Virulence Properties of Extended Spectrum β-Lactamase–Producing Klebsiella Species in Meat Samples

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ABSTRACT

The present study was carried out to identify virulence properties (siderophores, serum resistance, and hemolysin) and antibiotic resistance in extended spectrum β-lactamase (ESBL)–producing Klebsiella isolates from 60 calf and chicken meat samples purchased from various supermarkets in Ankara, Turkey. Of the 45 Klebsiella isolates, 24 (53%) were identified as K. oxytoca and 21 (47%) were identified as K. pneumoniae. A high proportion of Klebsiella isolates had virulence factors such as hemolytic activity (67%), siderophore production (44%), and serum resistance (38%). The double-disk synergy test was used to determine ESBL production. ESBL production was detected in 13 (29%) of the 45 Klebsiella isolates. Resistance to 14 antimicrobials was tested in all Klebsiella isolates by the disk diffusion method. All isolates were resistant to two or more antimicrobial agents. All ESBL-producing Klebsiella isolates were highly resistant to cephalosporins and monobactams. Our findings indicate that meat and its products represent potential hazardous sources of multidrug-resistant and virulent Klebsiella species.

Enterobacteriaceae cause a variety of nosocomial and community acquired (foodborne) infections, including those caused by Klebsiella (10, 36). Klebsiella species are opportunistic bacteria, commonly found in the environment and in the gastrointestinal tracts of a wide range of animals (36), especially animals raised for human consumption. Studies worldwide have revealed that Klebsiella can contaminate meat (29) and dairy products (50) and contribute to disease and spoilage (11). Common sources of food contamination by these bacteria are feces (of animal and human origin), personnel, water, and containers (13).

Extended spectrum β-lactamases (ESBLs) are enzymes that are often plasmid mediated and confer broad resistance to penicillins, cephalosporins, aminoglycosides, tetracyclines, chloramphenicol, sulfonamides, and trimethoprim (27). Among the organisms capable of ESBL production, Klebsiella pneumoniae is an important pathogen. These bacteria are ready receptors of R plasmids and have been implicated in serious nosocomial epidemic diseases (11).

Like other Enterobacteriaceae, Klebsiella strains synthesize and secrete iron-chelating compounds that efficiently remove iron from the host’s iron-binding proteins. Because elemental iron is a necessary cofactor for bacterial metabolism, the acquisition of iron in vivo represents an important step in Klebsiella pathogenesis (17, 36). The capacity to resist bactericidal activity of normal human serum (NHS) contributes to the virulence of many gram-negative pathogens (30). Serum resistance in bacteria has been attributed to their surface components such as the capsule, lipopolysaccharide, and outer membrane proteins (49). A strong correlation has been found between serum resistance and the ability of a variety of gram-negative bacteria to invade and survive in the human blood stream (30). Although Klebsiella is commonly described as nonhemolytic, the detection and determination of the hemolytic effect of certain isolates have been reported (1).

Because of the pathogenicity of Klebsiella, scientists have become increasingly aware of the potential health hazard associated with this organism and the need for monitoring Klebsiella in the environment, food, and clinical settings. The clinical significance of Klebsiella has been well established, but its potential as a public health problem in food needs more attention. To our knowledge, no studies on virulence factors (siderophore production, serum resistance, and hemolytic activity), ESBL production, and antibiotic resistance have been conducted with Klebsiella isolates from meat products.

This study was conducted to generate information on the prevalence and virulence properties of ESBL-producing Klebsiella isolates from calf and chicken meat processed for human consumption.

MATERIALS AND METHODS

Sample collection and preparation. Thirty samples of raw calf meat (minced and small chunks) and 30 samples of chicken parts (breasts and drumsticks) were collected from various supermarkets in Ankara, Turkey, between July 2007 and November 2008. Samples were collected in sterile polyethylene packs, placed on ice, immediately transported to the laboratory, and processed within 2 h after collection.
Samples (25 g) were weighed into sterile stomacher bags, diluted with 225 ml of 1% sterile peptone water (Merck, Darmstadt, Germany), and homogenized in a stomacher (Lab Lemco 400, Seward, Worthington, UK) for about 10 min. From each prepared sample, 0.1 ml was evenly spread on plates of sheep blood agar, tryptic soy agar, MacConkey agar, and eosin methylene blue (EMB) agar (Merck). For enrichment purposes, 0.1 ml of each sample preparation was inoculated into tryptic soy broth. The inoculated media were incubated aerobically at 37°C for 24 to 48 h. At least five suspect colonies characteristic of *Klebsiella* (large, viscous, dome-shaped, brownish colonies on EMB red and MacConkey agar, with the exception of *Klebsiella rhinoscleromatis*) were picked and inoculated onto triple sugar iron (Merck) slants. Suspect colonies were subjected to the standard procedures (15). *Klebsiella* species were identified and the reference strain *K. pneumoniae* ATCC 700603 was confirmed with the API 20E method (bioMérieux, Marcy l’Etoile, France).

