



PROJECT FINAL REPORT

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1. Executive summary

MagicBullet (Optimisation of treatment with off-patent antimicrobial agents of ventilator-associated pneumonia (VAP)) was a four year EU FP7 project running from 2012 to 2015. MagicBullet formed a European multidisciplinary research team composed of leading scientists in the field of infectious diseases; clinicians experts in diagnosis and treatment of infections due to MDR-GNB; microbiologists; experts in the study of genetics, biochemical and molecular bases of bacterial resistance to antimicrobials; basic researchers, experts in human pharmacokinetic studies and experimental infections by MDR-GNB; researchers experts in industrial RTD projects and experts in clinical trial operations and pharmacovigilance. The project brought together more than 60 researchers from 35 different institutions. The consortium included 7 European research institutions and 2 biotechnological SMEs. Besides, a network of over 30 hospitals in Spain, Greece and Italy took part in the clinical trial.

The aim of MagicBullet project was the optimization of the treatment of VAP caused by MDR-GNB, determining a gold standard empiric therapy and reducing the period of time needed for the determination of the etiology and susceptibility of pathogens. The main objective was to compare the efficacy and safety of two off-patent antimicrobial agents, colistin vs. meropenem, for the empirical treatment of VAP by means of the development of an international randomized clinical trial.

The clinical trial was the cornerstone of the project aimed at seeking solutions to MDR-GNB infections, so that the samples gathered from patients in the clinical trial (respiratory and rectal swabs samples) were re-directed to different collaborative laboratories in Spain (Seville, Barcelona and Coruña), France (Paris) and Germany (Cologne), in order to assess other specific objectives such as the evaluation of the impact of the antimicrobial treatment in the development of antimicrobial resistance and its specific mechanism of antibiotic use on the microbiome. Additionally two clinical centers (one in Spain and another in Greece) also participate in a PK/PD sub-study of colistin. Furthermore, the project relied on the participation of two SMEs, which participated in the trial designing and evaluating simple, rapid and reliable procedures to determine antibiotic susceptibility, using a DNA fluorescent staining technique and a novel microencapsulation technology in relevant bacteria isolated from patients with VAP.

From a clinical perspective, the results of the clinical trial MagicBullet will bring a change into clinical practice, since Colistin will become the antibiotic of choice for empirical treatment of VAP in areas with high prevalence of MDR-GNB. Furthermore MagicBullet establishes the ideal dose of colistin for the treatment of severe infections caused by MDR-GNB in critically ill patients. Additionally MagicBullet results, the recovery of an old antibiotic for the treatment of VAP, can be applied to other serious infections caused by MDR-GNB, so important in the postantibiotic era.

For more information on MagicBullet you can visit its website (www.magicbullet7fp.eu).

2. Summary description of the project context and the main objectives

Antimicrobial drug resistance is an increasingly serious public health problem in Europe. Severe hospital-acquired infections caused by antimicrobial drug resistant pathogens result in increased patient morbidity and mortality. Infections caused by multidrug-resistant gram-negative bacilli (MDR-GNB) are particularly important. The problem of antimicrobial drug resistance is aggravated by the immediate threat of a reduction in the discovery and development of new antibiotics.

In Europe, infections caused by drug resistant bacteria are increasingly prevalent, in particular *A. baumannii*, *P. aeruginosa* and the extended-spectrum beta-lactamase (ESBL)– producing or carbapenemase-producing Enterobacteriaceae. These organisms are highly efficient at up-regulating or acquiring genes that code for mechanisms of antibiotic drug resistance, especially in the presence of antibiotic selection pressure. Furthermore, they have available to them a plethora of resistance mechanisms, often using multiple mechanisms against the same antibiotic or using a single mechanism to affect multiple antibiotics. Compounding the problem of antimicrobial-drug resistance is the immediate threat of a reduction in the discovery and development of new antibiotics. As a consequence, a perfect storm has been created with regard to these infections: increasing drug resistance in the absence of new drug development. This context is likely the best example of the denominated “Post-Antibiotic Era”, with relevance even in non-specialized media.

