

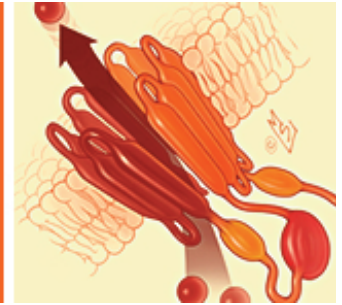


eLITERATURE
REVIEW

eCysticFibrosis Review
Podcast Issue

Presented by the Johns Hopkins
University School of Medicine and the
Institute for Johns Hopkins Nursing

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VOLUME 3 – ISSUE 4: TRANSCRIPT

Featured Cases: Pulmonary Exacerbation Therapies

At the conclusion of this activity, participants will demonstrate the ability to:

- Discuss the clinical implications of acute pulmonary exacerbations in cystic fibrosis,
- Describe the evidence that supports common treatment approaches to acute pulmonary exacerbation in cystic fibrosis, and
- Explain the complexities of assessing antimicrobial resistance patterns via sputum isolates in cystic fibrosis.

This audio activity has been developed for clinicians caring for patients with issues related to cystic fibrosis. You can also read the **companion newsletter**. In this edition Dr. Goss will help expand our understanding of the treatment approaches for managing pulmonary exacerbations in patients with cystic fibrosis, including the discussion some typical case scenarios.

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The author indicates that there will be no reference to unlabeled/unapproved uses of drugs or products in his presentation.

MEET THE AUTHORS



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Guest Faculty Disclosure

Christopher H. Goss, MD indicates that he has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of his presentation.

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LAUNCH DATE

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MR. BOB BUSKER: Welcome to this eCysticFibrosis Review podcast.

eCysticFibrosis Review is presented by the Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. This program is supported by an educational grant from Abbott Laboratories, Gilead Sciences Medical Affairs, and Vertex Pharmaceuticals.

This podcast is a companion activity to our October 2011 newsletter topic: Exacerbation Therapies.

Our guest is that issue's author — Dr. Chris Goss, from the University of Washington in Seattle.

This activity has been developed for physicians, nurses, respiratory therapists, dietitians, and physical therapists caring for patients with cystic fibrosis. There are no fees or prerequisites for this activity.

The Accreditation and Credit Designation Statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies and expiration dates and to take the post-test to receive credit on-line, please go to our website newsletter archive, www.ecysticfibrosisreview.org, and click on the November 2011 podcast link.

Learning objectives for this audio program are, that after participating in this activity, the participant will demonstrate the ability to:

- Discuss the current clinical definition of an acute pulmonary exacerbation in cystic fibrosis,
- Describe the current approach to the treatment of an acute pulmonary exacerbation, and
- Explain the complexities of assessing antimicrobial resistance patterns via sputum isolates.

I'm **BOB BUSKER**, managing editor of eCysticFibrosis Review. On the line we have with us our October newsletter issue's author. Dr. Chris Goss is associate director of the Adult Cystic Fibrosis clinic at the University of Washington and codirector of the CF Therapeutics Development Network Coordinating Center in Seattle. Dr. Goss is also an associate professor of medicine and an adjunct professor of pediatrics at the University of Washington.

Dr. Goss has disclosed that he receives grants and research support from the Cystic Fibrosis Foundation, NIH, Transave Inc., and Vertex Pharmaceuticals. He has also received honoraria from KaloBios Pharmaceuticals, Roche, and Transave, Inc.

His presentation today will not include discussion of any off-label or unapproved treatments for CF.

MR. BUSKER: Dr. Goss, welcome to this eCystic Fibrosis Review podcast.

DR. GOSS: Thank you very much for having me.

MR. BUSKER: In your newsletter issue, you presented some of the most relevant research findings on exacerbations and lung function and some of the most current data on treatment approaches. What I'd like to do today is focus on the implications that information has in the exam room and at the bedside. So please start us out by describing a patient.