**Determination of siderophore production.** Production of siderophores was studied in all isolates by cultivation on chrome azurol sulfate (CAS) agar. This agar was prepared according to the method of Schwyn and Neilands (40) by dissolving 60.5 mg of CAS in 50 ml of distilled deionized water. This solution was mixed with 10 ml of iron (III) solution (1 mM FeCl₃, 6H₂O, and 10 mM HCl) and added while stirring slowly to 72.9 mg of hexadecyltrimethylammonium bromide that had been dissolved in 40 ml water. The resultant dark blue liquid was autoclaved at 121°C for 15 min. Also autoclaved was a mixture of 750 ml of water, 15 g of agar, 30.24 PIPES (piperazine-N,N’-bis(2-ethanesulfonic acid)), and 12 g of a solution of 50% (wt/wt) NaOH to raise the pH to the pKₐ of PIPES (6.8). The dye solution was finally poured along the glass wall and agitated with enough care to avoid foaming. Petri dishes were prepared with 30 ml of appropriate medium for culturing each strain. After becoming solid, the medium was cut into halves, one of which was replaced by CAS agar (15 ml). The halves containing culture medium were inoculated with *Klebsiella* strains. The inoculum was placed as far as possible from the border between the two media. The plates were incubated at 37°C for 24 h. The CAS reaction rate was determined by measuring the advance of the color-change front in the CAS agar, starting from the border between the two media. A change in the color of the CAS agar from blue to orange red confirmed the ability of *Klebsiella* strains to produce siderophores.

**Determination of serum resistance.** NHS was obtained by pooling sera from healthy adult volunteers. Serum inactivated at 56°C for 30 min (human inactivated serum; HIS) was prepared for use as control. Both types of serum were stored as aliquots at −70°C. Log-phase cultures of the isolates grown in brain heart infusion broth were harvested by centrifugation and resuspended in phosphate-buffered saline (PBS). The suspensions were suitably diluted with PBS to visually adjust their turbidity to match the 0.5 McFarland turbidity standard. These suspensions were further diluted with PBS to 1 × 10⁶ CFU/ml. The bacterial suspension (0.1 ml) was mixed with 0.2 ml of NHS and 0.1 ml of peptone glucose bromothymol blue broth (10% peptone, 10% glucose, and 0.075% bromothymol blue; BDH, VWR, Lutterworth, UK). The volume was made up to 1 ml by adding 0.6 ml of sterile PBS. The final concentration of serum in the mixture was 20%. Different concentrations of serum can be prepared by suitably adjusting the volumes of NHS and PBS in the mixture. The use of a fixed volume of the 10× medium ensures that all the ingredients are available at a uniform concentration in the final reaction mixture when different concentrations of serum are tested. A control tube incorporating HIS in place of NHS was simultaneously included for each isolate. The mixtures were incubated at 37°C in a water bath. The tubes (NHS and HIS) were observed at hourly intervals, and time elapsed for any visible change in color from original green to yellow was recorded (34, 35).

**Determination of hemolytic activity.** Isolates were tested for the production of β-hemolysin on blood agar plates with sheep erythrocytes as previously described (16).

**Antimicrobial susceptibility testing.** Antimicrobial susceptibility testing of the isolated organisms was done by a disk diffusion method using the Kirby-Bauer technique (6) and as per the recommendations of the Clinical and Laboratory Standards Institute (12). All disks were obtained from Bioanalyse (Ankara, Turkey): meropenem (10 µg), imipenem (10 µg), amikacin (30 µg), ciprofloxacin (5 µg), gentamicin (30 µg), cefotaxime (30 µg), cefazidime (30 µg), cefepime (30 µg), trimethoprim-sulfamethoxazole (1.25 and 23.75 µg), ampicillin-sulbactam (each 10 µg), aztreonam (30 µg), piperacillin-tazobactam (100 and 10 µg), ampicillin (10 µg), and amoxicillin (25 µg). A standard reference strain of *K. pneumoniae* (ATCC 700603) sensitive to all antimicrobial drugs being tested was used as a control.

