



IVIIG In Pediatric Acute Onset Neuropsychiatric Syndrome: Costs

Roger H. Kobayashi, M.D
Clinical Professor
UCLA School of Medicine

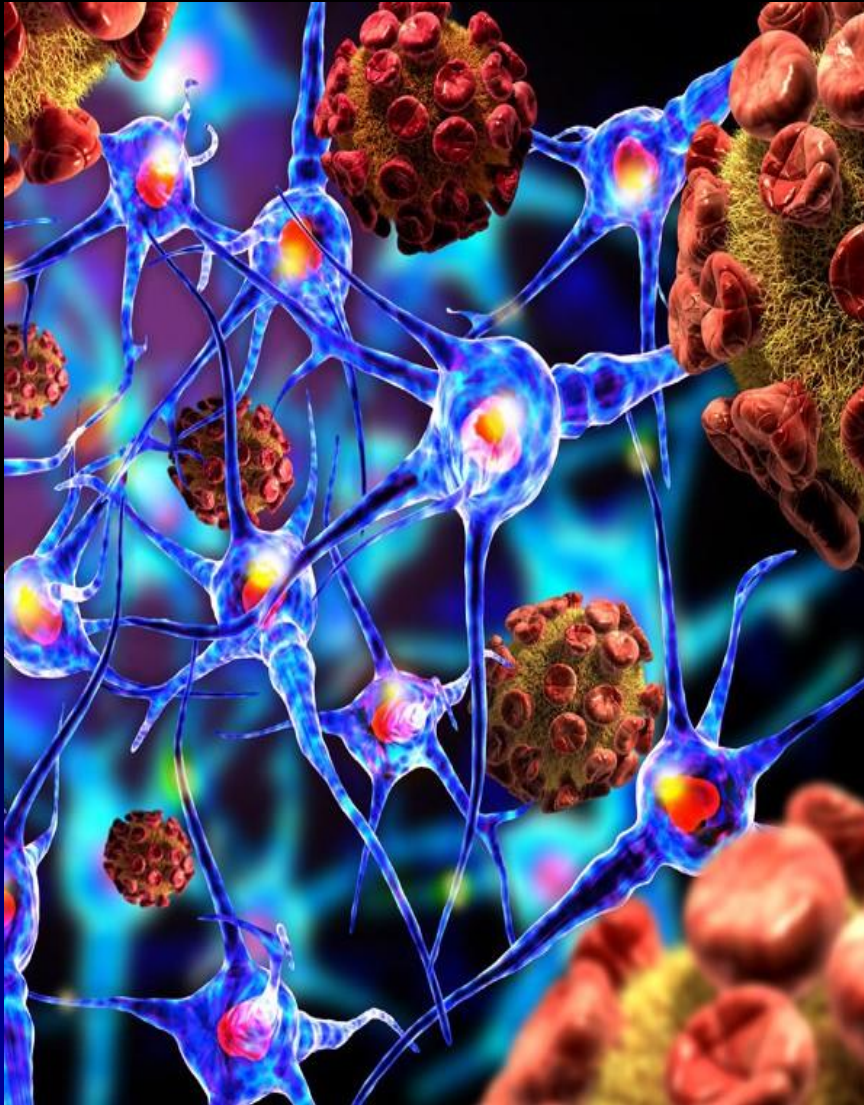
Testimony Kansas State Legislature
Committee on Finance February 10, 2021

Humble Country Doctor & Grandfather from Nebraska



- Disclosures
- Immunology/Chronic Infections: AAIA [Ten Doctors & 4 PA's]
- Manage >320 patients on IgG.
- Grant support Octapharma, Shire
- Clinical Professor: UCLA
- Lecturer: MMU Hanoi, Vietnam
- Reviewer: JACI-IP Frontiers
- Consultant IDF, USID. Shire, Octapharma,
- Board Member: IfPA; National Biologic Physicians Working Group, Asian-Pacific Physicians
- Research interests: Primary antibody Immunodeficiencies, Access to affordable care, Immune modulatory treatment for CoVID in rural areas.

