Can bacteriological upper airway samples obtained at intensive care unit admission guide empiric antibiotherapy for ventilator-associated pneumonia?

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Background: **Ventilator-associated pneumonia is associated with an increase in morbidity and mortality. The delay before adequate antibiotherapy is known to influence patients' outcome. We hypothesized that the results of upper airways samples performed at immediately intensive care unit admission could help the clinician to choose the adequate empiric antibiotherapy for a ventilator-associated pneumonia occurring during the first 5 days of intensive care unit admission.**

Objectives: **To compare the bacterial content of the upper airways samples to that of the pulmonary plugged specimen performed when ventilator-associated pneumonia was suspected.**

Design: **Prospective observational study.**

Setting: **Twenty beds in a surgical intensive care unit of a teaching hospital.**

Patients: **All patients between 1996 and 2001, who were ventilated for more than 48 hours and presented a suspicion of ventilator-associated pneumonia, occurring during the first 5 days.**

Interventions: **As compared to the results of pulmonary plugged specimen, upper airways samples performance was tested by determining sensitivity, specificity, and positive likelihood ratios for each microorganism.**

Measurements and Main Results: **Five hundred eighty-eight patients ventilated for more than 48 hours were suspected to suffer from a VAP and benefited from a pulmonary plugged specimen: 136 (48%) patients had a positive pulmonary plugged specimen and received antibiotics. Of these 136, 125 (92%) had had a positive upper airway samples at intensive care unit admission. For all microorganisms, upper airway sample specificity exceeded 85%. For all bacteria except *Streptococcus* species, the likelihood ratios exceeded 6, threshold considered as significant to rule in the diagnosis.**

Conclusions: **In this study, we found high specificities and likelihood ratios for upper airways samples to predict the microorganisms involved in a ventilator-associated pneumonia. These results suggest that upper airways samples might provide an adjunctive assistance in selecting therapy for ventilator-associated pneumonia. (Crit Care Med 2009; 37:2559–2563)**

KEY WORDS: ventilator-associated pneumonia; upper airways samples; empirical antibiotherapy

Among critically ill patients, ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection (1, 2). VAP is associated with a significant increase in morbidity and mortality (2–4). VAP often results from a continuous leak of the secretions from the upper to the lower airways through the space around the balloon of the tracheal tube (5–8). Several studies confirmed that the bacterial content of the pharyngeal and the tracheal secretions are similar (5, 8). Few studies (9, 10) reported a relationship between nosocomial sinusitis and VAP in patients undergoing prolonged mechanical ventilation, but data are still lacking concerning the relationship between upper airways bacterial content and the microbiology of VAP.

We hypothesized that the microorganisms detected in the upper airways at intensive care unit (ICU) admission would be those involved in VAP occurring in the early course of a patient's ICU stay. To validate this hypothesis, we compared the bacterial content of the upper airway samples (UAS) performed at ICU admission with that of the pulmonary secretions sampled when VAP is suspected.

MATERIALS AND METHODS

This prospective observational study was performed in the surgical ICU of a 700-bed teaching hospital in Paris. To detect colonization with multiresistant microorganisms in this ICU, UAS (a swab in a nostril and another inside the cheek) were obtained routinely for all patients, within the first 24 hrs after ICU admission. A protocol for VAP prevention was observed in the ICU. This protocol was based on different nursing approaches, such as minimum 30° proclive positioning, frequent tracheal suctions, mouth and sinuses care.

In the present study, we chose to focus on VAP occurring during the first 5 days post ICU admission. Because we know that bacterial flora will change during the patients' ICU stay (11), we speculate that, if a relationship did exist between UAS on day 0 and VAP, it would only concern an early episode of VAP before any significant change occurred in the patients' colonization of microorganisms.

Among ventilated patients, suspicion of VAP was assessed prospectively and daily following the clinical (fever, tracheal aspirates), biological (oxygenation, leukocytosis), and radiologic (new radiographic infiltrates) items used by Pugin et al to define the Clinical

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Pulmonary Infection Score (CPIS) (12). When we detected a pulmonary infiltrate with one clinical or biological sign, we obtained systematically and immediately a pulmonary plugged specimen (PPS) (Combicath, Plastimed, Le Plessis Bouchaq, France) using a fiberoptic bronchoscope according to the method described by Pham et al (13).