**Detection of ESBL by double disk synergy test.** ESBL was detected by a double disk synergy technique in which an augmentin disk (20 µg of amoxicillin and 10 µg of clavulanic acid) was placed in the center of a plate, and cefotaxime (30 µg), cefazidime (30 µg), ceftazidime (30 µg), and aztreonam (30 µg) disks were placed 30 mm (center to center) from the augmentin disk. The enhancement of the zone of inhibition of any one of the four drug disks toward the disk containing clavulanic acid suggested the presence of ESBLs (22). *Escherichia coli* NCTC 10418 was used as an ESBL-negative control, and *K. pneumoniae* ATCC 700603 was used as an ESBL-positive control.

**RESULTS AND DISCUSSION**

*Klebsiellae* are ubiquitous in nature and have two common habitats: the environment, where they are found in surface water, sewage, and soil and on plants; and the mucosal surfaces of mammals such as humans, horses, and swine (13). The primary source of *Klebsiella* contamination is generally considered to be raw meat and the hands of personnel (9).

During the study period, 24 *Klebsiella oxytoca* and 21 *K. pneumoniae* isolates were recovered from 60 samples of raw meat and chicken (Table 1). The identified species are commonly incriminated in different infections in either humans or animals (35). Similar isolation rates were also

### Table 1. Prevalence of Klebsiella isolates in calf meat and chicken samples

<table>
<thead>
<tr>
<th>Samples</th>
<th>No. of samples</th>
<th>K. oxytoca</th>
<th>K. pneumoniae</th>
<th>Total Klebsiella</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calf meat, minced</td>
<td>15</td>
<td>9 (60)</td>
<td>6 (40)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Calf meat, chunks</td>
<td>15</td>
<td>5 (45.4)</td>
<td>6 (54.5)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Chicken drumsticks</td>
<td>15</td>
<td>9 (75)</td>
<td>3 (25)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Chicken breasts</td>
<td>15</td>
<td>1 (14.2)</td>
<td>6 (85.7)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>24 (53.3)</td>
<td>21 (46.7)</td>
<td>45 (75)</td>
</tr>
</tbody>
</table>
reported by Singh and Kulshreshtha (43), Haryani et al. (19), and El-Sukhon (14) and Gundogan and Yakar (18) in seafoods, street foods, and milk and milk products, respectively. The current results indicate that raw meat and its products might represent important sources of pathogenic *Klebsiella* species.

Iron is required in trace amounts for crucial biochemical reactions in most microorganisms. Under iron-limited conditions, microorganisms produce siderophores to scavenge ferric ions, which bind to specific outer membrane receptors with high affinity. Siderophores contribute to the virulence of a wide variety of bacterial pathogens, including *K. pneumoniae* (30). Several studies have been conducted to assess the iron uptake systems in *Klebsiella* spp. isolated from various clinical specimens. However, there is little information concerning siderophore production by *Klebsiella* isolates from meat and chicken.

A CAS agar plate was used for the detection of siderophores. In our study, 20 isolates (44%) were siderophore producers: 11 *K. pneumoniae* isolates (55%) and 9 *K. oxytoca* isolates (45%) (Table 2). El-Sukhon (14) and Gundogan and Yakar (18) found that 27.7 and 63%, respectively, of *Klebsiella* strains obtained from milk and milk products produced siderophores. Koczura and Kaznowski (24) reported that 43 strains of *K. pneumoniae* isolated from clinical specimens gave positive results in the CAS assay, indicating production of iron-chelating compounds. Similarly, 14 *Klebsiella* strains from various sources, including blood, urine, and sputum, secreted iron-chelating compounds (49). Our results indicate that, similar to the clinical isolates, meat isolates of *Klebsiella* also can produce siderophores, which contributes to virulence in *Klebsiella* strains.

In the present study, serum resistance of the *Klebsiella* isolates was examined with human serum. Serum resistance was found in 17 (38%) of 45 *Klebsiella* isolates: 9 *K. pneumoniae* isolates (53%) and 8 *K. oxytoca* isolates (47%) (Table 2). Human serum was used to determine how *Klebsiella* isolates would behave if they were able to infect consumers. Similar results were also reported by El-Sukhon (14) and Gundogan and Yakar (18) in milk and milk products. Sharma et al. (42) reported that of the 125 *K. pneumoniae* strains isolated from clinical specimens, more than 50% were resistant to 20% NHS. Studies on the incidence of serum resistance in clinical and food isolates of pathogenic bacteria are useful for determining the health hazards associated with these isolates.