Key Points: IVIG & PANS



- *IVIG is very **expensive***
- *PANS Children may **respond** to IVIG [90% in data from PANS Consortium]*
- *Children should have **moderate to severe symptoms** & poorly responsive to NIH initial treatment protocols*
- *Doctors highly **experienced & skilled** should evaluate or consult [if possible]*
- ***More** than one infusion may be necessary*
- ***Objective evidence** of disease severity before infusion and response after infusion must be documented.*

Why Study & Treat PANS? “KODOMO NO TAME NI”



Kodomo no tame ni
For the sake of the children

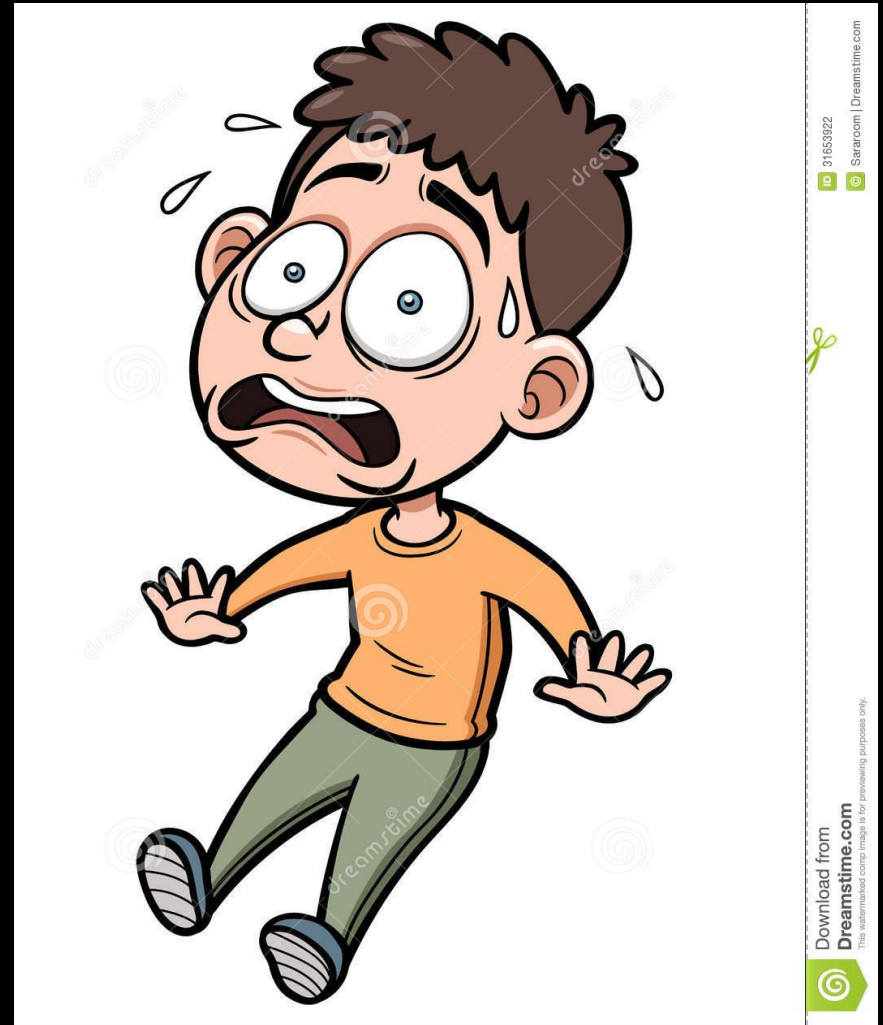


The Japanese American Experience in Hawaii

Dennis M. Ogawa

PANS is Thought to Be Different From Other Disorders

Abrupt Onset Dramatic Change in Behavior
Autoinflammatory/Autoimmune



NIH 2012 Criteria for PANS

- **Abrupt, dramatic onset OCD &/or Significant eating disorder or OCD &/or TICS.**
- **Plus At least 2 of the following 7 symptoms**
- **ALL other causes excluded**
- **Concurrent presence of additional neuropsychiatric symptoms, with**
- **similarly severe and acute onset, with at least two of the following:**

 - 1. Anxiety
 - 2. Emotional lability and/or depression
 - 3. Irritability, aggression and/or severely oppositional behaviors
 - 4. Behavioral (developmental) regression
 - 5. Deterioration in school performance
 - 6. Sensory or motor abnormalities
 - 7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency

Current Theories: Inflammation of Basal Ganglion

- Theory 1: **Cross-reacting antibodies** [or cells] cause basal ganglia to malfunction
- Theory 2: **Neuronal cells** in the brain precipitate inflammation in the basal ganglia

TABLE 1: EFFECTS OF BASAL GANGLIA INFLAMMATION

Basal Ganglia is a Relay Station through which Run Neurons that Control:	Inflammation may cause:
Mood & emotion	OCD, Mood lability, Anxiety
Behavior	OCD, Rage, Developmental regression
Procedural learning	Handwriting changes, Clumsiness
Motor movements	Tics, Choreiform movements
Cognition	Slow processing speed, Memory issues, specific Sensory learning deficits (often Math)
Sensory	Sensitivity to light, sounds, smells, tastes, textures

- M. Pincherio Up to Date

How Might PANS/ PANDAS Be Treated?

