Region Västra Götaland, HTA-centrum
Regional activity based HTA [Verksamhetsbaserad HTA]
Health Technology Assessment
HTA report 2020:115

Anti-inflammatory, antibiotic and immunomodulatory treatment in children with symptoms corresponding to the research condition PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Anti-inflammatory, antibiotic and immunomodulatory treatment in children with symptoms corresponding to the research condition PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)
[Behandling mot en förmodad hjärninflammation utan påvisad neurologisk eller medicinsk sjukdom hos barn med plötsligt debuterande tvångssymtom/begränsningar i matintag i kombination med minst två neuropsykiatriska symtom (”PANS”)]

Johnson M[1*], Ehlers S[2], Fernell E[1], Hajjari P[3], Svanberg T[4,5], Vikberg Adania U[4], Wartenberg C[5], Wallerstedt SM[5]

[1]Region Västra Götaland, Sahlgrenska University Hospital, Child Neuropsychiatry Centre, Gothenburg, Sweden
[2]Region Västra Götaland, Regional Knowledge Center for Mental Health, Sweden
[3]Region Västra Götaland. Kungälv, Paediatric Medicine, Sweden
[4]Region Västra Götaland, Sahlgrenska University Hospital, Medical Library, Gothenburg, Sweden
[5]Region Västra Götaland, HTA-centrum, Sahlgrenska University Hospital, Gothenburg, Sweden

[*]Corresponding author

Published April 2020
2020:115
Suggested citation: Johnson M, Ehlers S, Fernell E, Hajjari P, Svanberg T, Svensson, M, Vikberg Adania U, Wartenberg C, Wallerstedt SM. Anti-inflammatory, antibiotic and immunomodulatory treatment in children with symptoms corresponding to the research condition PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) [Behandling mot en förmodad hjärninflammation utan påvisad neurologisk eller medicinsk sjukdom hos barn med plötsligt debuterande tvångssymtom/begränsningar i matintag i kombination med minst två neuropsykiatriska symtom (”PANS”)] Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum: 2020.
Regional activity based HTA 2020:115

Table of contents

1. Abstract

Background In 2012, PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) was suggested as a diagnosis by a group of researchers in the United States. The condition was described as an abrupt, dramatic onset of obsessive-compulsive disorder (OCD) or severely restricted food intake, combined with other neuropsychiatric symptoms and in the absence of a verified neurological or medical disease. The research diagnosis was suggested to cover all conditions with this combination of symptoms, irrespective of etiology and including PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections). PANDAS had in 1998 been suggested as a new condition by the same research group. At that time, an infectious etiology was suspected and tics had a more prominent role. PANS/PANDAS is not included in the fifth diagnostic and statistical manual of mental disorders (DSM-5) or the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

The condition has a relapsing–remitting course. The treatment of children with symptoms as described above varies over Sweden and within Region Västra Götaland. Established psychologic and pharmacologic treatments for the separate symptom entities represent the basis everywhere. In routine health care, treatment against neuroinflammation and autoimmunity is only provided when an underlying disease is verified. As the symptom profile in research has been suggested to have an immunologic etiology, some centres provide anti-inflammatory, antibacterial and/or immunomodulatory treatment in severe cases without a verified underlying disease.

Question at issue Does anti-inflammatory, antibacterial or immunomodulatory treatment, compared with no such treatment, improve health-related quality of life (HRQL), level of functioning and symptoms in children with symptoms corresponding to the research condition of PANS/PANDAS? Is such treatment associated with complications?

Methods Two authors performed searches (August 2019) in PubMed, Embase, the Cochrane Library, CINAHL, PsycInfo, and a number of health technology assessment (HTA) databases. They independently assessed the abstracts, and selected, in consensus, full-text articles to be sent to the other authors, who then decided on inclusion/exclusion. The included studies were critically appraised, and data extracted. The certainty of evidence was assessed according to GRADE.

Results Four randomised controlled trials (RCTs), two cross-sectional studies and one before/after study were included in this HTA. All studies had major study limitations including selection, treatment, detection and reporting biases. All studies had some or serious limitations regarding directness and precision.

HRQL was not investigated in any of the studies.

Level of functioning was investigated in two small RCTs on antibiotics and in one RCT on intravenous immunoglobulins (IVIG) and plasma exchange. None of the RCTs reported significant treatment effects regarding the level of functioning.

> *Conclusion:* In children with symptoms corresponding to the research condition of PANS/PANDAS, it is uncertain whether antibiotic or immunomodulatory treatment improves the level of functioning. (Very low certainty of evidence, GRADE ⊕◯◯◯)

Symptoms were investigated in two cross-sectional studies on anti-inflammatory treatment, in two RCTs and one before/after study on antibiotics, and in two RCTs on immunomodulatory treatment. The cross-sectional studies reported significantly shorter acute neuropsychiatric deterioration with cyclooxygenase (COX) inhibitors and corticosteroids, respectively. Confounding by indication was a major issue in these studies.

None of the RCTs on antibiotics reported significant effects regarding OCD symptoms and tics, but one RCT reported a reduction in symptoms on a global impression scale, and the before/after study on antibiotics reported a reduction in the number of neuropsychiatric exacerbations. Regarding immunomodulatory treatment, one RCT reported an intra-individual reduction in OCD symptoms in both the IVIG and the plasma exchange groups. However, no between-groups comparisons were provided regarding IVIG versus control or plasma exchange versus control. The other RCT on IVIG reported no significant difference between the intervention and control group.

> *Conclusion:* In children with symptoms corresponding to the research condition of PANS/PANDAS, it is uncertain whether anti-inflammatory, antibiotic or immunomodulatory treatment improves symptoms. (Very low certainty of evidence, GRADE ⊕◯◯◯)

Complications were reported in three RCTs and in two cross-sectional studies. Adverse effects, which for the drugs were consistent with those listed in the summary of products characteristics (SPC), were reported for anti-inflammatory, antibiotic and immunomodulating treatment. They included abdominal pain and proteinuria for COX inhibitors; increased psychiatric symptoms, weight gain and Cushingoid symptoms for corticosteroids; loose/abnormal stools and prolonged QT for antibiotics; nausea, vomiting, headache, fever, and allergic reactions for IVIG; and vomiting as well as increased anxiety during plasma exchange.

> *Conclusion:* In children with symptoms corresponding to the research condition of PANS/PANDAS, anti-inflammatory and antibiotic drugs as well as IVIG can probably result in adverse reactions as listed in the SPC (Moderate certainty of evidence, GRADE ⊕⊕⊕◯), and plasma exchange may result in complications (Low certainty of evidence, GRADE ⊕⊕◯◯).

Costs for the assessed treatments are 2 to 10 SEK per day for anti-inflammatory and antibacterial treatments, 27,500 to 46,000 SEK for IVIG at weights of 30 to 50 kg, and 15,000 to 17,000 SEK for plasma exchange.

Ethical aspects to be considered regarding these treatments include the severity of the condition, the potential of a negative benefit-risk balance, that parents and legal guardians make decisions for the children, the risk of displacement of other care, and that use of antibiotics without a verified infection may be problematic from a resistance perspective. As PANS/PANDAS is a research condition, and not an established diagnosis, scientific evaluations of treatments are a challenge.

Conclusion In children with acute-onset OCD or restricted food intake, together with two or more neuropsychiatric symptoms and without a verified neurologic or medical disease (corresponding to the research condition of PANS/PANDAS), this HTA reveals very low certainty of evidence that anti-inflammatory, antibacterial or immunomodulating treatments would improve the level of functioning or reduce symptoms. Patient data for these outcomes are limited, and evidence regarding potential effects on HRQL is lacking. There is moderate certainty evidence that side effects known from use in other indications can occur.

2. Populärvetenskaplig sammanfattning – Swedish summary in plain language

I denna HTA-rapport har vi utvärderat frågeställningen:

- Förbättrar inflammationsdämpande, antibakteriell eller immunmodulerande behandling hälsorelaterad livskvalitet, funktionsnivå eller symtom hos barn med plötsligt debuterande tvångssymtom/begränsningar i matintag i kombination med minst två neuropsykiatriska symtom men utan påvisad neurologisk eller medicinsk sjukdom (”PANS/PANDAS”)? Är behandlingen förknippad med komplikationer?

Konklusion Vår genomgång av det vetenskapliga underlaget visar att det är osäkert om behandling mot en förmodad hjärninflammation förbättrar funktionsnivå eller symtom hos barn med de aktuella symtomen, som idag inte motsvarar en egen etablerad diagnos. Ett begränsat antal patienter har inkluderats i studierna och ingen studie har undersökt potentiella effekter på livskvalitet. Litteraturen visar att man hos denna patientgrupp kan förvänta sig samma typer av komplikationer/biverkningar som hos andra patientgrupper.

Bakgrund En grupp forskare i USA föreslog år 2012 PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) som en ny diagnos. Forskarna beskrev tillståndet som att ett barn plötsligt uppvisar allvarliga tvångssymtom och/eller begränsar sitt matintag, i kombination med flera andra neuropsykiatriska symtom och i avsaknad av medicinsk eller neurologisk förklaring. PANS föreslogs innefatta alla tillstånd med denna symtomkombination, oavsett bakomliggande orsak. Här ingår även PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections), ett tillstånd som föreslogs av samma forskargrupp år 1998 och där en infektiös orsak misstänktes och där tics hade en mer framträdande roll. PANS/PANDAS finns inte med i de etablerade diagnossystemen.