### Table 2. Siderophore production, serum resistance, and hemolytic activity of *Klebsiella pneumoniae* and *K. oxytoca* isolated from calf meat and chicken samples

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of isolates</th>
<th>Siderophore production</th>
<th>Serum resistance</th>
<th>Hemolytic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>K. pneumoniae</em></td>
<td>21</td>
<td>11 (55)</td>
<td>9 (53)</td>
<td>14 (47)</td>
</tr>
<tr>
<td><em>K. oxytoca</em></td>
<td>24</td>
<td>9 (45)</td>
<td>8 (47)</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>20 (44)</td>
<td>17 (38)</td>
<td>30 (67)</td>
</tr>
</tbody>
</table>

### Table 3. Number and percentage of *Klebsiella* isolates from 60 meat and chicken samples that exhibited resistance to antimicrobial agents

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th><em>K. pneumoniae</em> (n = 21)</th>
<th><em>K. oxytoca</em> (n = 24)</th>
<th>Total <em>Klebsiella</em> (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Imipenem</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>21 (100)</td>
<td>24 (100)</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>21 (100)</td>
<td>24 (100)</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>1 (5)</td>
<td>1 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1 (5)</td>
<td>2 (8)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>3 (14)</td>
<td>1 (4)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Trimethoprim-sulfoxazide</td>
<td>3 (14)</td>
<td>1 (4)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>4 (19)</td>
<td>3 (13)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>3 (14)</td>
<td>2 (8)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>4 (19)</td>
<td>3 (13)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>5 (24)</td>
<td>2 (8)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>6 (29)</td>
<td>5 (21)</td>
<td>11 (24)</td>
</tr>
</tbody>
</table>

* n, number of isolates.

The production of hemolysin among gram-negative bacteria is indicative of other virulence and enterotoxigenic factors (5). In the present study, hemolytic activity of *Klebsiella* isolates was investigated with blood agar and was found in 30 (67%) of 45 isolates: 14 *K. pneumoniae* isolates (47%) and 16 *K. oxytoca* isolates (53%) (Table 2). These percentages were consistent with the findings of El-Sukhon (14), Gundogan and Yakar (18), Albesa et al. (1), and Barberis et al. (4).

Multidrug resistance in *Klebsiella* is increasing throughout the world (45, 46). ESBLs usually are associated with resistance to various drugs, including β-lactam and non–β-lactam antibiotics (38). The results for 45 *Klebsiella* isolates from meat and chicken samples that were tested against 14 antimicrobial agents are presented in Table 3.

Carbapenems were the most effective antibiotics; 100% of the isolates were susceptible to meropenem and imipenem. This result is consistent with those obtained in previous studies (7, 25). However, continued surveillance and judicious use of these antibiotics is needed; a recent report from the United Arab Emirates included documentation of a carbapenem-resistant *E. coli* isolate (2).

Most *Klebsiella* isolates are naturally resistant to ampicillin due to a constitutively expressed chromosomal class A β-lactamase (26). All of the isolates were resistant to ampicillin and amoxicillin, which are not β-lactamase inhibitors. Resistance results for combinations that included a β-lactamase inhibitor were 4% resistance for ampicillin-sulbactam and 4% resistance for piperacillin-tazobactam. Amoxicillin and amoxicillin resistance has been reported in veterinary clinical isolates (8) and human clinical isolates (28).

Aminoglycosides are active against clinically important gram-negative bacilli (37). A low prevalence of amikacin resistance (7%) and gentamicin resistance (9%) was...
detected in Klebsiella isolates. For Klebsiella isolates from Pakistan, Ullah et al. (47) reported that 63.04% were susceptible to amikacin and 17.39% were susceptible to gentamicin. This higher level of activity may be due to increased use of amikacin and gentamicin in Pakistan compared with Turkey.

In our study, 9% of isolates were resistant to trimethoprim-sulfamethoxazole. Seid and Astrat (41) reported that most (65%) of the 57 Klebsiella isolates from clinical specimens were resistant to trimethoprim-sulfamethoxazole.

Ciprofloxacin is a broad spectrum fluoroquinolone antibacterial agent (33). The observed resistance of Klebsiella to ciprofloxacin was 16%. This level is lower than that previously reported by Ullah et al. (47) and Villegas et al. (48). Ciprofloxacin resistance in Klebsiella is predominantly due to a chromosomal mutation in the gyrA gene, which codes for the target of quinolone activity (3). As resistance to ciprofloxacin emerged, resistance to β-lactam antibiotics became prominent. This resistance was largely a result of ESBLs, which mediate resistance to newer β-lactam agents, such as ceftazidime, ceftriaxone, cefotaxime, and aztreonam, that have an oxyimino group (32).