If the patient exhibited signs of poor tolerance, empirical antibiotherapy was initiated immediately after the PPS. Otherwise, antibiotics were administrated only in case of confirmed pneumonia. Antibiotics were then started, after obtaining the first bacteriologic results, when the CPIS was >6. If needed, empirical antibiotherapy was decided according to the patient's history and the clinical presentation of the pneumonia: when the patient arrived from home (or was hospitalized for <48 hrs), empirical antibiotherapy usually consisted of ceftriaxone + ornidazole. When the patient was hospitalized for >48 hrs (or had any risk factor for a multiresistant microorganism carriage), initial antibiotherapy usually comprised piperacillin/tazobactam, ciprofloxacin, and vancomycin. In any case, initial antibiotherapy was modified according to the culture results.

Inclusion Criteria

All consecutive patients hospitalized in the ICU between 1996 and 2001 and presenting the following criteria were included in the analysis: a) mechanical ventilation for >48 hrs; and b) suspicion of VAP during the first 5 days after ICU admission. All of these patients were intubated at or immediately after ICU admission.

Exclusion Criteria

Patients without UAS or PPS were excluded from the analysis.

Microbiological Procedures

UAS were obtained using a swab for a nostril and another for the inside of the cheek. Specimens were cultured for 48 hrs at 37°C on sheep blood agar aero- and anaerobically, chocolate agar plate under 5% CO_2, Chapman agar (for selective isolation of *Staphylococcus*), and Drigalski agar (for selective isolation of Gram-negative bacteria). Cultures were examined daily and considered positive only in the presence of potential pathogens (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterobacter*, *Pseudomonas aeruginosa*, *Acinetobacter*, *Haemophilus influenzae*).

For the PPS, samples were obtained under fibroscopy, diluted with 1 mL of 0.9% saline, and transferred immediately to the microbiological laboratory. Specimens were Gram stained for direct examination and 10 μL was spread on each of the following medium: sheep blood agar aero- and anaerobically and chocolate agar plate under 5% CO_2; they were incubated for 48 hrs at 37°C and examined daily.

A PPS culture was considered positive for, at least, 10^3 colony-forming units (CFU)/mL.

All media were obtained from bioMérieux (Marcy l'Etoile, France). Bacteria were identified by conventional methods, including API strips (bioMérieux).

Antibiotic susceptibility was determined using the standard disk diffusion method on Mueller-Hinton agar (Bio-Rad, Marnes-la-Coquette, France) following the French National Antibiogram Committee guidelines (www.sfm.asso.fr).

Concerning atypical bacteria, specific investigations, such as *Legionella pneumophila* urinary antigen, were performed only when severe VAP (hypoxemia or sepsis/septic shock) was diagnosed.

Analysis

The following data were recorded: a) demography: age, gender, Simplified Acute Physiology Score II, diagnosis at ICU admission, length of mechanical ventilation and ICU stay, patient's route before ICU admission (i.e., patient coming from home or from ward); and b) occurrence of VAP. The diagnosis of VAP was confirmed in case of CPIS >6 (including a PPS with $>10^3$ CFU/mL in culture) and when the physicians in charge decided to continue the antibiotic treatment for >48 hrs.

The primary end point of the study was to test the accuracy of the UAS analysis to predict the microorganisms involved in a VAP.

Statistics

All data were expressed as mean ± SD. Student's *t* tests were used for continuous variables. A $p < .05$ was considered significant.

Considering the PPS as the determinant clinical tool for the diagnosis of VAP, UAS performance was investigated using a diagnosis analysis framework. Sensitivity (probability for a test to be positive when the pathogen of interest is present), specificity (probability of a test to be negative when the pathogen of interest is absent), and positive likelihood ratios (LRs) were determined with their 95% confidence intervals for each microorganism. The LR— ratio of the probability of the test result in people presenting the disease to the probability in people who do not present the disease—was used to describe the properties of a diagnostic or a screening test. LR is calculated as sensitivity divided by (1-specificity). An LR >1 indicates that the test result is associated with the presence of the disease, whereas an LR <1 indicates that the result is associated with the absence of the disease (14). The further LRs are from 1, the stronger the evidence for the presence or the absence of the disease. Sensitivities, specificities, and LRs were calculated in patients with positive PPS; number of bacteria detected in UAS and PPS were also computed. The aim of the present analysis was not to test the accuracy of UAS as a diagnostic tool for early-onset VAP but to predict pathogens in case of positive PPS.