Patienter med symtom enligt ovan behandlas på olika sätt på olika ställen i Sverige. Psykologisk och farmakologisk behandling utgör grunden överallt. Detsamma gäller behandling vid verifierad underliggande sjukdom. Det som skiljer sig är att man på vissa ställen, baserat på en forskningshypotes, behandlar patienter med särskilt allvarliga symtom för en förmodad hjärninflammation. Här ingår inflammationsdämpande, antibakteriella samt immunmodulerande behandlingar.

Metod Med hjälp av etablerade metoder identifierade vi vetenskapliga artiklar som kunde bidra till att få svar på den aktuella frågeställningen. För att veta hur pålitliga studiernas resultat är, granskades de enskilda studiernas kvalitet och det gjordes även en bedömning av den vetenskapliga kvaliteten på det sammanlagda underlaget.

Resultat Denna rapport baseras på de fyra randomiserade och tre icke-randomiserade studier som motsvarade frågeställningen. Dessa rörde två sorters inflammationsdämpande behandling, två olika antibiotika, antikroppar och utbyte av blodplasma. Alla studier hade allvarliga brister i kvaliteten. Studierna var också små och hade begränsningar vad gäller hur väl patienterna motsvarade de patienter som denna HTA-rapport avser.

Ingen studie hade undersökt effekter av behandlingarna på *hälsorelaterad livskvalitet*.

Funktionsnivå undersöktes i tre placebo-kontrollerade, randomiserade studier, varav två avseende antibiotika och en avseende immunmodulerande behandling. Någon skillnad mellan behandlade och icke-behandlade kunde inte påvisas.

Symtom hade undersökts i samtliga studier. Två tvärsnittsstudier visade att patienter som fått inflammationsdämpande behandling, cyklooxygenashämmare respektive steroider, hade kortare sjukdomsskov än patienter som inte hade fått sådan behandling. Ett problem med dessa studier är att den ordinerade behandlingen avgörs av symtombilden. Till exempel förskrevs under större delen av studietiden inte steroider till patienter med svårare psykiatriska symtom. Ingen av de två randomiserade studierna som undersökte antibiotika visade gynnsamma effekter på tvångssymtom eller tics, men i en av studierna rapporterades en minskning av symtom utifrån en övergripande skattning. Två randomiserade studier undersökte effekten av antikroppar. Den ena studien visade ingen signifikant skillnad i symtom mellan jämförelsegrupperna. I den andra studien gjordes ingen jämförelse mellan grupperna. Däremot redovisades en minskning av tvångssymtom hos de patienter som fått antikroppar. Utbyte av blodplasma undersöktes i en randomiserad studie. Här gjordes ingen jämförelse med kontrollgruppen som fick placebo för IVIG. Däremot redovisades en minskning av tvångssymtom hos de behandlade.

Komplikationer beskrevs i tre randomiserade studier och i två tvärsnittsstudier. De biverkningar som rapporterats i dessa stämmer väl överens med tidigare kända biverkningar av de aktuella läkemedlen. Avseende inflammationsdämpande läkemedel redovisades mag- och njurbiverkningar för cyklooxygenashämmare respektive psykiska biverkningar, viktuppgång och Cushing-symtom för steroider. För antibiotika redovisades förekomst av lös avföring och hjärtpåverkan. För antikroppsbehandling redovisades förekomst av illamående, kräkningar, feber och allergiska reaktioner. Vid utbyte av blodplasma noterades ökad oro och illamående.

Kostnaden för de utvärderade behandlingarna ligger idag mellan 2 och 10 kronor dagligen för inflammationsdämpande respektive antibakteriell behandling, 27 500 till 46 000 kronor för antikroppar om barnet väger mellan 30 och 50 kg, samt 15 000 till 17 000 kronor för utbyte av blodplasma.

Etiska aspekter att ta i beaktande i denna HTA-rapport är att symptomen kan ha en hög svårighetsgrad, att riskerna med de utvärderade behandlingarna enligt idag tillgängligt vetenskapligt underlag kan vara större än nyttan, att vårdnadshavare beslutar om behandling för sina barn, att undanträngningseffekter vid användning av behandlingarna inte kan uteslutas och att antibiotikabehandling utan verifierad infektion är problematiskt ur resistensutvecklingssynpunkt. Att tillståndet inte är etablerat utan under utforskning innebär en utmaning när det gäller att generera kunskap och behandlingsmöjligheter.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary in plain language is intended for decision makers and readers who are not familiar within this specific medical field and/or evidence synthesis.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, April 17th 2020

Kvalitetssäkerhetsgruppen	
Bergenheim, Anna	PT, PhD
Bergh, Christina	MD, Professor
Bernhardsson, Susanne	PT, Associate professor
Hakeberg, Magnus	OD, Professor
Jivegård, Lennart	MD, Senior university lecturer
Larsson, Anders	MD, PhD
Nelzén, Olle	MD, Associate professor
Petzold, Max	Statistician, professor
Rylander, Christian	MD, Associate professor
Sjögren, Petteri	DDS, PhD
Sjövall, Henrik	MD, Professor
Skogby, Maria	RN, PhD
Strandell, Annika	MD, Associate professor
Svanberg, Therese	HTA librarian
Svensson, Mikael	Health economist, Professor
Wallerstedt, Susanna	MD, Professor
Wartenberg, Constanze	Psychologist, PhD

DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of findings

Outcomes	Study design Number of studies	Relative effect (95% CI)	Absolute effect	Certainty of evidence GRADE[1]
Anti-inflammatory treatment vs no anti-inflammatory treatment				
HRQL	0 studies	-	-	-
Level of functioning	0 studies	-	-	-
Symptom change	2 cross-sectional studies	-	*Difference in duration of acute neuropsychiatric deterioration, treated minus untreated (mean)* Corticosteroids: 6.4 vs 11.4 weeks, P<0.01 NSAID: 2.56 fewer weeks, P=0.018	⊕◯◯◯[1]
Complications	2 cross-sectional studies	-	Temporary/transient complications recorded during treatment periods, including increased psychiatric symptoms, weight gain and Cushingoid for corticosteroids, and abdominal pain and proteinuria for NSAIDs	⊕⊕⊕◯[2]
Antibiotic treatment vs placebo				
HRQL	0 studies	-	-	-
Level of functioning	2 RCT	-	*CGAS (mean)* Penicillin V: 76.36 vs 78.86, P=0.41 Azitromycin: 53.71 vs 52.68, NS	⊕◯◯◯[3]
Symptom change	2 RCT 1 before/after study	-	*CY-BOCS (mean)* Penicillin V (RCT 1): Subscale obsessions: 3.27 vs 3.96, P=0.16 Subscale compulsions: 2.52 vs 2.96, P=0.08 Azithromycin (RCT 2): CY-BOCS total: 20.53 vs 23.45, NS *Neuropsychiatric exacerbations (mean number)* Penicillin V (before/after study): 2.1 vs 0.5, P<0.01 Azithromycin (before/after study): 1.8 vs 0.9, P<0.01	⊕◯◯◯[3]
Complications	1 RCT	-	Loose/abnormal stools: 53% vs 7% Significantly increased QT (ECG) in intervention group (within-group comparison: P=0.007), intervention vs control: P=0.06	⊕⊕⊕◯[4]
Immunomodulatory treatment vs placebo				
HRQL	0 studies	-	-	-
Level of functioning	1 RCT	-	*CGAS (mean)* IVIG: 67.4 vs 59.9, no P-value presented Plasma exchange: 73.0 vs 59.9, no P-value presented	⊕◯◯◯[5]
Symptom change	2 RCT	-	*CY-BOCS (mean)* IVIG: RCT1:14.7 vs 22.1; no P-value presented RCT2: 20.59 vs 25.67, P=0.44 Plasma exchange: 9.5 vs 22.1, no P-value presented	⊕◯◯◯[5]
Complications	2 RCT	-	IVIG: nausea/vomiting (RCT 1: n=5 vs n=0), vomiting (RCT 2: n=3 vs n=0), headache (RCT 1: n=3 mild/moderate vs n=1 mild; RCT 2: n=3 vs n=1), fever (n=4 vs n=0), and an allergic reaction in the intervention group Plasma exchange: vomiting (n=2 vs n=0) and increased anxiety (n=3 vs n=0)	IVIG: ⊕⊕⊕◯[4] Plasma exchange: ⊕⊕◯◯[6]

CGAS = Children's Global Assessment Scale (score 1-100, with high scores indicating better functioning), CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale (Score 0-40; higher score reflects more symptoms), ECG = electrocardiogram, HRQL = health-related quality of life, IVIG = intravenous immunoglobulin, NS = not significant, NSAID = non-steroid anti-inflammatory drug RCT = randomised controlled trial, SPC = summary of products characteristics

Footnotes:
[1]downgraded one step because of study limitations and indirectness; selection bias due to confounding by indication, and patients with more severe symptoms were excluded
[2]upgraded one step because the observed adverse effects were pharmacologically plausible given the doses provided, and concordant with adverse reactions listed in the SPC
[3]downgraded three steps because of study limitations (uncertainties regarding the comparability of the groups, unblinding due to adverse reactions, multiple comparisons, unclear primary endpoint), indirectness (diagnosis not established, enrichment by excluding prior non-responders) and imprecision (few patients, multiple comparisons)
[4]downgraded one step because of imprecision
[5]downgraded three steps because of study limitations (uncertainties regarding the comparability of the groups, unblinding due to adverse reactions), indirectness (only PANDAS patients, recruited before the research condition was published) and imprecision
[6]downgraded two steps because of imprecision and unblinded treatment

Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

CALS = Children's Affective Lability Scale
CGAS= Children's Global Assessment Scale
CGI-S/I = Clinical Global Impression Severity/Improvement
CI = confidence interval
CNC = Child Neuropsychiatry Centre
CNS = central nervous system
COX = cyclooxygenase
CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale
DSM-5 = fifth diagnostic and statistical manual of mental disorders
ECG = electrocardiogram
HRQL = health-related quality of life
ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems
IVIG = intravenous immunoglobulin
NIMH= National institute of mental health
NS = not significant
NSAID = non-steroid anti-inflammatory drug
OCD = obsessive-compulsive disorder
PANDAS = Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections
PANS = Pediatric Acute-onset Neuropsychiatric Syndrome
RCT = randomised controlled trial
SANE = Förbundet autoimmuna encefaliter med psykiatrisk presentation
SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Service
SCARED = Screen for Childhood Anxiety-Related Emotional Disorders
SD = standard deviation
SNAP-IV = Swanson, Nolan, and Pelham-IV Parent Scale
SPC = summary of product characteristics
TNF = tumour necrosis factor
TSURS = Tourette syndrome unified rating scale
YGTSS = Yale Global Tic Severity Scale

5. Background

Disease/disorder of interest and its degree of severity

Twenty-five years ago, Susan Swedo and colleagues at the United States National Institute of Mental Health (NIMH), based on case studies of Sydenham's chorea, proposed that a subgroup of children with obsessive compulsive symptoms, tics and other clinical symptoms suffered from manifestations of an antineural antibody-mediated dysfunction in the central nervous system (CNS) possibly localized in the basal ganglia (Swedo et al., 1994). They hypothesized that certain strains of group A β-hemolytic streptococcal infections could induce the clinical symptoms (Swedo et al,. 1998). In 1998, this research group suggested these symptoms to be clustered into a condition which they called PANDAS (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections; Swedo et al., 1998) characterised by five criteria:

- presence of OCD and/or a tic disorder
- pediatric onset
- episodic course of symptom severity
- association with a group A β-hemolytic streptococcal infection
- association with neurological abnormalities (particularly hyperactivity and choreiform movements).

Later, difficulties to confirm a temporal association between a streptococcal infection and the onset of neuropsychiatric symptoms were noted (Swedo et al., 2012, Chang et al., 2015). An additional problem was the difficulty to distinguish the onset of tics in the PANDAS group from the non-PANDAS tic disorders. The validity and utility of the PANDAS entity were challenged. To address these issues, a group of clinicians and researchers in the United States (PANS Research Consortium) assembled 2010 for a workshop (Swedo et al., 2012) and defined a new condition called PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) including all cases of acute onset OCD regardless of etiology. Besides infections, non-infectious causes as well as environmental factors were proposed as potential triggers of the condition. Due to the difficulties in separating PANDAS among primary tic disorders, tics were excluded from the criteria. However, the PANS Research Consortium still considered PANDAS a subgroup of PANS (fig 1. Swedo et al., 2012). Compared with PANDAS, the PANS criteria describe symptoms and clinical course, not etiology; OCD or severely restricted food intake became a mandatory criterion, tics only did not suffice; and a broad range of additional symptoms were included (Swedo et al., 2012):

- abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake
- concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories
    - anxiety
    - emotional lability or depression
    - irritability, aggression, or severely oppositional behaviors
    - behavioral (developmental) regression
    - deterioration in school performance
    - sensory or motor abnormalities
    - somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency
- symptoms are not better explained by a known neurological or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder, a neurometabolic disorder or others.

Although the symptom criteria were changed, the research consortium still assumed an underlying etiology of neuroinflammation and/or autoimmunity.

According to the Swedish National Board of Health and Welfare, the internal consistency of the PANS criteria is unclear and there are uncertainties regarding the diagnostic boundaries of PANS to other cases of acute-onset OCD (Socialstyrelsen, 2017).

A definitive etiological connection between streptococcal infections and PANDAS has not been established. Further, it has not yet been possible to identify reliable biomarkers for PANS or PANDAS. Several studies have been performed with suspected biomarkers such as streptococcal antibodies and antineuronal antibodies, reporting variable and inconclusive results (Chang et al., 2015). For example, Hesselmark et al. (2017) reported insufficient sensitivity/specificity for the Cunningham panel, a set of immunologic assays, whereas an association between this panel and changes in neuropsychiatric symptoms was observed by Shimasaki et al. (2020).

The condition has a relapsing–remitting course (Johnson et al., 2019). As two thirds of the patients do not attend school for several months (Johnson et al., 2019), the condition can be considered to have a high degree of severity. Symptoms often include obsessions/compulsions, anxiety, emotional lability/depression, irritability/aggression, deterioration in school performance, sensory/motor problems, and sleep disturbance (Johnson et al. 2019). More severe symptoms include violent outbursts as well as suicidal and homicidal thoughts and gestures (Frankovich et al., 2015). Further, the caregiver burden can be considerable (Frankovich et al., 2018). Long-term outcome is not known, but spontaneous recovery has been described.

Prevalence and incidence

As PANS and PANDAS are currently not established diagnoses and not included in the fifth diagnostic and statistical manual of mental disorders (DSM-5) or the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), the prevalence/incidence cannot be estimated. The prevalence of OCD in children and adolescents is 0.5-2% (Läkemedelsverket, 2016).

Over the last three-year period, 60 children from all over Sweden have been referred to the Child Neuropsychiatry Centre (CNC) at the Sahlgrenska University Hospital with queries regarding symptoms in line with the PANS criteria. Of these, about eight children each year have been considered to fulfill the research condition criteria. The first 23 cases at CNC during 2015-2017 have been described by Johnson et al. (2019). Descriptions of other Swedish cases/cohorts have been published by Hesselmark et al. (2017) and Gromark et al. (2019).

Present treatment

In routine health care, children presenting with psychiatric symptoms are evaluated with psychiatric and neuropsychological methods for classification of a diagnosis according to DSM-5. If presenting with signs or behavioral impairment that indicates a neurological, endocrine, metabolic or postinfectious disorder, the child is referred to a child neurology clinic and, when relevant, to an immunologist or infectious disease expert. Immunological and antibiotic treatment are provided to those with a verified neuroinflammation or a postinfectious autoimmunity reaction. Bacterial infections are treated according to recommendations. In routine health care, treatment of OCD and other psychiatric symptoms include cognitive behavioral therapy and psychoactive medications. The PANS/PANDAS classifications are not used routinely, but are used by specific centers in Sweden offering the treatments at issue in the present report, sometimes also without a verified neuroinflammation, infection or autoimmunity.

Present recommendations from medical societies or health authorities

Guidelines from the Swedish National Board of Health and Welfare recommend diagnostic efforts and treatment of PANS/PANDAS only within the framework of research and development because of the limited scientific basis (Socialstyrelsen, 2017).

In contrast, the PANS Research Consortium in the United States has published guidelines for the patients at issue including treatment with anti-inflammatory drugs, antibiotics, intravenous immunoglobulins (IVIG) and plasmapheresis (Swedo et al., 2017, Cooperstock et al., 2017, Frankovich et al., 2017, Thienemann et al., 2017).

In Sweden, a multidisciplinary team of specialists in Child Neurology, Rheumatology and Psychiatry at Karolinska University Hospital and Child OCD Research Centre has provided instructions for the management of the patients at issue (Karolinska Universitetssjukhuset, 2018 [Rutiner för handläggning av barn med misstänkt PANS (inklusive PANDAS)]).

6. Health Technology at issue

In the present HTA, anti-inflammatory, antibacterial or immunomodulating treatments are at issue, based on the hypothesis that neuroinflammation/autoimmunity is the underlying cause of acute-onset OCD or severely restricted food intake in children with other neuropsychiatric symptoms but without a verified neurological or medical disease. Antibiotics are presumed to prevent acute neuropsychiatric deterioration triggered by infections. Anti-inflammatory agents include cyclooxygenase (COX) inhibitors and glucocorticoids, whereas immunomodulating treatments include immunoglobulins, therapeutic plasma exchange, rituximab and tumour necrosis factor (TNF) inhibitors.

COX inhibitors

COX inhibitors, also known as nonsteroidal anti-inflammatory drugs (NSAIDs), are used for their anti-inflammatory, antipyretic and analgesic effects. There are many substances available with COX inhibiting properties. In pediatric care, these drugs are mostly used to treat fever and acute pain or inflammation. They are also used in rheumatic disorders such as juvenile idiopathic arthritis, including enthesitis-related arthritis (spondyloarthritis) and juvenile psoriasis arthritis. COX inhibitors are often administered orally. Some of the more common adverse effects include dyspepsia, nausea and headache and precautions should be taken for patients with renal dysfunction, cardiovascular disease, asthma, inflammatory bowel disease and previous gastrointestinal bleeding.

Glucocorticoids

Glucocorticoids are used in the treatment of endocrine, allergic and inflammatory diseases. In pediatric care, this includes for example asthma, allergy, autoimmune diseases such as inflammatory bowel disease, juvenile rheumatic disorders and autoimmune encephalitis. Treatment can be both acute and chronic and the route of administration is either local or systemic. The latter gives rise to more adverse effects compared to local administration. Adverse effects include increased susceptibility to infections, growth impairment, adrenal suppression, neuropsychiatric effects, weight gain, Cushingoid effects and gastrointestinal effects. Adverse effects are dose-dependent.