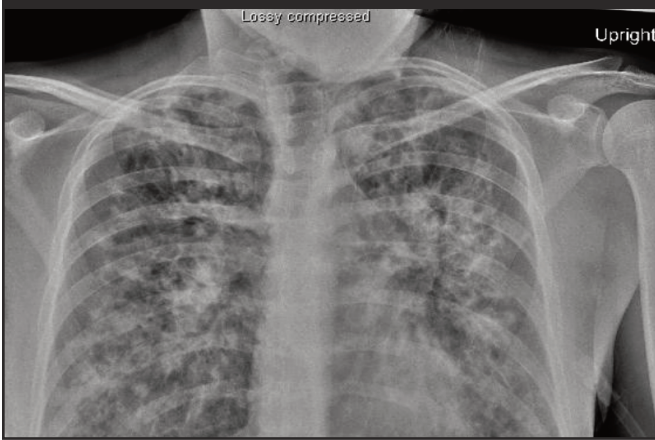
DR. GOSS: The first patient we're going to discuss is a 35-year-old woman with cystic fibrosis of genotype delta F508 homozygous who developed increasing congestion beginning a week ago. On evaluation, she was afebrile and had a mild tachycardia, heart rate 100, and normal oxygen saturation of 98% on room air.

On physical exam, the patient had bilateral upper lobe crackles, which were new. On laboratory evaluation, the patient was noted to have decreased lung function as evaluated by spirometry. Forced expiratory volume in 1 second, or FEV₁, was 1.03 liters, 31% of predicted. Forced vital capacity, or FVC, was 1.29 liters at 32% of predicted with a FEV₁ to FVC ratio of 0.84. Her prior FEV₁ was 1.15 liters and prior FVC was 1.53 liters, representing a significant drop in her lung function.

The patient was chronically infected with *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

MR. BUSKER: I just want to break away for a second to let our listeners know that patient's radiograph can be viewed in the transcript version of this podcast. So now my first question, Dr. Goss: Would we call this event an exacerbation?

Figure 1: PA chest radiograph



[Click to view radiograph](#)

DR. GOSS: This event is consistent with an acute pulmonary exacerbation in an adult with CF, with new-onset lower respiratory symptoms, new crackles on physical exam, and a dropped lung function of greater than 10% above the FEV1 and the FVC. It's important to note that there are no consensus diagnostic criteria for this clinical entity of acute pulmonary exacerbation, and there's no consensus either for the duration of symptoms that must precede the clinical presentation, and some clinical trials have used three or five days.

The clinical presentation of these events will likely differ by age and disease severity, so young children may not be able to tolerate spirometry. Also, it should be noted that dropping your lung function by 10% is easier when you have poor lung function because the magnitude of the 10% drop is much lower.

MR. BUSKER: Based on the research you reviewed in the newsletter, how should this patient be treated?

DR. GOSS: This patient should be treated as an inpatient, unless adequate resources exist at home for home IV therapy and airway clearance. Now, even though the evidence is very limited, the patient should receive two drugs with activity against *Pseudomonas aeruginosa* from the prior isolate the patient has had. One should also consider covering *Staphylococcus aureus*. It's important to note that routine maintenance medications and airway clearance should be continued during the current treatment of an acute pulmonary exacerbation.

MR. BUSKER: Let's look at follow-up for this patient. What would be required?

DR. GOSS: An excellent question. Lung function should be checked at the end of an antibiotic course to document recovery, regardless of the site of treatment, whether they're getting antibiotics at home or in the hospital. Symptom resolution should also be documented. If lung function recovery does not occur, one should look for complicating factors that affect cystic fibrosis. These include asthma, allergic bronchopulmonary *Aspergillosis*, and acquisition of a new organism.

MR. BUSKER: What are the chief clinical implications of this event?

DR. GOSS: Interestingly, upwards of 25% of patients do not appear to regain baseline function after this event. Patients averaging more than two exacerbations per year may have a higher risk of death or need for lung transplantation.

Patients averaging more than two exacerbations per year may also have a higher risk of losing 5% of their lung function, according to an observational cohort study in Canada highlighted in the newsletter. It's important to note that this may not apply to other care settings outside of Canada, but the data are concerning.