- **Antibiotics:** Penicillins, Cephalosporins, Macrolides
- **Anti-inflammatory/Immunomodulatory:** NSAIDS, Steroids, IVIG, Plasmaphoresis
- **Selective Serotonin Re-Uptake Inhibitors:** fluoxetine, fluvoxamine, sertraline, and paroxetine
- **Cognitive Behavior Therapy:**
- **Other therapies:** anti-inflammatory, anti-fungal, anti-histamines et al

What is IVIG?

- Highly purified gammaglobulin derived from 1000's of plasma donors. 1% of plasma.
- Gammaglobulin are antibody proteins which help fight infection, are anti-inflammatory and immune modulating.
- It was first used by von Behring & Kitasato in 1901
- First given by injection. Now mostly IVIG/SCIG.
- 30% PID, 70% neurology
- Over 20 million grams used
- Shortages in U.S. 2019-20
- Used in CoVID



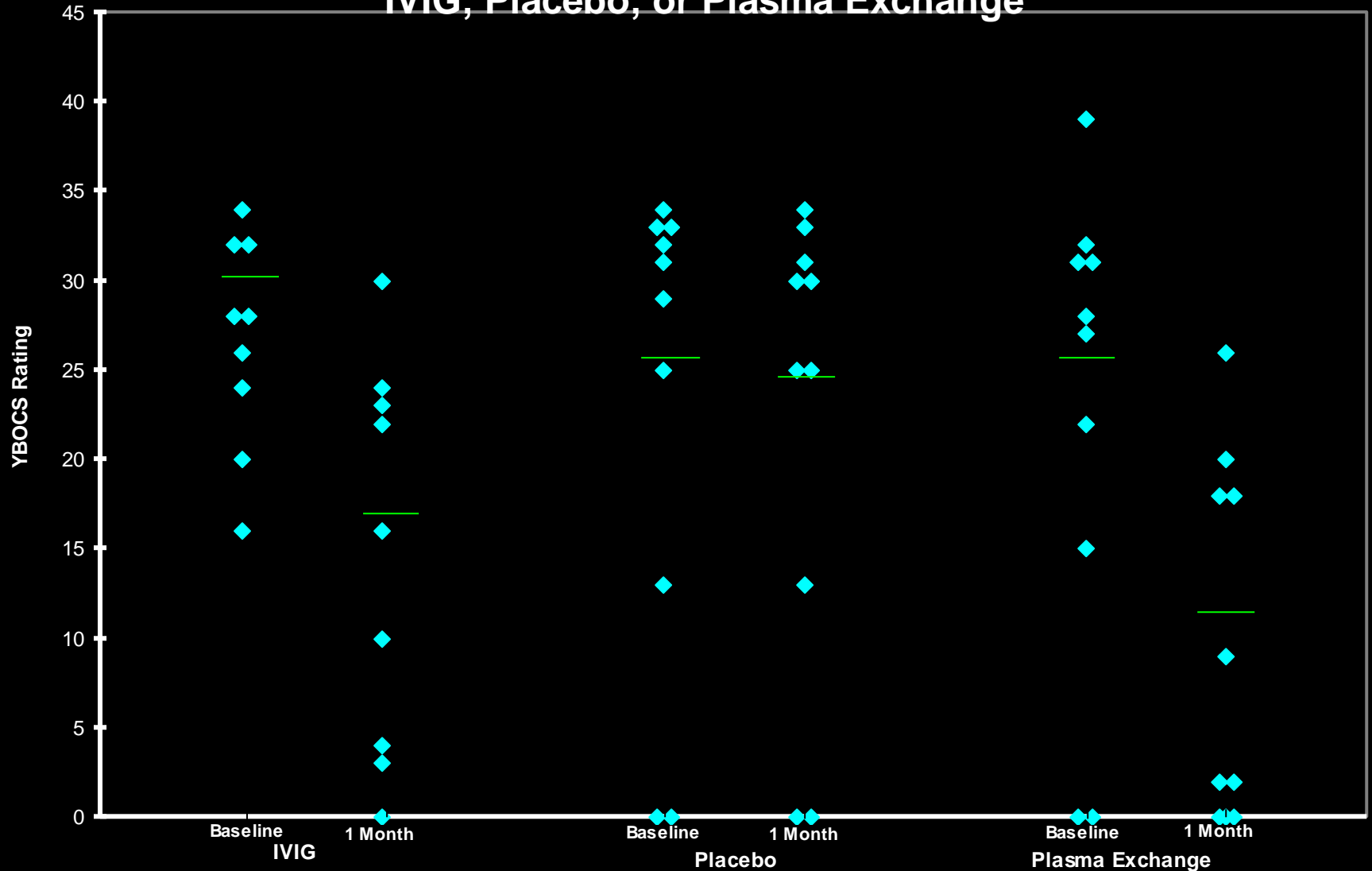
Clinical Benefit Established in Controlled Trials

