquid that could affect the final result. Both CTX-M and CARBA 5 showed better results in the cases of samples in which the enrichment protocol was performed, with a higher sensitivity, as expected, after enrichment. This difference was also observed in previous reports (16, 18). Therefore, if this procedure is implemented in the clinical microbiology laboratory to detect CTX-M and carbapenemases in rectal swabs, an enrichment step is advised. The length of enrichment may be reduced to 3 h as shown in several studies (21, 22).

Our results also demonstrate its effectiveness from directly positive blood cultures, urines, and this fact is important because this would further shorten the response times of the microbiology laboratory and would mean that appropriate antibiotic therapy could be started sooner. In a study conducted by Zboromyrska et al. (17) in urine samples from patients attending the emergency room where blood culture samples were also taken for possible bacteraemia from urinary origin, it demonstrates the effectiveness of BL-DetecTool to detect CTX-M and carbapenemases in the laboratory workflow by applying it from direct sampling and showed that, with these implementations in a 30% of the cases, the antibiotic treatment was modified (17). This is an example of the clinical impact of the use of these devices in daily clinical practice.

In comparison with other techniques such as MALDI-TOF-MS or molecular test to detect carbapenemases, some reports showed an accuracy around 90% (23, 24). In our study, the accuracy for all samples to detect both CTX-M or carbapenemases was over 89% even in rectal swabs. The BL-DetecTool for carbapenemases (CARBA 5) showed similar results with the advantage of being an easier test to use with a shorter response time.

With these results observed in our cohort of nine European centers, we believe that the implementation of the BL-Detect tool into routine laboratory practices could improve the workflow efficiency by providing a rapid result, mainly directly from urine samples or positive blood cultures, when a reliable direct identification is obtained. This would have direct implications on targeted antibiotic treatment, prompt infection control measures, and antibiotic stewardship.

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AUTHOR AFFILIATIONS

[1]Department of Microbiology, Hospital Clinic of Barcelona, Barcelona, Spain
[2]Institute for Global Health (ISGlobal), University of Barcelona, Barcelona, Spain
[3]CIBER de Enfermedades Infecciosas (CIBERINFEC), ISCIII, Barcelona, Madrid, Spain
[4]Team "Resist", INSERM Unit 1184, Faculty of Medicine, Université Paris-Saclay, Bacteriology-Hygiene Unit, Assistance Publique-Hôpitaux de Paris, AP-HP Paris-Saclay, Bicêtre Hospital Le Kremlin-Bicêtre, Le Kremlin-Bicêtre, France
[5]Laboratory of Clinical Microbiology, Attikon University General Hospital, Medical School, National Kapodistrian University Athens (Greece), Athens, Greece
[6]Microbiology Department, Hospital de Bellvitge. IDIBELL. UB. CIBERES, Barcelona, Spain
[7]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[8]Department of Medical Biotechnologies, University of Siena, Siena, Italy
[9]German National Reference Laboratory for Multidrug-Resistant Gram-negative Bacteria, Department of Medical Microbiology, Ruhr-University Bochum, Germany - (Germany), Bochum, Germany
[10]Central Microbiology Laboratory, Central Hospital of Southern Pest National Institute of Hematology and Infectious Disease, Budapest, Hungary
[11]Department of Bacteriology, Amiens University Hospital, Amiens, France
[12]Semmelweis University, Institute of Medical Microbiology, Budapest, Hungary
[13]Health Services Management Training Centre, Semmelweis University, Budapest, Hungary
[14]R&D Department, NG Biotech, Guipry, France
[15]Département Médicaments et Technologies pour la Santé (DMTS), Université Paris Saclay, CEA, INRAE, SPI, Gif-sur-Yvette, France
[16]IESE Bussiness School, Barcelona, Spain
[17]Department of Microbiology, Hospital Clinic of Barcelona, Barcelona, Spain
[18]Institute for Global Health (ISGlobal), University of Barcelona, Barcelona, Spain
[19]Department of Clinical Microbiology - CDB, University of Barcelona, Hospital Clínic, Barcelona, Spain
[20]CIBER de Enfermedades Infecciosas , Barcelona, Spain

AUTHOR ORCIDs

Mariana Fernandez-Pittol http://orcid.org/0000-0002-1685-7127
Thierry Naas https://orcid.org/0000-0001-9937-9572
Jordi Vila http://orcid.org/0000-0002-8025-3926

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AUTHOR CONTRIBUTIONS

Mariana Fernandez-Pittol, Conceptualization, Data curation, Investigation, Methodology, Writing – original draft | Jordi Bosch, Conceptualization, Data curation, Formal analysis, Writing – review and editing | Clara Ballesté-Delpierre, Conceptualization, Formal analysis, Supervision, Writing – review and editing | Camille Gonzalez, Conceptualization, Investigation, Methodology, Writing – review and editing | Alexandra Vasilakopoulou, Investigation, Methodology, Writing – review and editing | Dàmaris Berbel, Investigation, Methodology, Writing – review and editing | Eleonora Riccobono, Investigation, Methodology, Writing – review and editing | Sören Gatermann, Investigation, Methodology, Writing – review and editing | Katalin Kamotsay, Investigation, Methodology, Writing – review and editing | Sophie Reissier, Investigation, Methodology, Writing – review and editing | Dora Szabo, Conceptualization, Data curation, Validation, Visualization, Writing – review and editing | Albert Zoltan Aszalos, Conceptualization, Resources, Visualization, Writing – review and editing | Laura Francius, Conceptualization, Supervision, Validation, Writing – review and editing | Hervé Volland, Conceptualization, Visualization, Writing – review and editing | Milovan Stankov-Pugès, Conceptualization, Supervision, Validation, Writing – review and editing | Magda Rosenmöller, Conceptualization, Data curation, Formal analysis, Validation, Writing – original draft, Writing – review and editing | Thierry Naas, Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review and editing | Jordi Vila, Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing

ADDITIONAL FILES

The following material is available online.

Supplemental Material

Tables S1 to S7 (JCM01136-23-S0001.docx). Results individualized by hospitals.

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