This is a difficult and controversial topic to present. Instead of true false, I’ve fact, fiction or in between and we’ll be talking about the alphabet soup as well. I don’t have any disclosures and what I would like to do today is to trace the evolution of PANDAS and all the iterations that have gone through and discuss the proposed path of physiology. And I’m going to present some clinical studies and the diagnosis and the treatment of PANDAS, and then to review more recent thinking about PANDAS and its derivatives. Then hopefully to summarize if I could spell properly current thoughts about therapy.

So the issue of PANDAS came to light in 1998 when Susan Swedo who is an investigator at the National Institutes of Mental Health, published a study looking at 50 children who had an explosive onset of obsessive compulsive disorder and or tics following a group A streptococcal infection. In addition to this explosive onset, there were dramatic symptoms exacerbations following group A strep infection in these children.

Now this is actually a result of 2 parallel lines of investigation at the National Institutes of Mental Health, one looking at OCD and the other looking at Sydenham’s Chorea. And ultimately this led to kind of a melding of some of the research and thinking that went into what ultimately came out as PANDAS. It actually began a lot earlier in 1994 when Swedo published a report on 4 boys who had an abrupt onset of severe tics and or OCD with a temporal association with an antecedent infection. Two of those four boys had group A strep and two had a presumed viral infection. So Swedo and her associates termed this and this is the beginning of the alphabet soup, PITANDS. Not one term
that actually stuck very much; Pediatric Infection Triggered Autoimmune Neuropsychiatric disorders. And as that term implied, they believed that this was an autoimmune neuropsychiatric problem. This stemmed from the association of OCD and tics that had been seen also in Sydenham’s chorea. Indeed there had been prior reports of tics seen following group A strep infections and that the investigators noted OCD symptoms present in a large number of patients with Sydenham’s chorea. Furthermore in looking at Sydenham’s chorea as well as patients with OCD, they noted that there were volumetric changes in the basal ganglia in both of these groups of patients. And that when they were treated with either plasmapheresis, IVIG or steroids, that there was a decrease in the volume. So I don’t know if you can appreciate there this is before therapy and here after therapy that they observed the decrease in the volume of the basal ganglia following these treatment modalities indicating that there perhaps was a similar pathophysiology and that treatment in fact may be beneficial in reducing the inflammatory process or whatever was going on in the basal ganglia.

So that raised a question of the role of group A strep as a trigger using Sydenham’s chorea as a model for inducing neuropsychiatric disease. The issue of using Sydenham’s chorea based on the molecular mimicry model in which the group A streptococcal bacterium has in it’s wall certain antigens which are very similar to those antigens in the central nervous system and particularly the basal ganglia. This may in fact be a protective mechanism for the organism since the body would look at these antigens as perhaps being self antigens and therefore not stimulate an immediate
immunologic reaction against it and therefore protecting it. However when the immune reaction occurs antibodies would be directed against the basal ganglia as well.

Well as I had mentioned Swedo published the paper in 1998 looking at 50 children. These were collected over a 3 year period and she noted that there was a male predominance, 2.6 to 1. Eighty-six percent had OCD and 80% had motor tics. The OCD was characterized by fear of contamination, hoarding, magical thinking, excessive washing, cleaning and severe food restriction. They also had other comorbidities such as ADHD, Affective Disorders, anxiety, emotional labilities, separation anxieties, sleep disorders and a variety of other disorders.

In addition, she had talked about recurrent exacerbations, and Swedo noted in these 50 patients that exacerbations generally occurred within 6 weeks of a group A streptococcal infection. In fact within these 50 patients there were 144 exacerbations related to what she thought was group A strep. Now in looking more carefully at that particular paper, 23% of those patients had no symptoms of group A strep. She counted patients who had upper respiratory tract infections with group A strep exposure or sore throat with fever, but no throat culture. And this accounted for actually 44% of the exacerbations with soft criteria or no criteria for group A strep.

