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Development and Validation of Apolipoprotein AI-Associated Lipoprotein Proteome Panel for the Prediction of Cholesterol Efflux Capacity and Coronary Artery Disease

Article:
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Guest: Dr. Tobias Breidthardt is a senior consultant and clinical researcher at the Division of Internal Medicine at the University Hospital Basel in Switzerland.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Acute abdominal pain is one of the most common presenting symptoms in emergency department patients and its differential diagnosis can be extensive and challenging. Rapid and accurate diagnosis of urgent causes of abdominal pain is essential for the early initiation of effective therapy and efficient patient flow.

To see how the clinical laboratory can help in this process, a recent study that appeared in the February 2019 issue of *Clinical Chemistry* examined inflammatory biomarkers in the emergency diagnosis of urgent abdominal pain. Dr. Tobias Breidthardt is a senior consultant and clinical researcher at the Division of Internal Medicine at the University Hospital Basel in Switzerland and was the lead author of that paper. He is our guest in this podcast.

So, Dr. Breidthardt, why did your research focus on patients with acute abdominal pain? That's not really a very common research topic.

Tobias Breidthardt: Actually, over the last two years, emergency physicians worldwide have recognized acute abdominal pain as a growing problem. In the U.S., for example, the Center for Disease Control points out that about 7 million emergency department visits per year are due to acute abdominal pain, and this makes it the most common reason for Americans to visit the emergency department. This number is still increasing and between 2006 and 2011, for example, visits for acute abdominal pain increased by 20%.

So, acute abdominal pain is very common. And on top of this, it can be caused by urgent acutely life-threatening conditions such as, for example, a perforated viscus, but this is also because of harmless but painful conditions such as intestinal cramps or menstrual pain. Differentiating these urgent from non-urgent causes of abdominal pain is very

difficult and it is time consuming and is therefore very expensive to our healthcare systems.

In our study, for example, we found patients with acute abdominal pain to be treated in emergency departments for about, on average, five and a half hours. And then, 50% of these patients were subsequently admitted to hospital, but only a third of all patients in our study eventually suffered from an urgent cause of abdominal pain.

So, we believe that a tool to quickly and adequately differentiate those potentially life threatening and urgent causes of abdominal pain from non-urgent causes of abdominal pain would be very helpful for clinicians in the emergency departments. It would help initiate effective therapy in those patients who need it. It would allow an efficient patient flow through the emergency department and it would allow to increase patient satisfaction.

So, we believe that the provision of care for patients with acute abdominal pain can still be improved and that's why we focused on this special case of patients.

Bob Barrett: Your study shows that interleukin-6 significantly improves the early diagnosis of urgent causes of acute abdominal pain in the emergency department. Can you tell us just a bit about interleukin-6, and why did you specifically study this biomarker?

Tobias Breidthardt: The two reasons for us to investigate interleukin-6, the first reason is simple biochemistry. So, the release mechanism of interleukin-6. Interleukin-6 is a small protein and it is released from various immune and non-immune cells in response to tissue injury, to inflammation, to infections. That primary mode of action is the mediation of the acute phase response, which is the body's first line of untargeted defense, as characterized by fever, leukocytosis, but also the release of acute-phase proteins, such as, for example, C-reactive protein or CRP.

CRP is the most commonly used parameter in clinical practice to judge the severity, but also the presence, of inflammation and infection, and clinicians often base treatment decisions on CRP concentrations. However, the release of CRP depends on an interleukin-6 stimulus and therefore, there's a time delay of about 12 to 24 hours between the initial interleukin-6 response and the increase in CRP. And this delayed response led us to specifically investigate interleukin-6.

In our study, the interleukin-6 was significantly superior in detecting urgent causes of abdominal pain compared to CRP, which was an open-label blood parameter in our study.

The second reason to investigate interleukin-6 is a series of small pilot study observations, which suggested that interleukin-6 could be a disease severity parameter with higher levels being associated with the need for surgery in patients with suspected appendicitis, but also with higher levels being associated with the degree of tissue injury and even mortality in trauma patients.

So, the release mechanism of interleukin-6 and the earlier release compared to C-reactive protein, and previous pilot study of results, are the reasons why we specifically investigated interleukin-6.