Data analysis was performed using R (R Development Core Team. R: *A Language and Environment for Statistical Computing*. Vienna, Austria, R Foundation for Statistical Computing, 2008. ISBN 3-900051-07-0, http://www.R-project.org).

Patient Consent and Ethic Committee Approval

Because UAS was already part of our daily practice and the protocol did not alter our standards of care, no patient consent or ethics committee approval was needed for the present study.

RESULTS

Between 1996 and 2001, 2653 patients were hospitalized in our ICU. Among these patients, 1459 were ventilated for >48 hrs, 588 were suspected to suffer from VAP. Of these 588 patients, 283 (48%) had positive PPS. Of these 283 patients, 136 (48%) were considered as "confirmed" VAP (Fig. 1). All 136 patients were ventilated at or immediately after ICU admission. They all had UAS performed at ICU admission and were therefore included in the analysis. Demographic characteristics of these 136 patients are presented in Table 1.

Microbiology

Among the 136 patients with "confirmed" VAP, 125 (92%) had positive UAS

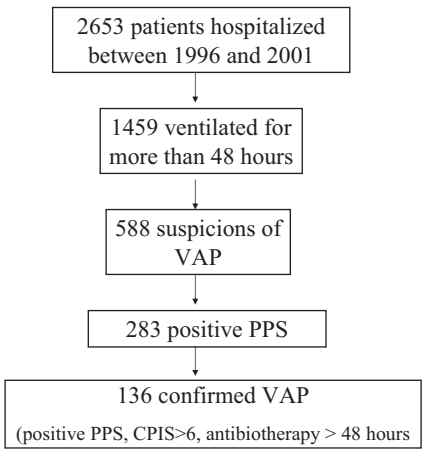

Figure 1. Flowchart. *CPIS*, Clinical Pulmonary Infection Score; *PPS*, pulmonary plugged specimen; *VAP*, ventilator-associated pneumonia.

Table 1. Demography of patients presenting a "confirmed" early ventilator-associated pneumonia

Patients, n	136
Age, yr	47 ± 20
Sex ratio, female/male	34/102
Death, n (%)	22 (16)
ICU length of stay, day	22 ± 19
Days of mechanical ventilation, n	16 ± 12
SAPS II	47 ± 16
Interval between UAS and PPS, hr	58 ± 72
Reason for ICU admission, n	
Heart failure	16
Acute bleeding	7
Neurological failure	33
Respiratory failure	28
Sepsis	20
Trauma	27
Others	5

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; UAS, upper airways samples; PPS, pulmonary plugged specimen.

at ICU admission. Table 2 shows the microbiological results of the UAS (*upper panel*) and PPS (*lower panel*) for these 136 patients. Among the 136 patients with VAP, 82 (60%) had a single microorganism in the PPS, 36 had two microorganisms, 18 had ≥3 microorganisms. Among the 125 positive UAS, 57 contained a single microorganism, 40 contained two microorganisms, 28 contained ≥3 microorganisms.

Sensitivity, Specificity, LR

Sensitivity, specificity, and LR were determined for the most frequent bacterial species (Table 3).

For all microorganisms, UAS specificity exceeded 85%. For the multidrug-resistant pathogens, the sensitivity of the UAS exceeded 65%: *P. aeruginosa* 69.8%, *Enterobacter* sp. 70.6%, *Acinetobacter baumanii* 72.7%, *Morganella morganii* 75.0%, methicillin-resistant *S. aureus* 85.5%, *Citrobacter* sp. 100%. For *M. morganii*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp., *A. baumanii*, methicillin-susceptible *S. aureus*, *H. influenzae*, and *Escherichia coli*, the LR exceeded 10 with a lower confidence limit >5 for *M. morganii*, *K. pneumoniae*, *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp., *A. baumanii*, methicillin-susceptible *S. aureus*, and *E. coli*. Such LR could be considered to provide strong evidence to rule in the diagnosis (14). For methicillin-resistant *S. aureus*, *Proteus* sp. and *P. aeruginosa*, the LR was between 2 and 5, which generates moderate evidence to rule in the diagnosis.