Cephalosporins are an important class of antibacterial agents in use for both humans and animals. Resistance to cefotaxime (11%), ceftazidime (16%), and cefepime (16%) was found in the present study. Different rates of cephalosporin resistance have been reported for Klebsiella. Ullah et al. (47) reported that 54.35% of Klebsiella isolates were resistant to third-generation cephalosporins (ceftazidime and cefotaxime). Singh and Goyal (44) reported 84% resistance to cefotaxime.

Aztreonam is a synthetic monocyclic β-lactam in the family of monobactams and is exclusively active (like aminoglycosides) against the aerobic gram-negative bacilli (39). In our study, we found 24% resistance to aztreonam. According to Nijsen et al. (31), aztreonam had moderate activity against K. pneumoniae and K. oxytoca (susceptibility rates of 82.1 and 87%, respectively).

Multiple resistance to antimicrobial agents was very common in the present study. Six (46%) of 13 Klebsiella isolates were resistant to one or more antibiotics, and 7 (54%) of these 13 isolates were resistant to five or more antibiotics (data not shown). Gundogan and Yakar (18) reported that 15 (35%) of the Klebsiella isolates isolated from milk and milk products were resistant to two or more antibiotics. Ullah et al. (47) reported that 71.73% of the Klebsiella isolates tested were multidrug resistant.

ESBLs are plasmidborne enzymes that can hydrolyze cephalosporins and monobactams (48). In this study, ESBL production was detected using a double disk diffusion test (12) to determine the presence of ESBL in Klebsiella isolates that were resistant to third- and fourth-generation cephalosporins or aztreonam. Thirteen (29%) of 45 isolates were identified as ESBL producers: 8 (38%) of 21 K. pneumoniae isolates and 5 (21%) of 24 K. oxytoca isolates (data not shown). Of these 13 ESBL producers, 5 (38%) were resistant to aztreonam, 6 (46%) were resistant to ceftazidime, 8 (62%) were resistant to cefepime, and 12 (92%) were resistant to aztreonam (Table 4). The majority of the ESBL producers were K. pneumoniae. Resistance to the antimicrobial agents tested was much higher in the ESBL-producing Klebsiella isolates than in isolates that did not produce ESBL (Table 4). Although Klebsiella isolates that produce ESBL are frequently reported worldwide (21), the antibiotic resistance and presence of ESBL-producing Klebsiella isolates in food samples has been poorly documented. ESBL detection rates in Klebsiella isolates from clinical specimens were 24.2% in Czech Republic (25), 51.9% in Brazil (27), 4.3% in North America (34), 4.2% in New Zealand (20), and 54.5% in Turkey (23).

In conclusion, the virulence properties (siderophores, serum resistance, and hemolysin) of Klebsiella isolates from meat are very similar to those in Klebsiella isolates from human clinical specimens. The epidemiological relationship between human and food isolates should be investigated to improve treatment and prevention of Klebsiella infections. The present study also revealed that multidrug resistant and ESBL-producing Klebsiella species can be transmitted by different foods, including beef and chicken products. Transfer of resistant bacteria to humans via the food chain has been reported previously. In the present study, a high prevalence of ampicillin and amoxicillin resistance was detected for Klebsiella isolates. Excessive ampicillin and amoxicillin usage in Turkey for treatment of infections in humans and animals can be regarded as one of the major causes of resistance to these antimicrobials among Klebsiella species.

All ESBL-producing Klebsiella isolates were highly resistant to cephalosporins (ceftazidime, cefotaxime, and cefepime) and monobactams (aztreonam). The use of antimicrobial agents in veterinary medicine and food production may lead to resistance to antimicrobials used

### TABLE 4. Number and percentage of ESBL-positive and -negative Klebsiella isolates resistant to various antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>K. pneumonia</th>
<th>K. oxytoca</th>
<th>Total ESBL (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>ESBL (+)</td>
<td>ESBL (-)</td>
<td>ESBL (+)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>4 (19)</td>
<td>1 (5)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>6 (28)</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Cefepime</td>
<td>7 (33)</td>
<td>3 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>7 (33)</td>
<td>5 (24)</td>
<td>5 (21)</td>
</tr>
</tbody>
</table>

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in human medicine. Thus, the use of these antibiotics for treatment of infections caused by ESBL-producing Klebsiella isolates may result in failure in a significant proportion of cases. In accordance with the current information, meropenem and imipenem should be the first choices of antibiotics to be used for ESBL-positive Klebsiella infections due to the highest antimicrobial activity.

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