Ventilator-associated pneumonia (VAP) is one of the most common and severe hospital-acquired infections, and MDR-GNB constitute the main etiology in many countries, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum beta-lactamase (ESBL)–producing or carbapenemase-producing Enterobacteriaceae. Current clinical guidelines recommend a carbapenem with antipseudomonal activity as an option for the initial therapy of VAP. Unfortunately, the resistance of these organisms to antibiotics, particularly to carbapenems, has posed important therapeutic challenges. Inappropriate empiric antimicrobial treatment in patients with VAP is associated with increased complications, prolonged stay in ICU and excess mortality. MDR-BGN increases the risk of inappropriate empiric antimicrobial treatment, including treatment with carbapenems. In this context of multiresistance, in which many of MDR-GNB are resistant to all antibiotics except colistin, empirical treatment of choice for VAP is unknown.

Colistin is an antibiotic discovered more than 60 years ago, and subsequently abandoned except in the treatment of respiratory infections in cystic fibrosis patients. Colistin, an “old” drug, is now the antimicrobial with greatest in vitro activity against MDR-GNB, but no randomized clinical trial with colistin had been carried out before. Besides, many additional aspects of colistin were not well known, such as the appearance of resistant strains or alterations in the intestinal microbiome during treatment. Furthermore, conventional

microbiological techniques take 48 to 72 hours to identify pathogens and determine their susceptibility, which is too long if empiric treatment is inappropriate and this fact translates into health problems and mortality for patients.

The project was therefore motivated by six main questions:

1. Which is the empirical treatment of choice for VAP in hospitals with high levels of MDR-GNB?
2. Is colistin as effective as meropenem in the empiric treatment of VAP?
3. Is colistin as safe as meropenem in the empiric treatment of VAP, including the impact on the intestinal microbiota and the ability to develop resistance?
4. What are the PK / PD parameters of colistin, administering a loading dose in critically ill patients?
5. In the diagnosis of VAP, is PCR as sensitive and specific as conventional microbiological techniques? And, how much faster is it?
6. Is it possible to accelerate the determination of antimicrobial susceptibility of pathogens isolated from patients with VAP?

The final goal of MagicBullet was the optimization of the treatment of VAP caused by MDR-GNB, determining a gold standard empiric therapy and reducing the period of time needed for the determination of the etiology and susceptibility of pathogens.

MagicBullet is the first study that characterizes the ecological impact of colistin therapy, providing information for optimizing ecological antimicrobial regimens (such a project linking clinical and molecular data has never been done to settle several important and controversial issues regarding the effect of antibiotic treatment on the intestinal microbiota).

MagicBullet is the first study that analyzes and compares the ability to develop resistance to therapy of colistin vs. meropenem, both combined with levofloxacin, in patients with VAP (this study will also serve to determine what is the level of clonal spread of MDR-GNB in the 26 participating hospitals, to distinguish between reinfection and the development of resistance by genetic analysis of pathogens, and to identify new mechanisms of resistance. This new knowledge could be applied for future control measures to reduce the appearance of colistin or carbapenem resistant strains, and to design new therapeutic targets).

Early microbiological diagnosis is essential for the successful management of VAP. Delays in the administration of appropriate antibiotic therapy are associated with excess mortality. Standard bacterial isolation, followed by identification and antimicrobial susceptibility testing usually takes no fewer than 48 to 72 hours in the microbiology laboratory. This is too long if the empiric antimicrobial treatment was inappropriate. MagicBullet proposes the validation of commercially available PCR-based techniques for the diagnosis of ventilator-associated pneumonia in hospitals with high rates of VAP caused by multidrug-resistant gram negative bacilli (this approach may allow for rapid identification of the causative species and the early initiation of targeted treatment, thereby reducing the mortality due to inadequate antimicrobial therapy).

Early antimicrobial susceptibility tests are also necessary to optimize the antimicrobial treatment of VAP. MagicBullet is the first study that develops two new methods for rapid antimicrobial susceptibility testing.

We strongly believe that the results of our project can be extrapolated to other serious infections caused by these pathogens that are more and more common and against which the current therapeutic resources are very limited and – unfortunately- in the mid-term there is no hope of increasing these therapeutic resources.