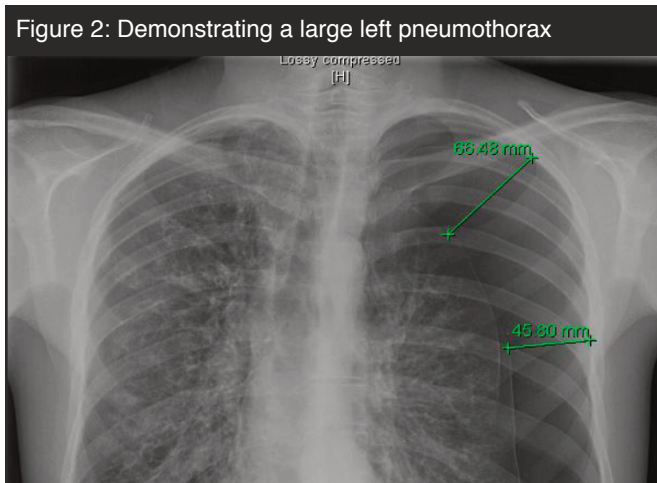
MR. BUSKER: Thank you, Dr. Goss. Please take us now to another patient.

DR. GOSS: Okay, I'd be glad to. This is a 22-year-old man with cystic fibrosis, genotype delta F508 homozygous, with mild pulmonary impairment, who developed increasing lower respiratory congestion and sputum production over the space of six days after a recent upper respiratory tract infection. He thought his symptoms would abate, but then he developed new-onset severe dyspnea.

His parents drove him to a local emergency room, where he was rapidly evaluated. His vital signs were notable for an oxygen saturation of 94%, but a respiratory rate of 28. He noted left-sided chest pain. A chest radiograph revealed a large left pneumothorax and clear evidence of bilateral saccular bronchiectasis consistent with cystic fibrosis. A chest tube was placed with resultant relief of dyspnea.

MR. BUSKER: Again, I want to let our listeners know that a radiograph of this patient is included in the podcast transcript. Now Dr. Goss, this patient's presentation is quite different from the first patient

you described. Would we also call this event an exacerbation?



[Click to view radiograph](#)

DR. GOSS: This patient has clinical symptoms, again consistent with an acute pulmonary exacerbation, but this time complicated by pneumothorax. Because of this pneumothorax, spirometry cannot be performed. This does not exclude a diagnosis of acute pulmonary exacerbation. Pneumothorax can occur independent of an acute exacerbation or in the setting of an acute exacerbation, as in this case. The key risk is likely bronchiectasis abutting the pleura.

On physical exam, it's apparent that she has a reduced body mass index at 18, suggesting malnutrition. There are crackles over the upper lobes when listening to her chest. She also has digital clubbing. In clinic she's seeking our input on her treatment regimen.

MR. BUSKER: Is there guidance in how long this patient should be treated with antibiotics?

DR. GOSS: The current recommendation is two weeks, but the evidence supporting this duration of therapy is weak. No clinical trials have specifically addressed antibiotic duration in CF exacerbation. Looking at observational data in the U.S. from the Cystic Fibrosis Registry, treatment duration varies widely.

MR. BUSKER: Dr. I want to ask you about synergy testing of the organisms grown from this patient's sputum. Can that be used to guide the antibiotic treatment?

DR. GOSS: A recent systematic review of literature by Flume and colleagues highlighted in the newsletter recommended against the routine use of synergy testing guiding therapy. Synergy testing is expensive, and in the one carefully designed prospective, randomized, controlled trial, it showed no demonstrable effect on outcome.

Clinicians typically select antibiotics based on standard susceptibility testing of the pathogens from the previous sputum. It is important to note that synergy testing should be considered for selected patients, like those with highly resistant organisms prior to lung transplantation.

MR. BUSKER: Talk to us about dosing, Dr. Goss. In the case you presented, let's say this patient grows *Pseudomonas* sensitive to tobramycin. Should he receive the tobramycin once a day or three times a day? Is there an optimum dosing schedule?

DR. GOSS: The standard approach to antibiotic treatment for CF patients infected with *P. aeruginosa* continues to be the use of two drugs with antipseudomonal activity to improve antibiotic activity while reducing selection pressure for resistant strains. One of these agents is usually an aminoglycoside, and tobramycin is the one most commonly used in the United States.