Antibiotics

Antibiotics have been used since mid-1940s to treat bacterial infections. In addition to treating manifested bacterial infections, antibiotics have also been used for prevention. In pediatric care, long-term antibiotic prophylaxis is used to prevent bacterial infections in patients with for instance immunodeficiency, infants with vesicoureteral reflux, and in patients with rheumatic fever. The most common ways of administration are oral and intravenous. Well known adverse effects are nausea, loose stools, and allergic reactions. In addition, the development of antibiotic resistance is a matter of concern, both for the individual and for the society.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is a blood product produced from the plasma of thousands of patients per batch (Jolles et al., 2005). In pediatric care, IVIG is used as replacement therapy for patients with antibody deficiencies in the range of 0.5-0.8 g/kg every 3 weeks. Additionally, IVIG is used as an immunomodulatory agent at high dose, usually 2 g/kg for patients with autoimmune and inflammatory disorders such as Kawasaki, Guillian-Barré and different types of autoimmune encephalitis. Adverse effects include headache, nausea/vomiting, pyrexia, hyper/hypotension and, more seldom, allergic reactions.

Therapeutic plasma exchange

Therapeutic plasma exchange is an extracorporeal treatment where cells or harmful substances such as autoantibodies and endotoxins are selectively removed from patients' plasma. The plasma is replaced by another fluid such as donor plasma, crystalloid or colloid depending on the indication for treatment. The therapy is more invasive compared to the other treatments described above due to the need for a reliable venous access e.g. a central venous catheter or two large durable peripheral veins. The patient's blood is passed through an extracorporeal device that separates the blood into its components. The plasma is collected in a separate container whereas the rest of the blood products return to the patient. In pediatric care, therapeutic plasma exchange is used for neurologic, immunologic and hematologic diseases such as autoimmune encephalitis, Guillain-Barré syndrome and thrombotic thrombocytopenia. Complications depend on the type of replacement fluid used in the treatment and include for example electrolyte imbalance, coagulation factor and immunoglobulin depletion, allergic reactions and hypotension. Vascular catheter complications could also occur.

Rituximab and TNF inhibitors

Rituximab is a monoclonal antibody that binds to CD20 expressed on the B-cells, leading to depletion of these cells in the circulation. TNF inhibitors suppress the body's response to tumour necrosis factor (TNF), an important cytokine in the inflammation cascade. In pediatric care, these drugs are used for rheumatic disease, malignant and autoimmune diseases including inflammatory disorders of the brain, bowel and hematologic disorders. Treatment implies an increased risk of infections.

7. Focused question

Does anti-inflammatory, antibacterial or immunomodulatory treatment, compared with no such treatment, improve health-related quality of life (HRQL), level of functioning and symptoms in children with symptoms corresponding to the research condition of PANS/PANDAS? Is such treatment associated with complications?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P: Patients: Children (<18 years) with symptoms corresponding to the research condition of PANS/PANDAS

I: Intervention: Anti-inflammatory, antibacterial or immunomodulating treatments (COX inhibitors, glucocorticoids, antibiotic, immunoglobulins, therapeutic plasma exchange, rituximab, TNF inhibitors)

C: Comparison: No anti-inflammatory, antibacterial or immunomodulatory treatment

O: Outcomes:

- Health-related quality of life according to validated scales
- Level of functioning (for example attendance at school, activities of daily living)
- Symptom change (reported by patients, caregivers and care staff)
- Complications

In order to confirm the relevance of the outcomes included in this PICO, the patient organisation (SANE) was asked to review the PICO. SANE confirmed that the included outcomes covered the most important aspects.

8. Methods

Systematic literature search (Appendix 1)

During August 2019 two authors (TS, UWA) performed systematic searches in PubMed, Embase, PsycInfo and the Cochrane Library. The web-sites of Swedish Agency for Health Technology Assessment and Assessment of Social Service (SBU) and Folkehelseinstituttet were searched, and reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches, selected studies, and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all authors. All authors read the articles independently of one another. In a consensus meeting, the authors decided which articles to include in the HTA.

Critical appraisal and certainty of evidence

The included studies and their design as well as patient characteristics are presented in Appendix 2. The excluded studies, including reasons for exclusions, are presented in Appendix 3. Included studies reporting patient relevant outcomes were critically appraised using the checklists for assessment of randomised controlled trials (RCT) and observational studies provided by SBU. In Appendix 4, the results and the quality of each study are summarised per outcome. Data were extracted by at least two authors. Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 9-10). The certainty of evidence was assessed according to GRADE (Atkins et al., 2004).

Ongoing research

Searches were performed in Clinicaltrials.gov (November 14, 2019) and WHO ICTRP (November 14, 2019)**.** The search terms are provided in Appendix 1. In all, 366 unique trials were identified, two of which were relevant for our PICO.

9. Results

Search results and study selection (Appendix 1)

After removal of duplicates, the literature search identified 1,564 articles. After reading the abstracts 1,508 articles were excluded. Another 30 articles were excluded by two authors after reading the articles in full text. The remaining 26 articles were sent to all authors, and seven articles were finally included in the HTA (Appendix 2). The 19 excluded articles are reported with reason for exclusion in Appendix 3.

Included studies

This HTA was based on seven studies, with randomised (n=4), cross-sectional (n=2) and before/after (n=1) designs. Two studies provided data on anti-inflammatory treatments (Brown et al., 2017a, Brown et al., 2017b), whereas three studies evaluated antibacterial treatment (Garvey et al., 1999, Murphy et al., 2017, Snider et al., 2005) and two studies focused on immunomodulating treatments (Perlmutter et al., 1999, Williams et al., 2016). The studies investigated effects of COX inhibitors (n=1), corticosteroids (n=1), penicillin V (n=2), azithromycin (n=2), IVIG (n=2), and plasma exchange (n=1). No studies investigated effects of rituximab or TNF inhibitors. The RCTs had a follow-up of four weeks to four months.

All studies had major study limitations including selection, treatment, detection and reporting biases. None of the studies provided a transparent description of the strategy for evaluating adverse effects. Regarding directness, the studies had major (n=1) or some (n=6) problems. A main issue is that the conditions PANS and PANDAS have only been suggested by a research group, i.e. are not established diagnoses.

Further, these conditions, composed by a number of criteria, have both been restricted and extended over the years and comprise a wide range of severity. The precision had major (n=4) or some (n=3) problems, with the RCTs including 30-37 patients and the non-RCTs 23-98 patients, and power calculations lacking in all but one study.

Results per outcome and intervention

Health-related quality of life
None of the included studies reported data regarding health-related quality of life.

Level of functioning (Appendix 4.1)

Anti-inflammatory versus no anti-inflammatory treatment
None of the included studies reported data regarding the level of functioning.

Antibiotic versus no antibiotic treatment
Effects on level of functioning were investigated in one RCT (Murphy et al., 2017) and in one randomised cross-over study (Garvey et al., 1999), both placebo-controlled. None of these studies reported significant effects of antibiotic treatment regarding this outcome. Both studies had major study limitations as, for example, the primary outcome was not clearly defined and reported, there were unclarities regarding the comparability of the randomisation groups, and the blinding could be unmasked by side effects.

> *Conclusion: In children with symptoms corresponding to the research condition of PANS/PANDAS, it is uncertain whether antibiotic treatment improves the level of functioning. (Very low certainty of evidence, GRADE ⊕OOO)*

Immunomodulating versus no immunomodulating treatment
IVIG and plasma exchange were investigated in one RCT (Perlmutter et al., 1999). The recruitment of patients into this study occurred before the PANDAS condition was suggested in a publication by this research group (Swedo et al., 1998). No significant intra-individual changes regarding level of functioning were found in the intervention or the control group, and between-group comparisons were not provided for the two types of immunomodulating treatment. The study had major study limitations as, for example, the primary outcome was not clearly defined and reported, the randomisation groups differed in baseline characteristics, and the blinding regarding IVIG could be unmasked by adverse drug effects (plasma exchange was not blinded).

> *Conclusions: In children with symptoms corresponding to the research condition of PANS/PANDAS, it is uncertain whether immunomodulating treatment, including IVIG and plasma exchange improves the level of functioning.*
> *(Very low certainty of evidence, GRADE ⊕OOO)*

Symptom change (Appendix 4.2)

Anti-inflammatory versus no anti-inflammatory treatment
COX inhibitors and corticosteroids were investigated in two cross-sectional studies (Brown et al., 2017b, Brown et al., 2017a). Both studies analysed symptoms in terms of duration of acute neuropsychiatric deterioration, reporting shorter duration in those treated with the drug group at issue. Both studies had major study limitations including confounding by indication. For instance, corticosteroids were, for most of the study period, not prescribed to those in worse psychiatric condition due to concerns about psychiatric adverse effects. Further, detection bias, with more thorough follow-up and contingency plans in those treated, cannot be excluded.