She coined the term PANDAS; Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections. The diagnostic criteria that she proposed was that number one it had to be a prepubertal onset anywhere from 3 years to puberty, that there had to be presence of OCD and/or
tics with an abrupt almost an explosive onset. There were dramatic exacerbations causing an episodic course and that there was a temporal association with group A strep infections and she did mention however that some of the exacerbations may not be associated with group A strep, and that they were associated with a variety of neurological abnormalities including increased motoric activity and unusual chorea form like movements, what’s called piano playing finger movements.

The proposed pathophysiology is as I kind of summarized before that they used Sydenham’s chorea related to the autoimmune process of molecular mimicry. And once the immune response was initiated, anti-neuronal antibodies cross reacted with brain tissues in the basal ganglia and that she found and others had noted, elevated anti-neuronal antibodies both in Sydenham’s chorea and PANDAS, and that the titers were higher in both of these disorders than in otherwise uncomplicated group A streptococcal disease.

They looked at animal models as well. Mice that had been immunized with group A strep developed a repetitive behaviors with anti-CNS antibodies and immune deposits noted within the brain. In addition that they noted that these behaviors were transferrable to naïve mice with the IgG from the immunized mice, and interestingly as well, that once these animals were depleted of IgG the behavior ceased. Also they noted that infusions of sera from patients who had PANDAS into rat brains striatum induced Tourette like symptoms. So this suggested to her that this was an autoimmune phenomenon, the pathophysiology autoimmune based, related to group A streptococcal disease causing anti-neuronal antibodies, cross reacting with brain antigens.
Treatment of course new, once these reports came out many investigators began looking at how to treat PANDAS. In one prospective study, over 4,000 children were reviewed. Out of those 4,000 children only 12 actually fit the stringent diagnosis of PANDAS syndrome. These children were appropriately treated for group A streptococcal disease, with rapid resolution of symptoms within 5-21 days. Also in these 12 patients, I’m sorry in 6 of these 12 patients there were 16 recurrences, all with positive throat cultures or with rapid strep and all of them responded to antibiotic therapy.

In addition people looked at other treatment modalities and there’s an early study looking at plasmapheresis and IVIG, compared with placebo. And this is IVIG, the center or placebo and this is the plasma exchange or plasmapheresis. On the Y axis is a scale, arbitrary scale looking at incidents of episodes over one month and at one year following the treatment. Now these treatments were just given once they were not continued over the year and in this particular study you can see that both IVIG at one month and at one year, had significantly fewer episodes as compared with placebo, similarly same thing with plasma exchange. Now that the effect persisted beyond 1 month to at least one year so this suggested to her that indeed that there were potential interventions that could be used to try to modulate this immuno response for PANDA syndrome.

Well also looking at Sydenham’s chorea as a model and rheumatic fever in treating prophylactically to prevent group A strep infections the question of prophylaxis for PANDAS was raised as well. In this particular study 2 antibiotics, Penicillin and Azithromycin were used to see if prophylaxis would
reduce the number of episodes. Now on the left, pre-treatment both with Penicillin and Azithromycin and post-treatment on the right, and both with Penicillin and Azithromycin there seemed to be significant reduction in the number of episodes when these antibiotics were used prophylactically.

Now this raises the question is PANDAS subset of rheumatic fever? Well when looking at PANDAS, there really are no indications that this is in any way related to being a part of rheumatic fever, that there was no increase in other rheumatic fever symptoms such as evidence of carditis in these patients and the nodules, they did not exhibit migratory polyarthritis or exhibit erythema marginatum. In addition, physicians must differentiate between true chorea and a choreiform movements with piano like finger movements. Now if in fact the patients had true chorea, then that was rheumatic fever Sydenham’s chorea. If they had the choreiform movements then they could not count them as being similar to rheumatic fever.

For example, this is Sydenham’s chorea. So notice in this particular patient you can see his left arm has involuntary movements, swings out watch his arm flails as he turns, he tries to control his arm, he holds his arm, you can see that he has a shuffling gait. He tries to hold his arm to keep it still, he also will try to use purposeful movements to disguise the movements, he also has facial grimacing as well. In contrast these are the choreiform piano playing finger movements that have been associated with PANDAS and you can see the significant difference in these movements. This patient also by
the way has autism spectrum disorder. So the piano like finger, piano playing finger movements are significantly different form the chorea demonstrated in Sydenham’s chorea.