In regard to aminoglycosides, once-daily versus three-times-daily intravenous dosing was evaluated in the systematic review by Flume and colleagues reported in the newsletter. The current recommendations note that it is preferable to employ once-daily dosing for aminoglycosides compared to three-times-daily dosing. One of the findings in a well-done prospective clinical trial on aminoglycoside dosing noted relative protection of the kidneys in two-day dosing. Once-daily dosing of aminoglycosides was graded as a "C" in the systematic review. That means there is moderate or high certainty that the net benefit is small.

MR. BUSKER: In the specific patient you described, what treatment was undertaken and what were the results?

DR. GOSS: This patient received the standard 14 days of intravenous antibiotics with intravenous ceftazidime and intravenous tobramycin. The tobramycin was dosed once daily. The patient also had a placement of a small-bore chest tube to drain

his pneumothorax. He had full recovery of lung function and no recurrence of his pneumothorax after removal of his chest tube.

MR. BUSKER: Thank you, Dr. Goss, for that discussion and explanation. I'd like to shift our focus to antibiotic selection. So please start us out with another patient presentation.

DR. GOSS: This next patient is a 16-year-old male with increased congestion and sputum production. The patient had a sputum culture from two months before when he was in clinic. The susceptibility tests were performed using standard methodologies on this sputum, with organisms based in a nonbiofilm-based sensitivity testing.

The sputum grew three colony types of *Pseudomonas*. Colony type 1 was resistant only to imipenem, an intermediate to levofloxacin and ciprofloxacin. Colonies Type 2 and 3 were resistant to both ciprofloxacin and levofloxacin.

This case points out the challenge of selecting antibiotics based on sensitivity to various antibiotics when subjects grow multiple colony types of bacteria, in this case *Pseudomonas*.

MR. BUSKER: Another note to our listeners: This patient's specific sputum sensitivity results are available in the transcript. Now Dr. Goss, tell us about the current standard approach to choosing antibiotics for a patient like this.

DR. GOSS: CF clinicians usually pick a combination of two antibiotics, representing the different classes of agents that best cover the organisms found in sputum. As you can see by this patient, the challenge is selecting antibiotics that cover all the organisms. A reasonable combination for this patient may be intravenous tobramycin and intravenous ceftazidime or meropenem. I would not use oral levofloxacin or oral ciprofloxacin, given the resistance patterns of the organisms noted.

MR. BUSKER: Is there any surety that the patient will respond to either of these medications or the combinations of these medications?

DR. GOSS: Unfortunately not. Most patients will respond, but good clinical studies have shown that choosing antibiotics based on susceptibility testing

in the sputum does not necessarily predict response. Formal susceptibility testing takes up to seven days after a sample is delivered to the laboratory. By this time, most patients have already improved on their current regimen, regardless of whether it is appropriate for the organisms grown in the sputum. Susceptibility testing may reflect only those organisms expectorated in one particular sample, at one point in time.

MR. BUSKER: We know that established pseudomonas airway infections in CF patients are likely to be growing a biofilm, which would enhance the organism's resistance to both host defenses as well as antibiotics. So shouldn't biofilm-based susceptibility testing methods improve clinical outcome?

DR. GOSS: Unfortunately, the answer appears to be no. The observed agreement between a drug class combination selected by biofilm's susceptibility and by conventional susceptibility testing is almost 50%.

In a subset of patients, biofilm susceptibility testing may benefit patients, but it's unknown how to characterize those patients. In a recent paper discussed in the newsletter, Dr. Moskowitz and colleagues showed a decrease in bacterial load in the sputum and improvements of lung function, regardless of which method the patient was randomized to, ie, standard susceptibility testing or biofilm-based susceptibility testing. Thus, there appears to be no clear clinical benefit from using biofilm's susceptibility testing versus standard susceptibility testing.

MR. BUSKER: The data by Moskowitz that you just outlined, and that you detailed in more depth in the newsletter issue, really seems counterintuitive to expectations. Do we know what might explain this lack of clear benefit of using biofilm-based susceptibility testing to guide antibiotic therapy?