Conclusion: In children with symptoms corresponding to the research condition of PANS/PANDAS, it is uncertain whether anti-inflammatory treatment, including COX inhibitors and corticosteroids, improves symptoms.
(Very low certainty of evidence, GRADE ⊕○○○)

Antibiotic versus no antibiotic treatment

Symptom change was reported in one placebo-controlled RCT (Murphy et al., 2017), in one randomised cross-over study (Garvey et al., 1999) and in one before/after study (Snider et al., 2005). None of the two RCTs reported significant differences regarding OCD symptoms using the established Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) or tics assessed with the Yale Global Tic Severity Scale (YGTSS). However, one of these RCTs reported a reduction in OCD symptoms according to the Clinical global impression severity scale (CGI-S; Murphy et al., 2017), and the before/after study reported a reduction in the number of neuropsychiatric exacerbations (Snider et al., 2005). Both RCTs had major study limitations as, for example, the primary outcome was not clearly defined and reported, there were unclarities regarding the comparability of the randomisation groups at baseline, and the blinding could be unmasked by side effects. The before/after study also had major study limitations. For instance, outcome data were collected retrospectively for the untreated period, and prospectively for the treated period. Further, there was a lack of clarity regarding what was actually measured.

Conclusion: In children with symptoms corresponding to the research condition of PANS/PANDAS, it is uncertain whether antibiotic treatment improves symptoms.
(Very low certainty of evidence, GRADE ⊕○○○)

Immunomodulating versus no immunomodulating treatment

IVIG was investigated in two placebo-controlled RCTs (Perlmutter et al., 1999, Williams et al., 2016), in one of which plasma exchange was a third un-blinded treatment arm (Perlmutter et al., 1999). Both RCTs were performed by the same research group. In the first one, investigating both IVIG and plasma exchange, patients were recruited before 1998, i.e. before the criteria for PANDAS were published by this group of researchers (Swedo et al., 1998). In this study, symptoms were assessed by several instruments, some of which not clearly defined and without a determined primary endpoint. In both active treatment groups, significant intra-individual improvements were reported using the established CY-BOCS as well as an undefined Global impairment score and an undefined Global severity score, whereas no improvement was observed on these scales in the placebo group. Between-group statistical comparisons with placebo were not provided for IVIG and plasma exchange separately. The authors reported a significant difference regarding the rating score for compulsions and obsessions for the combined IVIG and plasma exchange groups compared with the placebo group. The study had major study limitations as the randomisation groups differed in baseline characteristics, the blinding regarding IVIG could be unmasked by adverse drug effects, and plasma exchange was not blinded. In the second RCT, reporting no significant effect of IVIG in a between-groups comparison, the authors discuss that the design *per se* may have influenced how patients reported their symptoms, as all patients who reported no improvements during the blinded treatment period were guaranteed open IVIG treatment afterwards.

Conclusions: In children with symptoms corresponding to the research condition of PANS/PANDAS, it is uncertain whether immunomodulating treatment, including IVIG and plasma exchange, improves symptoms. (Very low certainty of evidence, GRADE ⊕○○○)

Complications (Appendix 4.3)

Anti-inflammatory versus no anti-inflammatory treatment
In the study investigating effects of COX inhibitors (Brown et al., 2017b), including those who tolerated treatment for a minimum of seven days, transient adverse effects were recorded in 11 of 57 patients with ≥1 acute neuropsychiatric deterioration treated with a COX inhibitor, most frequently abdominal pain and proteinuria. In the study investigating effects of corticosteroids (Brown et al., 2017a), adverse effects were recorded in 45 out of 102 courses of oral corticosteroids given for a neuropsychiatric deterioration, most frequently increased psychiatric symptoms. Further, 8 of 15 patients who received corticosteroids for more than 5 days or ≥3 courses within one month experienced increased weight (n=2), Cushingoid features (n=2) or both (n=4). The observed adverse effects were pharmacologically plausible given the doses provided, and concordant with those listed in the summary of products characteristics (SPC).

> *Conclusion: In children with symptoms corresponding to the research condition of PANS/PANDAS with anti-inflammatory treatment at the used doses, adverse effects in line with the summary of product characteristics can probably occur.*
> *(Moderate certainty of evidence, GRADE ⊕⊕⊕◯)*

Antibiotic versus no antibiotic treatment
Adverse effects were systematically recorded and reported in one of three studies (Murphy et al., 2017). In this placebo-controlled study investigating the effects of azithromycin, loose/abnormal stools were significantly more common in patients who received antibiotics. Further, a statistically significant increase in electrocardiogram QT was found in the azithromycin group at week 4 compared to baseline. Four patients out of 17 receiving azithromycin had borderline QT at follow-up, none above 460 ms. Two of these also had borderline QT at baseline. One case with possible bacterial resistance was noted during the study, but antimicrobial resistance was not studied at a laboratory level. The other two studies of antibiotic treatment (Garvey et al., 1999, Snider et al., 2005) did not provide information on adverse effects. In addition to the relevant between-group differences in adverse events, the observed adverse effects were pharmacologically plausible and concordant with those listed in the SPC.

> *Conclusion: In children with symptoms corresponding to the research condition of PANS/PANDAS with antibiotic treatment at the used doses, adverse effects in line with the summary of product characteristics can probably occur.*
> *(Moderate certainty of evidence, GRADE ⊕⊕⊕◯)*

Immunomodulating versus no immunomodulating treatment
Adverse effects were systematically recorded and reported in two RCTs (Perlmutter et al., 1999, Williams et al., 2016). In the first one, nausea and vomiting occurred in five out of nine patients on IVIG and low-grade fever in four. Two patients vomited during the plasma exchange, and three reported increased anxiety. None of the patients on placebo had any of these reactions. Headache of mild to moderate severity occurred in three patients on IVIG, and mild headache in one patient on placebo. In the second RCT, vomiting was reported in three out of 17 patients on IVIG, and in none of the patients on placebo. Headache was reported in eight IVIG patients and three placebo patients (P=0.053). One patient had a possible allergic reaction to IVIG which resolved without complication. In addition to the relevant between-group differences in adverse events, the observed adverse effects of IVIG were pharmacologically plausible and concordant with those listed in the SPC. For plasma exchange, the certainty of evidence was rated lower, as the evaluation was based on one open treatment arm in a placebo-controlled RCT and complications are not systematically surveyed and assessed by a regulatory agency.

Conclusion: In children with symptoms corresponding to the research condition of PANS/PANDAS with IVIG treatment at the used doses, adverse effects in line with the summary of product characteristics can probably occur.
(Moderate certainty of evidence, GRADE ⊕⊕⊕◯)
In children with symptoms corresponding to the research condition of PANS/PANDAS, plasma exchange may result in complications. (Low certainty of evidence, GRADE ⊕⊕◯◯)

10. Ethical aspects

This HTA suggests that the benefit-risk balance may be negative for providing treatment against a hypothesised underlying neuroinflammation/autoimmunity to children with acute-onset OCD, or severely restricted food intake, combined with other neuropsychiatric symptoms but without a verified neurological or medical disease. The ethical principle not to harm by medical treatment weighs heavier than the principle to do good. At the overall level, there was very low certainty evidence regarding potential beneficial treatment effects whereas the evidence that the treatment has adverse effects had moderate/low certainty. Nevertheless, the patients can have a condition with a high degree of severity; about two thirds do not attend school for several months. In addition to obsessive-compulsive symptoms, the patients often present with anxiety, emotional lability/depression, irritability/aggression, behavioural regression, deterioration in school performance, sensory/motor problems, fatigue and sleep disturbance (Johnson et al., 2019). These composite symptoms in children also put strains on parents and legal guardians, thereby affecting third parties. Other treatment alternatives, both psychological and pharmacological, form the basis for the symptom entities.

Regarding the compatibility with ethical values, the interventions evaluated in this HTA may be at risk of violating equality and justice as the provision of the interventions varies over the country and within the region. Consequently, professional values may affect the interventions provided when a patient is presenting with the symptoms at issue and unequal access to the interventions cannot be ruled out. Further, a stakeholder association advocates the use of the interventions, a fact which may contribute to health care based on demands rather than needs. An additional complicating aspect is that of autonomy; parents and legal guardians make decisions for their children. In the information to patients and their parents/legal guardians, it is therefore important to emphasise that – given the current evidence base regarding benefit and risk – there may be restrictions on whether anti-inflammatory, antibiotic or immunomodulatory treatment can be offered to patients. Further, the children must not be withheld established treatment for their symptoms.

Given the very low certainty evidence for beneficial effects, the cost-effectiveness of the intervention can be questioned. In particular, immunomodulatory treatments are relatively costly as they include nursing costs in a day care center or a ward. Further, the costs for IVIG is non-negligible. Use of immunomodulatory treatment in routine health care may therefore displace other patient care activities. However, this treatment alternative is currently only used in the most severe cases. Regarding treatment with antibiotics, long-term risks not only for the treated individual but also at a society level need to be considered. Use of this intervention without a verified underlying infection may add to antibiotic resistance, an increasing problem worldwide, with severe societal and health care implications. In this context, use of low doses over long periods, as in the studies included in this HTA, may be particularly problematic.

In summary, taking into account the current evidence base of the benefit-risk balance, the availability of alternative treatments, the severity of the condition and the potential conflicts with ethical values, it may be ethically reasonable to require that the assessed treatments are provided only within the framework of research. Clinical studies need to be adequately designed, that is, hold the potential to contribute to an increased level of evidence. However, as the evidence is premature regarding the research condition *per se*, it may be a challenge to define the patient population at issue.

Further, as the symptoms forming the criteria for the condition cover several domains, a valid approach to evaluate potential treatment effects needs to be developed.

11. Organisational aspects

Time frame for the putative introduction of the new health technology

As the present HTA refers to a research condition, not an established diagnosis, and as the analysis raises questions regarding the evidence base for the assessed interventions, it is too early to speculate about a timeframe for a putative introduction in routine health care. Beforehand, clinical studies funded within research and development are required for an increased level of evidence.