Table 2. Microbiological results of UAS (upper panel) and PPS (lower panel) among patients with "confirmed" early ventilator-associated pneumonia (n = 136)

Microorganisms	UAS (n = 125)
Gram-positive	
MSSA, n (%)	60 (48.0)
MRSA, n (%)	8 (6.4)
Streptococcus sp., n (%)	16 (12.8)
Gram-negative	
Haemophilus sp., n (%)	21 (16.8)
Pseudomonas aeruginosa, n (%)	27 (21.6)
Acinetobacter baumanii, n (%)	9 (7.2)
Klebsiella sp., n (%)	18 (14.4)
Enterobacter sp., n (%)	13 (10.4)
Citrobacter sp., n (%)	8 (6.4)
Serratia sp., n (%)	4 (3.2)
Morganella sp., n (%)	2 (1.6)
Stenotrophomonas maltophilia, n (%)	3 (2.4)
Other Gram-negative, n (%)	16 (12.8)

Microorganisms	PPS (n = 136)
Gram-positive	
MSSA, n (%)	62 (45.6)
MRSA, n (%)	7 (5.1)
Streptococcus sp., n (%)	21 (15.4)
Gram-negative	
Haemophilus influenzae, n (%)	29 (21.3)
P. aeruginosa, n (%)	19 (14.0)
A. baumanii, n (%)	5 (3.7)
Klebsiella sp., n (%)	10 (7.3)
Enterobacter sp., n (%)	11 (8.1)
Citrobacter sp., n (%)	2 (1.5)
Serratia sp., n (%)	3 (2.2)
Morganella sp., n (%)	2 (1.5)
S. maltophilia, n (%)	4 (2.9)
Other Gram-negative, n (%)	16 (11.8)

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; UAS, upper airway samples; PPS, pulmonary plugged specimen.

DISCUSSION

The aim of the present study was to assess the accuracy of the UAS analysis performed within the first 24 hrs after ICU admission to predict the microorganisms involved in VAP.

The microbiological flora reported in this group of patients had two particularities. The first is the high prevalence of *S. aureus* in the PPS. This result is consistent with the data previously published on neurologic ICU patients or neurotrauma patient (15), who represented the major part of our study sample. As previously described, *S. aureus* is the most frequent pathogen involved in VAP in this type of patient (15). The second is the high prevalence of multiresistant microorganisms isolated in the UAS. This might be explained by the fact that a majority of patients admitted in our ICU did not come from home but from a hospital ward, especially the surgical ward. Microorganisms may gain access to the lower respiratory tract by one of four mechanisms: 1) aspiration of secretions from the oropharynx directly or secondary by reflux from the stomach; 2) extension of a contiguous infection; 3) inspiratory contaminated gases; or 4) hematogenous carriage. The major route is considered to be the oropharyngeal colonization (16).

Based on this pathophysiology, the microorganisms present in the upper airways secretions should be the same as those involved in the VAP, and UAS analysis performed at ICU admission could be used to predict the microorganisms involved in VAP. Because our goal was not to propose the use of UAS to diagnose VAP, we decided not to express the result by suspicion of VAP. We chose to evaluate the qualitative correlation between UAS and PPS by determining sensitivity, specificity, and LR for each microorganism, considering PPS as the gold standard method for the diagnosis of VAP. For all pathogens, UAS specificity was very high, >90%. This high specificity encourages us to consider the results of the UAS analysis to guide the empirical antibiotherapy for VAP. Sensitivities were lower than specificities, especially for the microorganisms considered as commensals. For all microorganisms except *Streptococcus* sp., the LR exceeded 6, a threshold considered very significant to rule in the diagnosis. However, the lower LR reported for commensal species, such as *Streptococcus* sp., does not alter the focus of UAS analysis, as these microorganisms are generally susceptible to narrow-spectrum antibiotics. Consistent with our results, Berdal et al (17) reported a strong correlation between oropharyngeal and bronchoalveaolar lavage aspirates. The authors reported positive and negative predictive values of 73% and 95%, respectively, for oropharyngeal aspirates to predict the microorganism present in the bronchoalveolar lavage. Because of high-specificity UAS, the presence of a specific microorganism in the UAS should definitely be taken into account for the antibiotic prescription. However, because of the relatively low sensitivities, the absence of a specific microorganism in the UAS does not signify that it will not be present in the PPS.