3. Description of the main S & T results/foregrounds

a. Clinical trial

The MagicBullet clinical trial is designed as a phase IV, randomized, controlled, open label, non-inferiority and international trial to assess the safety and efficacy of colistin versus meropenem in late onset VAP. This is an investigator-driven clinical study with noncommercial objectives within the general objectives of a global project titled 'Optimisation of treatment with off-patent antimicrobial agents of ventilator-associated pneumonia (VAP)' funded by European public competition in the Seventh Framework Program of the European Commission.

The clinical trial has been performed in 32 reference hospitals in Spain (16 centers), Greece (10 centers) and Italy (six centers). The coordinating trial site is located in the same public hospital leading the study, CTU-HUVR, and was responsible for the whole coordination of the study and all the sites involved, submitting the administrative authorizations of the study, handling regulatory affairs, contact with ethics committees and response, drug management, labeling and distribution of the IMPs, safety monitoring and pharmacovigilance responsibilities of the sponsor, as well as logistic coordination and providing a contact point for all the 32 clinical teams participating in the study and monitoring activities.

In order to ensure the quality of all the activities and resolving specific country aspects related to the approval or local administrative requirements in Italy and Greece, two CROs have been subcontracted. Monitoring activities in Spain were performed by clinical research associates (CRAs) pertaining to the Spanish Clinical Trial Network in public hospitals.

A webpage for the study was publically available, with specific content requiring login and being password-protected, including the eCRF for the clinical trial, of which managing and updating is the responsibility of the project management team. IBIS-HUVR was in charge of the management of the entire number of samples, including reception, classification and delivery to collaborating laboratories.

A Data and Safety Monitoring Board (DSMB) was foreseen and has been carried out when 50% of the sample size was recruited. The DSMB was charged with monitoring the accumulating

data from the clinical trial to detect and report early evidence of pre-specified or unanticipated benefit or harm to trial participants that may be attributable to one of the treatments under evaluation. The DSMB conducted an independent objective review of all accumulated data from the clinical trial in such a manner as to maximize benefit to the trial participants and to the research effort.

The initial recruitment period was two years, but due to the different initiation dates and situation in Spain, Italy and Greece, an extension of the project has been agreed with the European Commission. After the extension, the project reached the sample size needed to evaluate the efficacy and DSMB interim analysis has been conducted in September, 2015, encouraging that the non inferiority of colistin vs. meropenem regarding the main end-point of mortality was confirmed, so that, in agreement with the Italian and Greek coordinators of the study, and considering the lack of benefit of continuing recruitment, the end of the recruitment period for the study has been fixed on 13 October, 2015

Activities such as monthly conferences with the active sites, constant communication with investigators and CROs, updated information via monthly newsletters, other specific communications and the external and internal parts of the website of the project have been a key part of the coordination activity. In parallel, onsite and phone meetings have taken place between the CTU-HUVR and the monitors of the clinical trial in order to enhance recruitment at a local level. Recruitment stimulation through personal communication from the study leader, who is responsible for the clinical trial, has been a key factor in the work carried out by the coordination of the clinical trial since its beginning, and will continue in the future in order to achieve the sample size needed for the study.

MagicBullet has put in motion one of the first investigator-driven clinical trials of off-patent antibiotics funded by the European Union. In order to initiate this independent clinical trial without the support of the pharmaceutical industry, many tasks had to be developed: selection of the participating hospitals, approval of the trial by the ethics committees of each hospital, authorization of the study and drug management system from the regulatory authorities in the three countries, contracting of two CROs and public procurements for the provision of the eCRF and website, study drugs, transportation of the biological samples and drug handling. For the implementation of all these tasks, great effort was devoted, as international coordination and resources available in public settings are not comparable with the pharmacy industry or private sponsors and CROs.

b. Pharmacokinetic (PK) and pharmacodynamic (PD)

The pharmacokinetic and pharmacodynamic (PK/PD) of colistin and levofloxacin have been determined by taking blood samples from 30 patients with VAP included in the clinical trial at different time-points. Samples have been processed and quantified using high resolution

chromatographic methods. Using the PK data, Monte Carlo simulations have been performed in order to quantify the probability of achievement of population PD targets.

Also, population pharmacokinetic has been done to study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving colistin.