DR. GOSS: There are a number of possible explanations for the negative results of this study. First, it was a fairly small study, with a small sample size, and since both groups had a good clinical response to therapy when stable, showing a significant difference would require a very large sample size. The subjects were also clinically stable, and the investigators were fairly unlucky based on the antibiotic resistance patterns of the organisms.

Maybe it would work in a setting of an acute exacerbation or in a subset of patients in whom the antibiotic choices differ substantially between the two susceptibility testing methods.

Susceptibility testing of a few isolates may vastly underestimate the microbiological diversity of chronic CF lung infections, and maybe neither method is adequate to trying to select appropriate antibiotics for patients with CF who are being treated for an acute pulmonary exacerbation.

MR. BUSKER: Thank you for that explanation. We'll return with Dr. Chris Goss in just a moment.

MR. BUSKER: Welcome back to this eCystic Fibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Chris Goss, from the Adult Cystic Fibrosis Center at the University of Washington in Seattle. Our topic is Pulmonary Exacerbation Therapies.

We've been discussing how the information in the research publications reviewed in our October 2011 newsletter can help improve patient care. Dr. Goss, please present us another patient scenario.

DR. GOSS: The next case is an 18-year-old female with cystic fibrosis genotype delta F508 homozygous who presented with two weeks of increasing congestion and sputum production. She denied any pleurisy or chest pain with deep inspiration, nor hemoptysis. She did feel that her appetite was markedly decreased and had lost almost five pounds since her last clinical evaluation. She was afebrile in clinic, with normal blood pressure and a heart rate of 75.

On physical exam, her chest was clear without crackles, but she did have scattered rhonchi that cleared with cough and bilateral wheezes. Her FVC was 4.25 liters, 106% of predicted, and this is down about 100 cc from her baseline. FEV₁ was 3.02 liters, or 87% of predicted, down 350 cc from her baseline. Her FEV₁ to FVC ratio was 0.71.

Sputum culture from her last clinic evaluation grew 2+ methicillin-sensitive *S. aureus*, 1+ *P. aeruginosa*, and 3+ *Stenotrophomonas maltophilia*. Her chest radiograph was unremarkable, except for mild bilateral upper lobe bronchiectasis.

She received two weeks of antibiotics and felt improved symptomatically, but did not have recovery of her lung function to baseline. Repeat sputum culture grew a new organism and the same organisms noted above. The new organism was methicillin-resistant *S. aureus*, or MRSA. Additional treatment for MRSA led to resolution of her lung function back to her baseline.

MR. BUSKER: First question: which action or combination of actions potentially prevented more long-term lung function loss in this patient?

DR. GOSS: This patient was followed closely, including documentation of improvement in lung function, rather than just symptomatic assessment. This assessment may have prevented an unrecognized long-term lung function decline. In a recent paper by Sanders and colleagues, highlighted in the newsletter, upwards of 25% of CF patients do not recover to within 10% of their determined pre-exacerbation baseline lung function. In this case, one potential reason for failure to recover was the presence of MRSA, which had not been detected in earlier sputum cultures.

Several recent epidemiologic studies have noted that MRSA may lead to more rapid lung function decline and earlier death in CF. It is important to document resolution to both symptoms and spirometry at the end of a pulmonary exacerbation to ensure that that does not lead to incremental lung function loss.

MR. BUSKER: Tell us about other potential reasons that a patient's clinical response to antibiotics may not correlate with antimicrobial sensitivities noted in the sputum.

DR. GOSS: Recent work from Mohad and colleagues outlined in the newsletter noted that *P. aeruginosa* within each sputum specimen had tremendous diversity and that there was rapid turnover of haplotype through time. Isolates within a patient's sputum had significant phenotypic variation regarding virulence factors and importantly, resistance patterns in patients in this study. Given this data, an isolate picked from the sputum may not be the dominant organism related to clinical decline. Antibiotic resistance patterns from that isolate picked from the sputum may have nothing to do with their clinical decline, and antibiotics tailored to that organism may not improve their symptoms.

MR. BUSKER: Has the research uncovered other potential biomarkers for *P. aeruginosa* that might correlate with acute pulmonary exacerbation?