So in comparing PANDAS versus Rheumatic fever there are substantial differences between the two. Clearly age of onset in Sydenham’s chorea anywhere between 5 and 15 years of age, in PANDAS by definition is prepubertal. Male and female ratio in Sydenham’s chorea is 1:1 and in contrast PANDAS has a male predominance. The duration of symptoms for Sydenham’s chorea may last up to 6 months but in PANDAS they have a relapse in remitting course. The lag time from the time of onset of the group A streptococcal infection to the onset of the disorder is longer in Sydenham’s chorea, a matter of weeks, but significantly shorter, a matter of days, with PANDAS syndrome. Chorea is obligatory and you have choreiform movements rather than chorea in PANDAS. Tics are relatively uncommon with Sydenham’s chorea but are characteristic in PANDAS. And OCD may be seen in Sydenham’s chorea, and again is characteristic in PANDAS. Motor impairment present in both, ASO titers can be positive or can be negative in both disorders and group A streptococcal absorbable anti brain antibodies are positive in Sydenham’s chorea but numerous reports subsequently really could not significantly identify group A strep absorbable anti-brain antibodies in PANDAS syndrome.

So investigators with all of these pieces of information, the data that they had in fact began to construct elegant hypotheses and theories about this disorder called PANDAS syndrome. But
whenever you critically look at the papers that had been studied and new information came back this house of cards had fallen.

So in looking critically at the diagnosis of PANDAS, number one trying to associate group A strep and tics for example, we know that group A strep is very common in children particularly school aged children and particularly in winter months. We also know that tics themselves are very common, up to maybe 19%-20% of children may exhibit tics sometime in their life. So it seems obvious that there may be a temporal relationship between the two but not necessarily a causal relationship.

In addition when looking at the papers a critical review of most of these papers and studies will have patients who did not have antecedent group A strep infections or that the data for that was quite weak. And even in Swedo’s own papers in her first paper from 1994 2 out of the 4 patients did not have group A strep infections and in her subsequent paper of 50 children, 44% of patients did not have hard evidence of group A streptococcal disease.

In addition the attempts to document group A strep infection can be very difficult. Positive throat cultures that some of the investigators use to demonstrate that they had a strep infection the positive throat culture may only be indicative of a carrier state and not necessarily a true infection. And so serial anti-streptococcal antibody titers should have been used in many of the papers to try to document a true infection. But even this can be subject to misinterpretation because both, because
the antistreptococcal antibodies may be non specifically elevated by immune stress. A patient who has infectious mononucleosis or some other illness with immune stress, may have a non-specific elevation not only of antistreptococcal antibodies but other antibodies as well. Then ultimately with time, they may fall. And so if following these titers they may non specifically be elevated and subsequently fall suggesting that there may in fact have been a group A strep infection when in fact there really was not.

And many of the authors have tried to incorporate Tourette’s Syndrome under the umbrella diagnosis of PANDAS. However, most studies show no association between ASO titers and Tourette’s Syndrome. Also in looking at group A strep and the onset of tics or OCD there have been large case controlled studies looking at and finding no significant increased risk of earlier group A strep infections in patients with OCD, tics or Tourette’s Syndrome. Similarly community based studies, one study looking at over 400 children with group A strep infection found that they were not at greater risk for neuropsychiatric symptoms when compared with healthy children or those children who had simple viral infections. So when looking at large populations of children we’re not seeing a strong association between the two.

Similarly new group A strep infections were not good predictors of tics or other symptoms. Now what these infections did show or these papers did show was that infections did enhance the prediction of psychosocial stress in predicting future tic or OCD severity but they were not good prediction of tics or other symptoms. In another study looking at a one year follow up of 30 children
who had OCD, Tourette or both, they found no association between symptom exacerbation and new infection. In other words, these disorders by themselves without being associated with PANDAS syndrome, also potentially had exacerbating courses. And so the exacerbations may be part of the underlying disease and not necessarily indicative of PANDAS syndrome.