Table 3. Sensitivity, specificity, and likelihood ratio of the UAS for the major microorganisms involved in the early VAP

Bacteria (Number Detected in UAS/PPS)	Sensitivity (95% CI)	Specificity (95% CI)	LR (95% CI)
Morganella morganii (4/4)	75.0 (19.4–99.4)	99.6 (98.0–100.0)	209.2 (27.3–1603.8)
Klebsiella pneumoniae (22/14)	85.7 (57.2–98.2)	96.3 (93.3–98.2)	23.1 (12.1–43.9)
Serratia sp. (10/8)	50.0 (15.7–84.3)	97.8 (95.3–99.2)	22.9 (8–65.6)
Enterobacter sp. (21/17)	70.6 (44–89.7)	96.6 (93.7–98.4)	20.9 (10.2–42.5)
Citrobacter sp. (17/2)	100.0 (15.8–100.0)	94.7 (91.3–97.0)	18.7 (11.4–30.6)
Acinetobacter sp. (20/11)	72.7 (39.0–94.0)	95.6 (92.4–97.7)	16.5 (8.5–31.9)
MRSA (82/69)	85.5 (75.0–92.8)	86.7 (80.7–91.4)	6.4 (4.3–9.5)
MSSA (30/17)	82.4 (56.6–96.2)	93.2 (89.2–96.1)	12.2 (7.2–20.5)
Haemophilus influenzae (14/53)	18.9 (9.4–32)	98.3 (95.6–99.5)	10.8 (3.5–33.3)
Klebsiella oxytoca (15/4)	50.0 (6.8–93.2)	95.3 (92.2–97.5)	10.7 (3.52–32.7)
Escherichia coli (33/27)	63.0 (42.4–80.6)	93.8 (90.0–96.4)	10.0 (5.8–17.6)
Proteus (17/10)	40.0 (12.2–73.8)	95.2 (92.0–97.4)	8.4 (3.3–21.2)
Pseudomonas aeruginosa (52/43)	69.8 (53.9–82.8)	90.8 (86.5–94.2)	7.6 (4.9–11.9)
Streptococcus sp. (29/41)	22.0 (10.6–37.6)	91.7 (87.5–94.9)	2.7 (1.3–5.4)

UAS, upper airways samples; VAP, ventilator-associated pneumonia; PPS, pulmonary plugged specimen; CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