The main outcomes from the work done on this Work package are:

1. With a 4.5 MU CMS iv loading dose we achieve the PK levels obtained at steady state since the first dose.
2. With 4.5 MU CMS iv loading dose and 3 MU CMS / 8h iv maintenance doses, in patients with RRF and RD, it is reach the PK and PD levels considered optimal in previous studies if the MIC \leq 0.5.
3. Montecarlo simulation model is able to describe properly the experimental data following the loading dose and the maintenance doses, especially at steady-state.

c. Impact of Empirical Treatment Using Colistin-Levofloxacin vs. Meropenem-Levofloxacin in the Intestinal Microbiome of VAP Patients

In order to achieve these objectives, rectal swabs were collected at different time-points in all patients, to study the abilities of two different antibiotic regimens, used in the clinical trial, to select changes in the intestinal microbiome of patients.

Overall, 867 rectal swabs with Amies transport medium and 867 swabs without transport medium ("dry swabs) have been received from 232 different patients. We have collected 1454 isolates from 149 different patients out of 230 patients studied, which means that 64% of patients carried at some point a bacterial isolate resistant to either carbapenems, cephalosporins, colistin or quinolones.

At the final stage of the clinical trial, colistin and carbapenem resistance among Gram-negative isolates recovered from the rectal tract of patients included in the trial amount to 27.5% and 65.1% of all isolates, although there are significant differences depending on each bacterial species and country of origin, with carbapenem resistance among *K. pneumoniae* and *A. baumannii* being as high as 85% and 99%, respectively, and colistin resistance among the same species being of 47% and 20%, respectively.

Results indicate that the overwhelming majority of *A. baumannii* and *K. pneumoniae* strains recovered from stool samples in patients with VAP were carbapenem resistant in both study groups already at early time points.

Preliminary analyses suggest that carbapenem resistance among these bacterial species rarely developed under treatment but rather reflected the endemic nature of carbapenemase-producing *K. pneumoniae* and *Acinetobacter baumannii* in each country hospital. Some *P. aeruginosa* strains, especially those from Spain and Italy, might have developed carbapenem-resistance due to mutations that alter membrane permeability or promote the induction of the chromosomally-encoded AmpC-type beta-lactamase.

Colistin resistance, on the other hand, slowly developed upon colistin treatment among *Klebsiella pneumoniae* and *Acinetobacter baumannii* but rapidly colonised the intestinal tract of patients under meropenem treatment in those hospitals with endemic carbapenem resistant strains. Co-selection of carbapenem and colistin resistance in such hospitals seemed to favour the clonal spread of highly resistant epidemic lineages.

d. Analysis of antibiotic resistance mechanisms

The main aim was to evaluate the impact of the antimicrobial treatment in the development of antimicrobial resistance and the specific mechanism, in all bacterial strains isolated at baseline and at follow-up.

The objectives of the analysis of antibiotic resistance mechanisms were the following:

1. To analyze the resistance of *P. aeruginosa*, *A. baumannii* and Enterobacteriaceae recovered from respiratory tract samples from patients with ventilator-associated pneumonia (VAP) to any of 3rd generation cephalosporins, carbapenems, or colistin analyzed by using molecular, biochemical, and microbiological methods.
2. To characterize, through molecular epidemiology experiments, the genetic relatedness of the bacterial isolates of the same species isolated from the patient during the course of the antibiotic treatment (on day 0, 3, and 8), the end of treatment and at test-of-cure (TOC).
3. To assess the molecular basis for antimicrobial resistance to the above described antibiotics/bacterial isolates combinations.
4. To evaluate the impact of the antimicrobial treatment on the development of phenotypic antimicrobial resistance and their specific mechanisms.
5. To support the experimental approach attempting to design rapid antimicrobial susceptibility testing by two new technological approaches.

In order to evaluate the impact of the antimicrobial treatment in the development of antimicrobial resistance and the specific mechanism, bronchial aspirate samples were collected from patients included in the study and were processed according to the MagicBullet / COLMER protocol. Three different labs have been working on this objectives.

Research activities have been developed on antibiotic resistance traits of the three bacterial species investigated in Magic Bullet research proposal, Enterobacteriaceae, *Pseudomonas* spp and *Acinetobacter baumannii*. Most of the research projects are related to genetics, biochemistry and epidemiology of β -lactam resistance genes. These resistant bacteria have then been used to evaluate and develop point-of care technologies in order to rapidly determine the resistance traits of gram-negative bacteria. Better knowledge on currently spreading genes is a prerequisite for efficient analysis of the different resistance mechanisms present in the bacterial isolates from the clinical trial.