Present use of the technology in other hospitals in Region Västra Götaland

Over the last three-year period, 60 children from all over Sweden have been referred to the Child Neuropsychiatry Centre (CNC) at the Sahlgrenska University Hospital with queries regarding symptoms in line with the PANS criteria. The first 23 cases fulfilling the criteria of the research condition PANS at CNC during 2015-2017 have been described by Johnson et al. (2019), all of whom presenting with a preceding verified or suspected infection (bacterial n=10, viral n=13). In all, 19 of the 23 cases had been prescribed antibiotics, three had been treated with anti-inflammatory drugs and two had received IVIG.

Consequences of the new health technology for personnel

Given the current evidence base for the assessed interventions, it is too early to speculate about potential personnel consequences.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

To increase the evidence base for the caretaking of children with acute-onset OCD or severely restricted food intake, combined with other neuropsychiatric symptoms but without a verified neurological or medical disease, national multidisciplinary collaboration within research and development would be needed.

12. Economic aspects

There is no established course of treatment for the condition evaluated in this HTA. Further, the number of treatment courses as well and the treatment duration of each course are not stipulated. It is therefore hard to estimate the costs. Below, the approximate costs per patient and day are presented. For anti-inflammatory and antibacterial treatments, the costs may vary according to dose but are relatively low:

- COX inhibitors: 2-3 SEK per day
- Glucocorticoids: 2-10 SEK per day
- Antibiotics: 5 SEK per day

For IVIG and therapeutic plasma exchange, the costs are relatively high:

- IVIG: The costs will vary substantially with regard to dose and weight. With a dose of 2 g/kg, as provided in the studies in this HTA, the cost would be 27,500 and 46,000 SEK for patients with a weight of 30 and 50 kg, respectively (based on Privigen price of 457 SEK/gram). Costs for administration are not included in these figures.
- Plasma exchange: 15,000 to 17,000 SEK per exchange

13. Discussion

Summary of main results

This HTA, based on seven studies with major study limitations and problems regarding directness and precision, shows that conclusive evidence is largely lacking regarding potential beneficial effects of anti-inflammatory, antibiotic and immunomodulatory treatments for children with acute-onset OCD or severely restricted food intake, combined with other neuropsychiatric symptoms but without a verified neurological or medical disease. The compiled evidence also indicates that adverse reactions similar to those previously known can probably be expected in this patient group.

Overall completeness and applicability of evidence

The evidence is incomplete and uncertain, mainly because of study quality problems, indirectness for example related to the absence of an established diagnosis, and small samples sizes with insufficient power. Further, rituximab and TNF inhibitors considered within the PICO as well as the outcome HRQL have not been studied. HRQL may be a particularly valuable outcome as it reflects the net effect of a treatment, that is, the benefit-risk balance.

Agreements and disagreements with other studies and reviews

A systematic review with searches up to October 2017, including controlled studies, case series and case reports, concluded that published studies had a high risk of bias (Sigra et al., 2018). These findings are in accordance with the present HTA.

The results of this HTA is in agreement with guidelines from the National Board of Health and Welfare in which treatment of PANS/PANDAS is only to be performed within the framework of research and development because of the limited scientific basis (Socialstyrelsen, 2017).

Implications for research

In this HTA, we found that all studies used symptom change as an outcome measure, using a variety of scales covering different aspects of the condition. If/when a diagnosis has been established and verified, it could be of value to define a core outcome measure reflecting the key symptoms of the condition. Further, as adverse reactions may unblind blinded active treatment, efforts to minimise assessment bias are important. In addition, confounding by indication has to be handled in future non-randomised studies; COX inhibitors and corticosteroids would probably not be prescribed to children with more severe psychiatric symptoms within the research condition of PANS/PANDAS because of their adverse reaction profile. In the evaluation of symptoms, it would be relevant to reflect the perspectives of the patient, the parents and legal guardians, as well as the health care providers.

The immaturity of the condition may contribute to difficulties to evaluate potential treatment effects; the patient population at issue may be hard to distinguish from other OCD patients. The criteria have been modified over the years and indirectness may continue to be a major problem for research on treatment effects until a diagnosis with clear boundaries can be defined and verified. In the process, it is essential to elucidate if neuroinflammation is a feature in common. For instance, it could be of interest to further explore immunological mechanisms including cytokine profiles, autoimmunity and human-leukocyte antigen (HLA) class II genes. Indeed, increased rates of autoimmunity have been reported in OCD (Mataix-Cols et al., 2018). Further, etiological mechanisms suggested for OCD include, in addition to genetic predisposition, immunological abnormalities, autoimmune processes and environmental triggers, such as infections (Lamothe et al., 2018). In addition, an enrichment of the human leukocyte antigen/antigen D-related 4 (HLA-DR4) serotype allele has been found in patients with OCD (Rodriguez et al., 2019). In summary, these findings highlight that the boundaries between the condition of PANS/PANDAS and OCD in general need to be further explored.

14. Future perspective

Scientific knowledge gaps

Through this report, we have identified the need for well-designed and adequately powered studies on treatment effects. This applies to all reviewed treatment options, that is, anti-inflammatory, antibiotic as well as immunomodulatory treatments. To further investigate possible effects of different treatment alternatives, there is a need for validation of the diagnostic criteria. Identifying biomarkers would be valuable in this context. In addition, outcome measures reflecting important patient aspects could deserve increased attention in future research on treatment effects, such as school attendance and HRQL. Long-term studies evaluating the course of the condition would also be valuable.

Ongoing research

In clinicaltrials.gov, we identified two ongoing studies that fulfil our PICO. The first one is a 12 week double-blind RCT, planning to include 30 children with symptoms corresponding to the research condition of PANDAS and investigating the effects of adding an antibiotic to sertraline (sertraline administered to both intervention and control groups) regarding obsessive compulsive symptoms and tics (NCT01769027). The antibiotic at issue is benzathine penicillin G 1,200,000 U every 3 weeks or, in case of allergy, azithromycin 500 mg/week. Patients not responding will be treated with IVIG (2 g/kg over 5 days for 5 consecutive months). This study record has not been updated since 2013, and recruitment had not yet started at that time.

The second study is a double-blind RCT (NCT04015596), planning to include 70 children with symptoms corresponding to the research condition of PANDAS and investigating the effects of the anti-inflammatory agent naproxen regarding obsessive compulsive symptoms after an eight-week treatment period. As of July 2019, the study is not yet recruiting patients.

15. Participants in the project

The question was nominated by

Marie Carlsson, Head of Department, Department of Neurology, Psychiatry and Habilitation, Queen Silvia´s child and adolescent Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden

Participating healthcare professionals

Stephan Ehlers, MD, PhD, Regional Knowledge Center for Mental Health, Gothenburg, Sweden
Elisabeth Fernell, MD, Professor, Child Neuropsychiatry Centre, Sahlgrenska University Hospital, Gothenburg, Sweden
Parisa Hajjari, MD, Resident in Paediatric medicine, Kungälv, Sweden
Mats Johnson, MD, PhD, Child Neuropsychiatry Centre, Sahlgrenska University Hospital, Gothenburg, Sweden, and Gillberg Neuropsychiatry Centre, Sahlgrenska Academy, Göteborg University, Sweden

Participants from the HTA-centrum

Susanna Wallerstedt, MD, professor, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden
Constanze Wartenberg, Psychologist, PhD, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden
Therese Svanberg, Librarian, Medical library, Sahlgrenska University Hospital, Gothenburg, Sweden
Ulla Vikberg Adania, Librarian, Medical library, Sahlgrenska University Hospital, Gothenburg, Sweden

Administrative support

Pernilla Rönnholm, Project coordinator, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden

External reviewers

Ulla Karilampi, Researcher PhD/Psychologist MSc, Sahlgrenska University Hospital, Mölndal, Sweden
Marie Studahl, M.D, Ph.D, Associate professor, Department of Infectious Diseases, Sahlgrenska Academy Gothenburg University, Gothenburg, Sweden

Declaration of interests

M Johnson and E Fernell work at the Child Neuropsychiatry Centre and the Gillberg Neuropsychiatry Centre, to which referrals of patients occur, for assessments and treatment, when the research condition PANS/PANDAS is suspected. M Johnson has received research grants from Shire and Vifor Pharma and has been engaged as a speaker or consultant by Eli Lilly, Shire, Vifor Pharma, Ginsana, PCM Scientific, Evolan, and New Nordic. M Svensson contributes in a research project funded by Pfizer.

S Ehlers, P Hajjari, T Svanberg, U Vikberg Adania, C Wartenberg, SM Wallerstedt declare no conflict of interest.
Both external reviewers declare no conflict of interest.

Project time

The HTA was accomplished during the period of 2019-06-05 – 2020-04-17
Literature searches were made in August 2019

Appendix 1: PICO, study selection, search strategies, and references

Question at issue:
Does anti-inflammatory, antibacterial or immunomodulatory treatment, compared with no such treatment, improve health-related quality of life (HRQL), level of functioning and symptoms in children with symptoms corresponding to the research condition of PANS/PANDAS? Is such treatment associated with complications?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P: Patients: Children (<18 years) with symptoms corresponding to the research condition of PANS/PANDAS

I: Intervention: Anti-inflammatory, antibacterial or immunomodulating treatments (COX inhibitors, glucocorticoids, antibiotic, immunoglobulins, therapeutic plasma exchange, rituximab, TNF inhibitors)

C: Comparison: No anti-inflammatory, antibacterial or immunomodulatory treatment

O: Outcomes:
- Health-related quality of life according to validated scales
- Level of functioning (for example attendance at school, activities of daily living)
- Symptom change (reported by patients, caregivers and care staff)
- Complications

In order to confirm the relevance of the outcomes included in this PICO, the patient organisation (SANE) was asked to review the PICO. SANE confirmed that the included outcomes covered the most important aspects.