Further studies emphasize the need for intensive attention to detail for diagnosis group A strep. As I mentioned, the diagnosis of a group A strep infection can be very difficult and in one study in which there was a marked attention to documenting group A strep infections, 40 PANDAS patients did have higher group A strep infections, but that 75% of these exacerbations were not temporarily related to infection and that there was no relationship in the changes of anti group A strep antibody titers and exacerbations. So that they could not document group A strep infection and that the antibody titers did not waver or were not, did not change in association with exacerbations.

Another study, a blinded longitudinal study found no differences in the number of newly diagnosed group A strep infections or the number of exacerbations in PANDAS or non-PANDAS patients. In one particular study, 6 out of 52 cases of new infection that had been followed by tic and/or OCD within 2 months all of them occurred in the non-PANDAS group. So again, it raises question about the role of group A strep in PANDAS.

Indeed, many investigators have noted that other agents may be associated with PANDAS like symptoms and/or the exacerbations including Borrelia, HSV, Varicella Zoster, HIV, or even
rhinovirus. Now the inclusion of rhinovirus in this list is it’s so common of course that it may be temporally associated with almost anything and so trying to make a strong association with rhinovirus and PANDAS like symptoms I think would be fraught with great difficulty.

So investigators trying to use antibiotics have risen do antibiotics suppress symptoms. Well if you think about the possible pathophysiology in this there had been almost immediate cessation of symptoms within 21 days and usually within 5-7 days after initiation of antibiotics. And so treatment with antibiotics for group A strep raises the question about how does this work because the antibiotic would have no significant effect on the immune system itself and so how, what is behind this. What is the mechanism of this? It doesn’t make sense and so it also leads us to think that there must be other pathophysiologies or other mechanisms that are poorly understood that we don’t understand. The role of antibiotics interrupting this pathophysiologic process doesn’t really make sense.

Prophylactic antibiotics. Well if we go back to the study looking at Penicillin and Azithromycin, if you look at that study there was no placebo group. In addition the reductions that were seen after treatment were compared to historical data and found to be exactly the same, so that reductions were similar to those in a 2 year prospectus study without the used of antibiotics. And so the reduction that was seen was similar to historical follow up of patients as well as a prospective study in which there was a natural decline in the number of exacerbations without antibiotic treatment. And so the
lack of inclusion of a placebo group in that study raises serious questions about the validity of that data.

Well also you can look at PANDAS criteria itself. So PANDAS is by definition a prepubertal disorder and therefore by definition omits cases in adolescents, so why is this? This constricts the diagnosis of PANDAS and there certainly are patients, adolescent patients who may have PANDAS like symptoms. In addition it requires the presence of tics or OCD and again both are very common and may temporarily coincide with group A strep infections. And similarly, why does the definition only include OCD instead of other neuropsychiatric disorders? Again it tends to be constrictive. The criteria also state that it must be a sudden, explosive onset with worsening with group A strep infection. Now in looking at the numerous papers and the literature, this criterion was not consistently adhered to in many studies. And in fact some of the studies included evolution of symptoms over a 10 day period rather than a sudden, explosive onset. In addition the acute sudden onset is not limited to PANDAS and it can be seen in other neuropsychiatric disorders as well, including Tourette’s Syndrome and so it can be seen in other problems without having the association with PANDAS.

I had spoken about the choreiform for movements versus chorea and if the patient has overt chorea this suggested Sydenham’s chorea rather than PANDAS. Also the criteria suggests that there had to be worsening of behavioral symptoms with exacerbations. Well certainly we know that group A strep may cause behavioral changes. However, in looking at patients with PANDAS that tics and
OCD were not associated with an increased severity in psychiatric comorbid conditions such as anxiety, motoric behavior, oppositional behavior, emotional ability, and other disorders. So that the worsening of behavioral exacerbations were not seen in many of the PANDAS patients.