Bob Barrett: Doctor, your study was, of course, was a blinded diagnostic study, meaning, physicians treating the patients in your study were not aware of the interleukin-6 values. How do you suggest that physicians use interleukin-6 values in patients with acute abdominal pain?

Tobias Breidthardt: I think this is a very important question. And one, our key finding was that interleukin-6 was not a standalone test, but provided incremental diagnostic value on top of all other clinical information. Meaning, low interleukin-6 levels helped clinicians on top of all the other information they had already gathered for that patient to adequately and quickly rule out urgent abdominal pain, to identify patients without urgent abdominal pain.

On the other side, very high levels helped to identify patients with urgent abdominal pain, again, on top of all other clinical information. So, interleukin-6 can be an important additional tool on top of our clinical knowledge. To best integrate this into clinical practice, we derived a treatment algorithm putting patients either in a rule out category, which has a very low risk of urgent abdominal pain and sensitivity of 97% to rule out urgent abdominal pain. This was 20% of all patients in our study.

And on the other side, a rule in category with very high-risk patients, again, a specificity of 93% of patients having actually urgent abdominal pain. So, the clinical consequences of these two strategies would be patients ruled out to have a very low probability of urgent abdominal pain and these patients you could consider early discharge from the emergency department and early outpatient management.

On the other side, due to very high specificity of the combined algorithm for urgent abdominal pain, patients in the high-risk group should probably have a quick abdominal CT scan performed and also quickly be seen by a surgeon.

These will be the consequences in how we would advocate to use interleukin-6 on top of our clinical knowledge.

Bob Barrett: What do you see as the benefit of using the combined triage algorithm in clinical practice?

Tobias Breidthardt: To best answer this, we probably need to look at the two other major symptoms that lead to emergency department presentations worldwide. This is acute dyspnea and acute chest pain. In both of these settings biomarkers, namely nitrite and peptides for acute dyspnea and high-sensitive troponin for acute chest pain, have significantly increased the diagnostic accuracy over the clinical judgment alone. So very similar to the setting we are currently describing for interleukin-6 and acute abdominal pain.

And in both of these situations, acute chest pain and acute dyspnea, biomarkers have shown to adequately decrease the time to therapy, to decrease the need for further diagnostic work up, to decrease the time in the emergency department, and to decrease treatment cost.

So, these biomarkers in chest pain and dyspnea are quietly used in clinical practice, and are supported by Class I recommendations throughout the world and clinical practice guidelines.

Our study, as you said, was not an intervention-designed study, but a diagnostic study. So, we cannot comment on the economic impact of our management strategy, but we find it highly likely that interleukin-6 will also reduce the time to discharge and reduce treatment costs in the emergency department.

Bob Barrett: Well, finally, Dr. Breidthardt, let's look ahead. What are the next steps of your investigation?

Tobias Breidthardt: Going back to what I just said, we cannot comment on the economic impact of interleukin-6 yet. So, I think there are two next steps. The first one clearly has to be the clinical implementation of our combined triage algorithm into clinical practice. But at the same time, we need to prove this economic impact of the strategy on our patient treatment. We're currently looking at two possible study designs.

So, the first will be a patient-level randomized trial, comparing patients treated either according to this combined treatment algorithm using interleukin-6 and clinical judgment, versus patients treated just according to clinical judgment. They are randomized patient by patient into one of these two treatment algorithms.

And the second possible trial will be a cluster-randomized trial, basically before and after trial, in which you compare all patients before a certain date that were treated according to clinical standards compared to all patients treated afterwards, after you have initiated this clinical standard into practice. So, you compare before and afterwards.

We are looking at both of these possibilities and we will use one of the mechanisms to show the economic impact of interleukin-6 on our patients.

Bob Barrett: That was Dr. Tobias Breidthardt from the Division of Internal Medicine at the University Hospital Basel in Switzerland. He has been our guest in this podcast about inflammatory biomarkers in the diagnosis of abdominal pain. That article appears in the February 2019 issue of *Clinical Chemistry*. I'm Bob Barrett, thanks for listening!