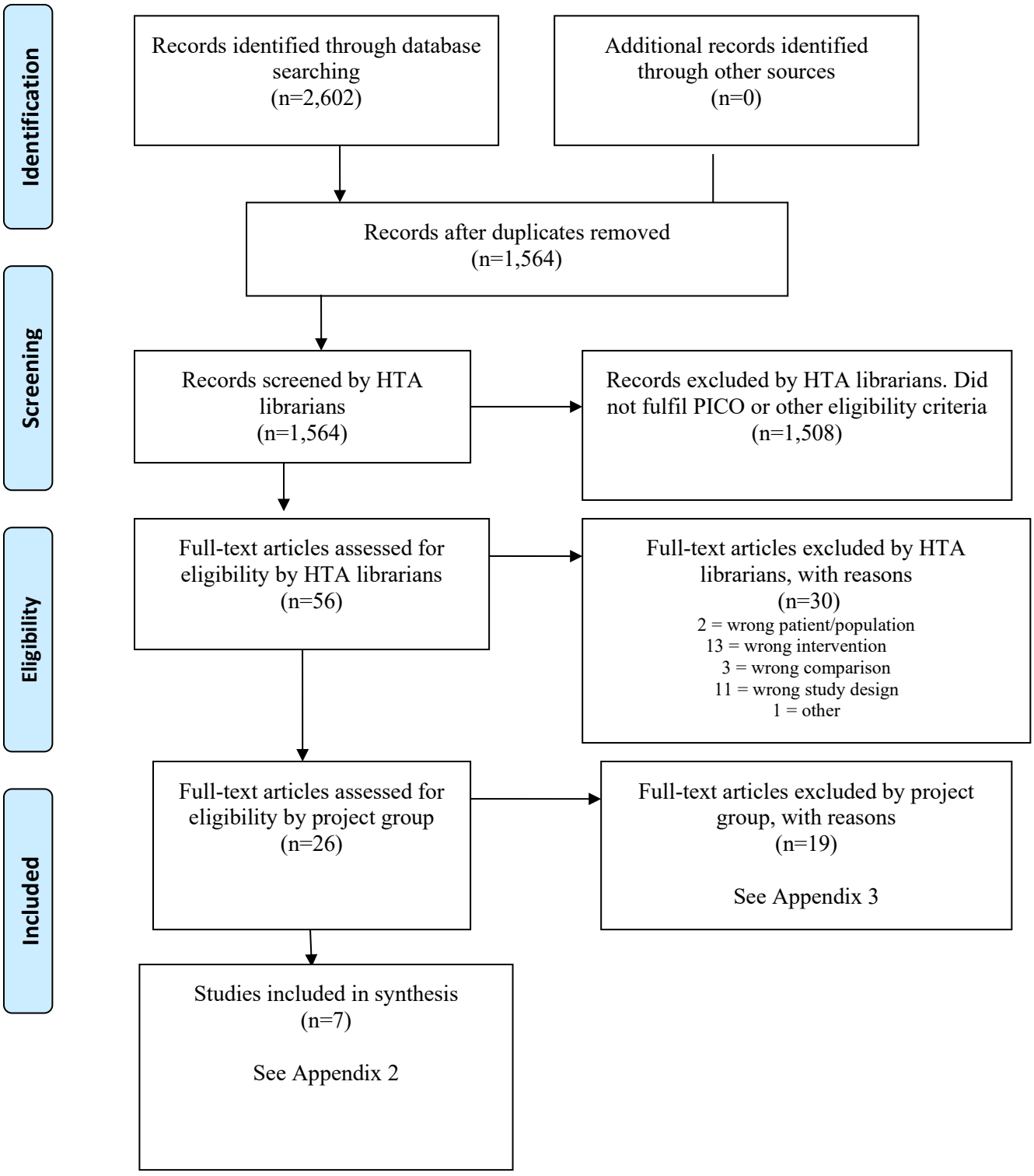
<u>Eligibility criteria</u>

Study design: Randomised controlled trials (RCT), cohort studies, case-control studies, cross-sectional studies, case studies >200 patients (for complications)

Language: English, Swedish, Norwegian, Danish

Publication date: 1998 -

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 22 Aug 2019
No. of results: 911

Search	Query	Items found
#10	**Search #6 NOT #7 Filters: Publication date from 1998/01/01; Swedish; Norwegian; English; Danish**	**911**
#9	Search #6 NOT #7 Filters: Swedish; Norwegian; English; Danish	1,022
#8	Search #6 NOT #7	1,090
#7	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]	1,753,875
#6	Search #1 NOT #5	1,139
#5	Search #2 OR #3 OR #4	4,930,918
#4	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4,611,370
#3	Search animal[ti] OR animals[ti] OR rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR rodent[ti] OR rodents[ti] OR dog[ti] OR dogs[ti] OR cat[ti] OR cats[ti] OR hamster[ti] OR hamsters[ti] OR rabbit[ti] OR rabbits[ti] OR swine[ti] OR murine[ti]	1,830,757
#2	Search giant panda*[tiab] OR red panda*[tiab] OR greater panda*[tiab]	673
#1	Search PANDAS[tiab] OR PANS[tiab] OR ((pediatric OR pediatric-onset OR paediatric-onset OR childhood OR childhood-onset OR children OR child) AND (autoimmune OR acute OR acute-onset OR recent-onset) AND (neuropsychiatric OR neuro-psychiatric))	1,623

Database: Embase 1974 to 2019 August 21 (OvidSP)
Date: 22 Aug 2019
No. of results: 1074

#	Searches	Results
1	(PANS or PANDAS).ab,kw,ti.	1,535
2	(p?ediatric or p?ediatric-onset or childhood or childhood-onset or children or child).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2,602,306
3	(autoimmune or acute or acute-onset or recent-onset).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,943,825
4	(neuropsychiatric or neuro-psychiatric).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	43,579
5	2 and 3 and 4	1,159
6	1 or 5	2,312
7	(giant panda$ or red panda$ or greater panda$).ab,kw,ti.	659
8	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or swine or murine).ti.	1,942,617
9	(animal not (animal and human)).sh.	1,044,840
10	7 or 8 or 9	2,753,087
11	6 not 10	1,882
12	limit 11 to yr="1998 -Current"	1,720
13	limit 12 to ((embase or medline) and (article or article in press or conference paper or note or "review"))	1,177
14	**limit 13 to (danish or english or norwegian or swedish)**	**1,074**

Database: PsycInfo (EBSCOhost)
Date: 22 Aug 2019
No. of results: 522

#	Undran	Resultat
S9	**Begränsa S8 till Akademiska tidskrifter**	**522**
S8	S1 OR S5 Avgränsare - Publikationsdatum: 19980101-20191231 Begränsa genom att Language: - english	583
S7	S1 OR S5	648
S6	S1 OR S5	682
S5	S2 AND S3 AND S4	499
S4	neuropsychiatric or neuro-psychiatric	39,543
S3	autoimmune or acute or acute-onset or recent-onset	99,894
S2	p#ediatric or p#ediatric-onset or childhood or childhood-onset or children or child	845,644
S1	TI ("pans" OR "pandas") OR AB ("pans" OR "pandas")	365

Database: The Cochrane Library
Date: 22 Aug 2019
No. of results: 95
Cochrane reviews 1
Trials 94

ID	Search	Hits
#1	("pans" OR "pandas"):ti,ab,kw	63
#2	(p*ediatric or p*ediatric-onset or childhood or childhood-onset or children or child):ti,ab,kw	142,848
#3	(autoimmune or acute or acute-onset or recent-onset):ti,ab,kw	131,348
#4	(neuropsychiatric or neuro-psychiatric):ti,ab,kw	2,931
#5	#2 AND #3 AND #4	51
#6	**#1 OR #5**	**95**

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
23 Aug 2019
Nothing relevant to the question at issue was found

A comprehensive review of reference lists brought no new records

Searches in clinicaltrials.gov and WHO ICTRP

A search in Clinicaltrials.gov (Nov 14, 2019) using the search terms AREA[ConditionSearch]: *PANDAS OR ((pediatric OR pediatric-onset OR paediatric-onset OR childhood OR childhood-onset OR children OR child) AND (autoimmune OR acute OR acute-onset OR recent-onset) AND (neuropsychiatric OR neuro-psychiatric))* **identified 27 studies.**

A search in WHO ICTRP (**Nov 14, 2019**) identified a total of 356 trials using the search terms:
condition, Recruitment status ALL:
(pediatric AND autoimmune) OR (pediatric AND acute) OR (pediatric AND acute-onset) OR (pediatric AND recent-onset)
OR
(pediatric-onset AND autoimmune) OR (pediatric-onset AND acute) OR (pediatric-onset AND acute-onset) OR (pediatric-onset AND recent-onset)
OR
(childhood AND autoimmune) OR (childhood AND acute) OR (childhood AND acute-onset) OR (childhood AND recent-onset)
OR
(childhood-onset AND autoimmune) OR (childhood-onset AND acute) OR (childhood-onset AND acute-onset) OR (childhood-onset AND recent-onset)
OR
(children AND autoimmune AND neuropsychiatric) OR (children AND acute AND neuropsychiatric) OR (children AND acute-onset AND neuropsychiatric) OR (children AND recent-onset AND neuropsychiatric)
OR
PANDAS OR PANS
identified 356 trials.