DR. GOSS: Mohad and colleagues found that isolates that produced excessive pyocyanin were more common in specimens obtained during the exacerbation compared to when patients were stable before the exacerbation and after recovery from exacerbation. This may explain the potential increased virulence of the strain they were studying. They were specifically studying the Liverpool epidemic strain isolated from their clinical care centers. They also found that approximately half of the diversity in the study as a whole could be attributed to phenotypic diversity between isolates within the same samples.

Interestingly, Mohad and colleagues found very little haplotype variation during antibiotic therapy compared to periods of clinical stability, so it appeared that diversity decreased during antibiotic therapy.

MR. BUSKER: Thank you, Doctor. Let me shift our focus now to a more general discussion. In your opinion, what are the key knowledge gaps that remain in our understanding of pulmonary exacerbations?

DR. GOSS: Some of the key gaps remaining in our knowledge of the management of acute pulmonary exacerbations were highlighted in the systematic review covered by Flume and colleagues in the newsletter. They include, what is the optimal duration of therapy? As I noted, we commonly treat for 14 days. That may not be optimal. An additional important question is, for patients infected with *Pseudomonas*, are two antibiotics needed? Often, we use one agent of each antibiotic class, based on susceptibility testing.

Another important question that really is not answered is, are standard susceptibility testing methods of any utility in the clinical management of patients with CF? I do believe that they are helpful to document the evolution of new resistant strains, but their clinical utility has not been shown.

There's also a very important question about what is happening to bacterial populations in diversity before, during, and after an acute pulmonary exacerbation. I think the paper by Mohad and colleagues has only highlighted the complexity of sputum microbiology, and I think many studies must be done in this area.

MR. BUSKER: Let me follow up then on that last point. What other studies are currently under way – including research that has not yet published – that might address these specific gaps?

DR. GOSS: The Cystic Fibrosis Foundation has launched an important initiative to start to create the infrastructure to conduct comparative trials in the management of CF pulmonary exacerbation in real-world settings. Some have termed these clinical trials “comparative effectiveness trials.” A number of investigators have also begun work to unravel the complexities of bacterial communities inhabiting the CF-affected lung. These studies may help clarify the past physiology in acute exacerbation and may help justify how we choose our antibiotics.

A large NIH- and CF-supported study is just beginning to try to evaluate the efficacy of identifying pulmonary exacerbations earlier using home spirometry and home symptom monitoring. This study will test the hypothesis that identifying these events earlier can improve clinical outcome in patients, based on lung function and symptoms and quality of life.

MR. BUSKER: Until more evidence-based data become available, what's your best advice for clinicians in managing exacerbations?

DR. GOSS: I will continue to obtain sputum culture sensitivities, and I will continue to use those sensitivity data to make my antibiotic choices. I will also continue to use two antipseudomonal agents for 14 days to treat an acute exacerbation in cystic fibrosis. In regard to the site of care, I will continue to employ home IV antibiotics in selected cases where I believe standard airway clearance and nutritional support can be provided, in cases where families and patients can safely deliver home intravenous antibiotics. In cases where I don't believe this can be delivered appropriately and safely, I would recommend that the patients continue to be hospitalized for two weeks.

MR. BUSKER: Dr. Goss, please take the final word on exacerbation therapies.

DR. GOSS: I think it's important to place pulmonary exacerbations in the realm of new therapies. My hope is that new therapies prevent pulmonary exacerbations and that they prevent the potential lung function decline associated with those exacerbations.

I do believe pulmonary exacerbations are a very important clinical event in the lives of patients with CF. They are associated with significant health care costs, quality of life issues, increased symptoms, and burden of therapies. I believe that if we can prevent them or treat them better and more efficiently, we will improve the lives of our patients with CF until therapies can be developed that actually prevent lung function decline and prevent CF lung disease.

MR. BUSKER: Dr. Chris Goss from the University of Washington, thank you for participating in this eCystic Fibrosis Review podcast.

DR. GOSS: I want to thank you very much for having me. It's been a great pleasure to be involved in this.

MR. BUSKER: This podcast is presented in conjunction with eCystic Fibrosis Review, a peer-reviewed CME and CNE-accredited literature review emailed monthly to clinicians treating patients with cystic fibrosis.

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