Hematology	Neurology	Rheumatology	Transplant Medicine
<ul style="list-style-type: none">•ITP	<ul style="list-style-type: none">•Multiple sclerosis•Guillain-Barré syndrome•Chronic inflammatory demyelinating polyradiculopathy•Myasthenia gravis•Multifocal motor neuropathy•Stiff person syndrome	<ul style="list-style-type: none">•Kawasaki syndrome•Dermatomyositis (corticosteroid resistant)•Antineutrophil cytoplasmic•Autoantibody-positive vasculitis	<ul style="list-style-type: none">•Prevention of graft-versus-host disease in allogeneic bone marrow recipients

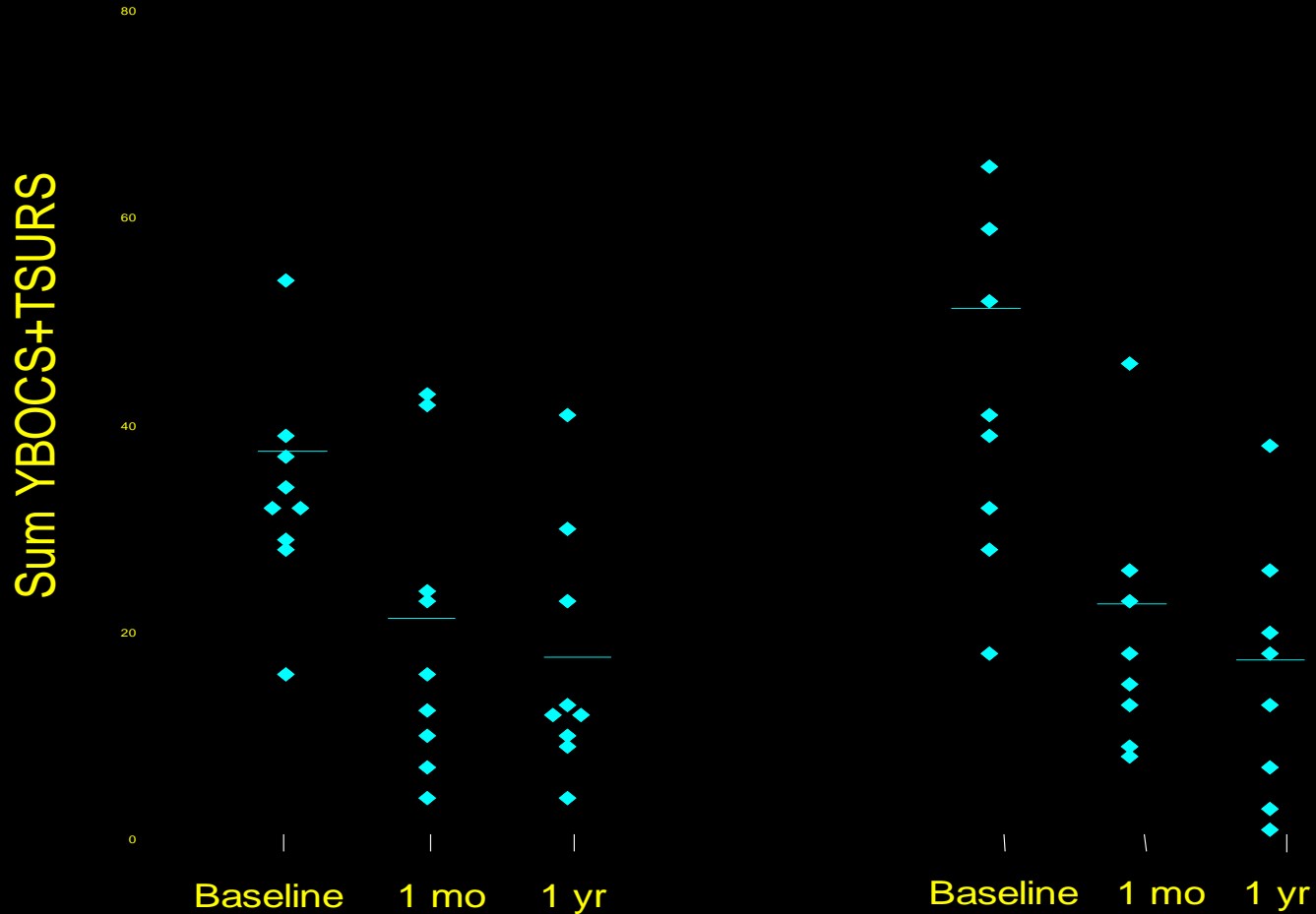
Clinical Benefit Established in Well-Controlled Trials

•The clinical benefit of IGIV has been established in well-controlled trials for a number of disorders, as shown on the slide.