Well there is a differential diagnosis of these symptoms and I put this slide up not to go through it but basically to show that there is an extensive differential diagnosis. And that if you were to investigate the differential diagnosis the laboratory evaluation would be fairly extensive and expensive as well and so I’m not sure that we should be doing all of these studies trying to track down and underlying disorder.

Now the problem with the criteria and the definition of PANDAS raised several problems. The emphasis of the fact that group A strep was necessary for the diagnosis in PANDAS, significantly limited the definition since in fact even Swedo herself had indicated that not all cases have group A strep as the initial event or associated with exacerbations.

Harvey Singer, a pediatric neurologist at Johns Hopkins suggested not PANDAS but rather CANS; Childhood Acute Neuropsychiatric Symptoms. His particular definition did emphasize the fulminant onset and did not specify a specific organism. So that group A strep in his definition was omitted as a necessary requirement. However, his definition used the term childhood and so therefore still tended to exclude older patients.
Well the objections to that also led to the National Institutes of Mental Health ultimately convening a conference in 2010 to try to analyze the information and understand and come up with a consistent definition that can be used and applied for further research. So they came up with another acronym, PANS; Pediatric Acute Onset Neuropsychological Syndrome. Now the important points of this particular definition is that like CANS it omits the necessity of having a specific trigger organism. It also emphasized the acute onset of symptoms. It includes older patients, adolescents and it did not imply a specific pathophysiology.

The diagnostic criteria for PANS, one or did require abrupt, dramatic onset of OCD or severely restricted food intake and that there had to be a concurrent onset of additional neuropsychiatric symptoms with similarly severe acute onset, so both the onset of OCD, tics or severely food restriction and sudden onset of other neuropsychiatric symptoms that were from 2 of 7 categories. The 7 categories included anxiety, emotional lability or depression, irritability, aggression or oppositional behavior, behavioral or developmental aggression, deterioration in school performance, sensory or motor abnormalities, and somatic signs and symptoms that included sleep abnormalities, enuresis, or urinary frequency. And that it must symptoms should not be explained by other known neurological or medical conditions such as Sydenham’s chorea, Tourette’s Disease, or lupus or other medical conditions.

The new definition therefore, allows investigators to identify a unique group of patients with similar clinical characteristics. But just like any of the other possible diagnoses, the criteria must be
validated and that has to be an ongoing process. This definition is purposely broad and inclusive. PANS is an umbrella diagnosis that includes PANDAS and other fulminant onset OCD or neuropsychiatric disorders.

So controversies still abound about what is PANDAS and what is its pathophysiology. The diagnosis or the definition of PANDAS is overly restrictive in its definition and may exclude other disorders which may more properly be part of a broader inclusive disorder. Similarly then PANS is more inclusive and it emphasizes the abrupt onset of OCD and neuropsychiatric symptoms.

So there’s no evidence that treatment with antibiotics are indicated unless you have a documented group A streptococcal infection. There’s no evidence that prophylactic treatment is indicated with antibiotics. There’s no evidence exists to support plasmapheresis or IVIG. Now having said that, I will say that in 2012 the National Institutes of Mental Health instituted a study looking at the use of IVIG. I’m not aware that that study has been published yet and perhaps someone may know, I don’t know. Supposedly it’s to be released in the very near future and may have recommendations about the use of IVIG. I do have some concerns about that that perhaps we could talk about later.

The underlying approach I believe is that we should treat the disorders that are present rather than trying to treat a poorly defined umbrella diagnosis. That if the patient has a group A streptococcal infection we should treat the group A streptococcal infection with antibiotics. If the patient has obsessive compulsive disorder, we should treat the obsessive compulsive disorder. If the patient has
a tic disorder, we should treat the tic disorder. But we should not necessarily until we have better
evidence available, try to treat a broad group of symptoms with one particular therapeutic modality
until we have a much better understanding of pathophysiology and how we’re approaching this.
And I believe that further studies therefore are needed. We need to define the differential diagnosis,
identify to a much greater extent, what is the underlying pathophysiology, what are the other
etiologies beside group A strep, what treatment modalities do we have, and how are they best used
for a large number of patients and then of course what is the long term prognosis for these patients.