Thus through frequent patient transfer from abroad, and through international collaborations, we were able to investigate the occurrence of several currently spreading beta-lactamase genes and to elucidate the genetics sustaining the spread for : NDM; KPC; OXA-48; GIM-1, GES-14, CTX-M-15. We have evaluated a novel real-time probe-ligation assay for Rapid Detection of KPC, OXA-48, VIM, IMP and NDM-1 carbapenemases. We were able to identify a novel chromosomally encoded ESBL from an environmental bacterial isolate and finally we identified molecular mechanisms of colistin resistance.

e. Rapid assay for the detection of the microorganism

The work aimed to validate a PCR-based technique for the early detection of the microorganisms involved in VAP and use of a PCR-based technique to measure the ability of two different antibiotic therapies to clear bacteria from the lung.

For these studies commercially available PCR-based kits that are capable of detecting pathogens commonly associated with ventilator-associated pneumonias (VAP) in respiratory samples were being used. We have used a new kit for the identification of causative microorganisms of VAP that is called BioFire FilmArray Blood Culture Identification (BCID) Panel, which consists in a panel that is able to detect 8 Gram-positive bacteria, 11 Gramnegative bacteria, and 5 *Candida* species by RT-PCR in only 1 hour.

Clinical samples (endotracheal aspirates or BAL) from the all patients enrolled in the clinical trial were used for the validation of this technique. we have analyzed 167 samples obtained from 165 patients. The samples were divided into two, and half the samples are used to for diagnosis based on PCR following the protocol suggested by the manufacturer of the kit, and the other half are used by institutional clinical microbiology laboratories for diagnosis using standard methods. For this validation study, treatment is not guided by results of the PCR-based technique.

Once samples have been analyzed by both techniques, the following parameters were calculated using the standard culture-based technique as the gold standard: sensitivity, specificity, positive predictive value and negative predictive value.

We came to the conclusion that the use of the BioFire FilmArray Blood Culture Identification Panel could have clinical utility in rapidly ruling out causative microorganisms of VAP due to its high specificity and negative predictive value, specifically for multidrug resistant Gram-Negative Bacteria, potentially carbapenem resistant (98.5%), which allows to simplify empiric treatment in patients. In addition, the FilmArray System is highly specific (98.1%) for the detection of KPC containing microorganisms in respiratory samples.

f. Rapid antimicrobial susceptibility test

The objectives of the Rapid antimicrobial susceptibility test, in which 2 SMEs took part were the design and evaluation of a simple, rapid and reliable procedure to determine the susceptibility, using DNA fluorescent staining technique and the design and evaluation of a simple, rapid and reliable procedure to determine the susceptibility, using a novel microencapsulation technology.

The rapid fluorescence assay to determine susceptibility or resistance to antibiotics was optimized for meropenem, ciprofloxacin, ceftazidime and colistin, specifically in *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*. The procedure has been validated for a rapid determination of susceptibility or resistance to ciprofloxacin, meropenem and ceftazidime in a high number of clinical isolates of *A. baumannii*, *K. pneumoniae* and *P. aeruginosa*. The criterion for effectiveness or not for meropenem and ceftazidime was the release or not of the nucleoids, whereas for ciprofloxacin was the fragmentation or not of the nucleoids. Susceptibility or not for each antibiotic was established in 3 h 15 min. The results of the fast test were practically similar to those of the standard antibiogram. Only a relative high frequency of false negatives of resistance to ceftazidime was detected in *P. aeruginosa*. The procedure was validated for *A. baumannii* to demonstrate susceptibility or resistance to colistin. In this case, scoring < 11% of cells with cell wall damage identified the strain as no-susceptible, with 100% sensitivity and 96% specificity. The procedure distinguished the susceptible and non-susceptible strains for colistin, in 3 h 30 min. Regarding high throughput analysis, the MLBE device can be considered as a cheap and effective media to assess bacterial susceptibility to antibiotics but with a need of improvement in terms of optics to progress in image resolution and need to be stabilized in term of software design.