Change in OCD Severity 1 Month Following Treatment With IVIg, Placebo, or Plasma Exchange



Response to Immunomodulatory Therapy with IVIG (n=9) or Plasmapheresis (n=8) Small Study Suggesting Prolonged Effect



IVIg Therapy In PANDAS

- 9 Studies in literature with 179 patients total : 4 single cases
- Dose, dosing schedule, length of treatment varied
- Younger study largest [non-blinded] 64% improved 19% permanent remission.
- 2015 Frankovic and Swedo: double blind – no difference after induction; open label 6 month study 62% improved
- Melamed: 2017 1 year open label study. 21 children - all improved
- Pavone P: 2018 34 children. 2 gm/kg. All improved . Some needed more than one dose.
- PANS consortium: IVIG most effective, followed by anti-inflammatories, antibiotics and last-psych meds.
- Problem:
Very few blinded studies and those results varied
- No biologic markers Melamed study proposes markers
- Insurance companies don't cover IVIG

IVIG Treatment for PANS is Expensive

- **Cost per gram:** \$81 to \$120/gram ASP Hospitals and infusion centers may charge 1 to 5 times this price
- **Supplies:** range from \$200 to \$300 per infusion
Nursing time: \$150/hour Three to 6 hours → \$450 to \$900 per infusion
Facility charges: ~\$200 - \$500 per infusion
- **Example:** Child 40 kg [88 pounds] would receive between 40 gms [1 gm/kg/dose] and 80 gms [2 gms/kg/dose]. If receiving 2 gms/kg, this would require **two days infusion** per month.
- **Low end charges:** \$4,000-\$8,000 ASP for product, supplies/infusion = \$250/hr, nursing time = \$750/infusion [5 hours], facility charges/infusion = \$350
- **Total costs/treatment = \$5,350 to \$10,700** Emphasize: these are the LOW END charges.

Other Critical Considerations

- a] Site of infusion: home infusion generally less expensive. Hospital most expensive.
- b] infusion service company critical: some are reasonable and some unfortunately are not.
- c] IVIG product price varies
- d] out of pocket costs vary depending on insurance coverage.
- e] if services not covered, the non-negotiated maximum price is charged to the patient which can be substantial.

Example of a 20 y/o Student with Neuropathy who had Three Insurance Companies in One Year

Insurance Company	Rate Charged	Amount Written Off	Amount the Hospital Received
GEHA (Aetna Contract)	\$28,405.99	\$7,669.62	\$20,736.37 [*]
Blue Cross Alabama	\$29,756.15	\$25,930.71	\$3,827.45
Cigna	\$28,755.17	\$25,436.17	\$3,319.00 ^{**}

*\$4,260.90 was what I (the patient) had to pay

** \$221.82 was what I had to pay

Massachusetts Legislature

To the extent IVIG becomes FDA-approved for PANDAS/PANS, Medicaid and State plan expenditures increase by an indeterminate amount. According to a 2015 [analysis](#) of similar legislation proposed in Massachusetts, the total cost of IVIG therapy (based on 2012 claims data) was \$7,059 per treatment. The analysis concluded that requiring coverage for treatment of PANDAS/PANS by fully insured health plans in Massachusetts would result in an average annual increase, over five years, to the typical member's monthly health insurance premiums of between \$0.003 (0.001%) and \$0.039 (0.008%) per year.

Summary Regarding IVIG in PANS/PANDAS

- IVIG must be reserved for children who do not respond to NIH modified therapy or psychiatric medications and counseling
- Strict NIH diagnostic criteria must be adhered to
- To date, this is a behavioral clinically diagnosed disorder.
- To date, there are no reliable laboratory markers to diagnose, monitor or predict disease outcome.
- Cost analysis studies will be needed to support the use of IVIG.



“Ho'okahi ka 'ilau like ana” Put Your Paddle in and Join the Effort

- However, there are strong evidence in animal models and similar diseases in humans that suggest anti-inflammatory, immune modulatory intervention may be effective.
- IVIG is routinely used in inflammatory/autoimmune diseases
- Where the NIH criteria are fulfilled, other diseases are excluded and other treatments are not helping the child, I strongly believe a trial of IVIG is warranted. All we are asking for is a chance to try.