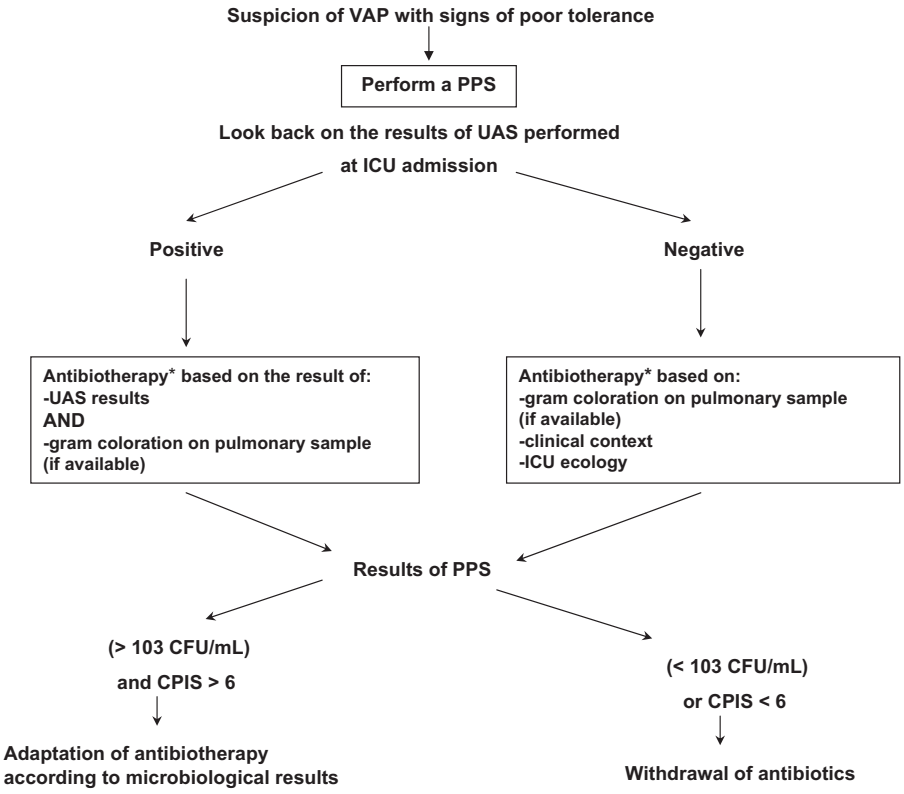

Figure 2. Algorithm for initial antibiotic prescription in case of ventilator-associated pneumonia (*VAP*). *CFU*, colony-forming units; *PPS*, pulmonary plugged specimen; *UAS*, upper airways samples; *ICU*, intensive care unit; *CPIS*, Clinical Pulmonary Infection Score.

Our study strongly suggests that the results of UAS, obtained within the first 24 hrs after ICU admission, could help the clinician to choose the adequate initial "empirical" antibiotherapy. In critical infections, the delay before the administration of the adequate antibiotherapy has been reported to markedly influence the patients' outcome (18–21). In our institution, 36 to 48 hrs are required to perform a microbiological identification with an antibiogram. In the present study, the mean delay between obtaining the UAS and the suspicion of a first episode of VAP, triggering the first PPS, was also about 48 hrs. Results of the UAS analysis were therefore often available at the onset of a VAP. Accordingly, a strategy based on the results of UAS analysis could be proposed to guide the prescription of empirical antibiotherapy for VAP with signs of poor tolerance (Fig. 2). Such a strategy should be validated in a prospective manner.

Because of the criteria used by the investigators to classify the patients as definite VAP (a positive PPS and an antibiotic treatment for >48 hrs), only 48% of the patients with positive pulmonary samples were finally considered as confirmed VAP. A daily evaluation based on the clinical, biological, and radiologic items of the CPIS was used to indicate PPS. As soon as the first bacteriologic results were available, the CPIS was recalculated to double-check the reality of the VAP. In many cases, several items of CPIS had disappeared after a couple of hours and, despite a positive culture, the criteria for VAP were not present. Then, despite positive PPS, physicians reconsidered the initial suspicion of VAP and decided not to treat the patients.

A second limitation of the present study is that we focused on the episode of VAP occurring during the first 5 days of the ICU stay. Further studies would be needed to evaluate the interest of UAS analysis in VAP occurring later on in the ICU stay.

Another limitation is that the large majority of the study patients received antibiotics before ICU admission. Another study would be needed to confirm the present results in patients without prior antibiotherapy.

Finally, another limitation would be that a strategy for empirical antibiotic prescription based on UAS (as proposed in Fig. 2) would probably not be appropriate for VAP due to inhalation of contaminated inspiratory gases or hematogenous carriage. One can argue that such a strategy based on systematic UAS can generate excessive costs. Nevertheless, such samples are already widely performed to follow patients' colonization of microorganisms and ICU ecology. Hence, excessive costs might be balanced by the benefits of an adequate treatment and by a limited use of wide-spectrum antibiotics.

In conclusion, our study compared UAS to PPS in patients presenting with VAP during the first 5 days of their ICU stay. We demonstrated high specificities and LRs for UAS to predict the microorganisms involved in VAP. Further pro-

spective studies are needed to adopt UAS as a cornerstone to guide empirical antibiotherapy for VAP.

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