Regarding the microencapsulation, defined as the process of coating molecules, solid particles or liquid globules of different kinds of material to yield micron sized particles: although microencapsulation technology is widely distributed in pharmaceutical companies and in food industry, for encapsulation of molecules, compounds, aromas and many other different molecules, the encapsulation of living cells for the application in health system is very limited. This limitation is based in the effect that the encapsulation process applied could have in the cell to be encapsulated, vibrational, electrostatic and mechanical forces can have deleterious effect over cell viability. The application of Flow Focusing® technology for the encapsulation of

living cells could provide with a powerful tool for the analysis of microbial phenotype, in the context of this project, for the analysis of the resistance pattern of an individual strain. The necessity of substituting the cytometry analysis for a more easy, fast and convenient technique after the first analysis of the *A. baumannii* strains was encountered. The technique found to be the most resolute and the one that solved most of the problems encountered was the automated image analysis. The Gel Microencapsulation assay coupled with image analysis is a semi-automated process, in order to be fully automatized process for high-throughput screening, changes in the industrial design must be included.

4. Description of the potential impact (including the socio-economic impact and the wider societal implications of the project so far) and main dissemination activities and the exploitation of results

a. Description of the potential impact

Knowledge generated by MagicBullet produces important advances in the diagnosis, treatment and prognosis of VAP, one of the most serious and frequent nosocomial infections. In many areas of Europe that have a high prevalence of MDR-GNB, the empirical treatment of VAP is suboptimal, increasing complications, prolonged stay in ICU and excess mortality.

MagicBullet results will allow clinicians to maximise clinical benefit in terms of reduction of mortality caused by the appearance of VAP in critically ill patients and decrease of morbidity related to VAP caused by MDR-GNB due to a rapid and well conducted treatment, with the subsequent reduction in costs derived from length of stay in ICU, thanks to the results of the clinical trial and the technology brought by Research-intensive SME. The outcomes are relevant for patients and must change the clinical practice with the subsequent reduction of length of stay in ICU and the use of colistin as empiric treatment by practitioners.

b. Main dissemination activities

The dissemination and communication strategy of MagicBullet included two main sets for action:

- Production and circulation of dissemination material, mailing, newsletters, media communication and awareness-raising aimed both at the scientific community and the public in general.
- Participation in scientific events.

According to the Communication Plan, the communication and dissemination objectives include knowledge sharing, greater public awareness and transparency:

- Drawing the attention of national governments and regional authorities (Public Health Services) to the needs and eventual benefits of the research;
- Attracting the interest of potential partners and incorporate other clinical sites to ensure the consecution of the trial (reaching the necessary sample size of the clinical trial);
- Encouraging talented scientists to join the Consortium and establishing long-term collaboration;
- Enhancing the reputation of participants, at local, national and international level;
- Where appropriate, aiding the search for financial backers, licensees or industrial implementers to exploit the results, generating market demand for the developed products; and

In order to be successful, MagicBullet has been supported by a comprehensive communication strategy running throughout the whole project execution period

MagicBullet developed its communication plan in order to:

- Establish a shared and efficient process to produce, review and circulate content that communicates the objectives, results and deliverables of each activity;
- Share knowledge, methods, tools and templates, seeking for consistency and efficiency;
- Generate project material for general dissemination, such as brochures and posters, that partners can bring to external events; and
- Communicate project results to relevant stakeholders through various communication channels in order to reach a broad audience.

MagicBullet has been presented in scientific journals, meetings and in general press, disseminating the information on the objectives and results of the project, both to the scientific society and to the public in general.

c. Exploitation of results

Patents are present within the objectives of the project:

1. To design and evaluate a simple, rapid and reliable procedure to determine the susceptibility, using DNA fluorescent staining technique.
2. To design and evaluate a simple, rapid and reliable procedure to determine the susceptibility, using a novel microencapsulation technology.
3. To determine synergies between both technologies in order to characterize the susceptibility.
4. To automate both procedures for high-throughput screening.
5. To initiate procedures for future patenting and commercial development.

Biomedal (Partner 9), in collaboration with SAS (Partner 1), registered a national (P201330933) and international (PCT/ES2014/070511) patent application on the rapid antimicrobial susceptibility tests by microencapsulation.

5. Consortium and contact information

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