Reference lists

Included studies:

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Project: Treatment within the research condition of PANS/PANDAS
Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Length of follow-up	Study Groups; Intervention vs control	Patients	Age, years Mean (SD)	Men Percentage	Outcome variables
Brown 2017a USA	Cohort study	Retrospective study Data collection September 2012 - January 2016	Acute neuropsychiatric deteriorations treated: with corticosteroids vs without corticosteroids	PANS/ PANDAS n=98	At PANS onset: I: 8.6 (3.2) C: 7.8 (3.8)	I: 67% C: 57%	Duration of acute neuropsychiatric deteriorations Complications Based on review of medical records
Brown 2017b USA	Cohort study	Retrospective study Data collection September 2012 - October 2016	Acute neuropsychiatric deteriorations treated: with prophylactic NSAID/ NSAIDs within 30 days vs without NSAID	PANS/ PANDAS n=95	At PANS onset: 7.90 (3.44)	61%	Duration of acute neuropsychiatric deteriorations Complications Based on review of medical records
Garvey 1999 USA	Randomised cross-over study	4 months penicillin 4 months placebo	Penicillin V vs Placebo	PANDAS n=37	9.61 (2.59)	73%	Care staff ratings of level of functioning (CGAS, NIMH) and symptoms (CY-BOCS, YGTSS)
Murphy 2017 USA	RCT	4 weeks	Azithromycin vs Placebo	PANS n=32	8.26 (2.78)	63%	Care staff ratings of level of functioning (CGAS) and symptoms (CY-BOCS, YGTSS CGI-S, CGI-I) Parent-rated symptoms: (SNAP-IV, CALS, SCARED), complications
Perlmutter 1999 USA	RCT	1 month	IVIG/Plasma exchange vs Placebo	PANDAS n=30	I: 9.1 (2.4) (IVIG), 10.3 (2.8) (plasma exchange) C: 9.4 (2.3)	63%	Care staff ratings of level of functioning (CGAS, NIMH) and symptoms (CY-BOCS, CGI). Additional scales for global functioning, anxiety, depression and emotional lability

Project: Treatment within the research condition of PANS/PANDAS
Appendix 2 – Characteristics of included studies

Author Year Country	Study design	Length of follow-up	Study Groups; Intervention vs control	Patients	Age, years Mean (SD)	Men Percentage	Outcome variables
Snider 2005 USA	Before/after study (using data from an RCT comparing penicillin V versus azitromycin)	1 retrospective baseline year compared with 1 prospective study year	Azithromycin/penicillin V prophylaxis vs No antibiotics	PANDAS n=23	7.9 (1.3)	65%	Number of neuropsychiatric exacerbations
Williams 2016 USA	RCT	6 weeks	IVIG vs. Placebo	PANS/ PANDAS n=35	I: 8.99 (2.37) C: 9.61 (2.32)	I: 70% C: 61%	Care staff ratings of symptoms (CY-BOCS, CGI-I)

C = comparison, CALS = Children's Affective Lability Scale, CGAS= Children's Global Assessment Scale, CGI-S/I = Clinical Global Impression Severity/Improvement Scale, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale, I = intervention, IVIG = Intravenous immunoglobulin, NIMH= National institute of mental health, NSAID = non-steroid anti-inflammatory drug, PANDAS = Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections, PANS = Pediatric Acute-onset Neuropsychiatric Syndrome, RCT = randomised controlled trial, SCARED = Screen for Childhood Anxiety-Related Emotional Disorders, SNAP-IV = Swanson, Nolan, and Pelham-IV Parent Scale, YGTSS = Yale Global Tic Severity Scale

Project: Treatment within the research condition of PANS/PANDAS
Appendix 3 - Excluded articles

Author Year	Reason for exclusion
Calaprice 2018	Wrong P (2-38 years)
Cooperstock 2017	Wrong design (guidelines)
Demesh 2015	Wrong I (tonsillectomy)
Farhood 2016	Wrong design (systematic review)
Farmer 2018	Wrong I (validation study)
Frankovich 2017	Wrong design (guidelines)
Frankovich 2018	C missing, outcome not complications
Hesselmark 2019	Wrong P (mix of suspected and confirmed PANS), no C
Johnson 2019	Wrong I (no intervention), no C (no comparison), symptom description
Leon 2018	C missing
Lepri 2019	C missing, no systematic information about complications
McClelland 2015	Wrong design (qualitative study)
Murphy 2013	Wrong I (tonsillectomy)
Murphy 2015	Wrong P (OCD and/or tics)
Pavone 2014	Wrong I (tonsillectomy)
Rosa 2018	Wrong I (food)
Sigra 2018	Wrong design (systematic review)
Spartz 2017	C missing
Thienemann 2017	Wrong design (guidelines)

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.1
Outcome variable: Level of functioning

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Antibiotic versus no antibiotic treatment									
Garvey 1999 USA	Randomised cross-over study	PANDAS n=37	5 dropouts	**Pencillin V** **CGAS** mean (SD) Baseline: 74.27 (10.83) 4 months:76.36 (10.31) Between-groups comparison at 4 months: P=0.41 **NIMH Global Scale** mean (SD) Baseline: 4.21 (1.41) 4 months: 4.48 (1.82) Between-groups comparison at 4 months: P=0.39	**Placebo** **CGAS** mean (SD) Baseline: 74.27 (10.83) 4 months: 78.86 (11.67) **NIMH Global Scale** mean (SD) Baseline: 4.21 (1.41) 4 months: 4.33 (1.76)	19 randomised to penicillin followed by placebo; 18 randomised to placebo followed by penicillin Dose: Penicillin V 250 mg x 2 during 4 months During the first two years of the study, throat culture was evaluated monthly, and open label antibiotics provided irrespective of treatment group if found positive. During the third year, physicians and parents were blinded to the results of the routine culture. No significant difference in the number of streptococcal infections was found between the treatment periods	-	-	-

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.1
Outcome variable: Level of functioning

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Murphy 2017 USA	RCT	PANS n=32 I=18 C=14	One in the intervention group was removed from the analysis due to food refusal as primary presentation One in the placebo group did not complete week 4	**Azithromycin** **CGAS** mean (SE) Baseline: 46.07 (2.03) Week 4: 53.71 (2.03) Between-groups comparison at week 4: NS	**Placebo** **CGAS** mean (SE) Baseline: 49.07 (2.24) Week 4: 52.68 (2.27)	Dose: Azithromycin 10 mg/kg (max 500 mg/day)	?	-	-
Immunomodulating versus no immunomodulating treatment									
Perlmutter 1999 USA	RCT	PANDAS n=30 I: n=10 (IVIG); n=10 (plasma exchange) C: n=10	1 dropout 2 lost to follow-up	**IVIG** **CGAS** mean (SD) Baseline: 56.0 (9.7) 1 month: 67.4 (12.1) Change from baseline NS Between-groups comparison not reported **Plasma exchange:** **CGAS** mean (SD) Baseline: 56.0 (13.1) 1 month: 73.0 (15.3) Change from baseline NS Between-groups comparison not reported	**Placebo** **CGAS** mean (SD) Baseline: 58.3 (10.5) 1 month: 59.9 (11.4) Change from baseline NS	Dose given in the study: IVIG 2 g/kg Plasma exchange: 5-6 times Placebo given as sham IVIG Plasma exchange group not blinded Patients in the placebo group who did not improve during study treatment were offered active treatment About 70% of patients had concomitant psychotropic drugs	?	-	-

C = comparison, CGAS= Children's Global Assessment Scale Scale (score 1-100, with high scores indicating better functioning), I = intervention, IVIG = Intravenous immunoglobulin, NIMH= National institute of mental health (Information on minimum and maximum values is not provided in the publication), NS = not significant (P-value not provided in publication); PANDAS = Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections, PANS = Pediatric Acute-onset Neuropsychiatric Syndrome, RCT = randomised controlled trial, SD = standard deviation, SE = standard error of the mean

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.2
Outcome variable: Symptom change (reported by patients, caregivers and care staff)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Anti-inflammatory versus no anti-inflammatory treatment									
Brown 2017a USA	Cohort study	PANS/ PANDAS n=98	Not applicable	**Corticosteroid** 85 acute neuropsychiatric deteriorations **Duration of acute neuropsychiatric deterioration** mean (SD) All deteriorations: 6.4 (5.0) weeks Between-groups comparison: P<0.01 (controlled for covariates) First deterioration: 10.3 (5.7) weeks Between-groups comparison: P<0.01 (controlled for covariates)	**No corticosteroid** 318 acute neuropsychiatric deteriorations **Duration of acute neuropsychiatric deterioration** mean (SD) All deteriorations: 11.4 (8.6) weeks First deterioration: 16.5 (9.6) weeks	102 courses of oral corticosteroids were given to 54 patients Course doses: 1–2 mg/kg orally for 5 days (max dose 60 mg x 2) Multilevel linear model accounting for within-subject correlation, with the covariates: age, gender, weeks of PANS, other treatments	?	-	?
Brown 2017b USA	Cohort study	PANS/ PANDAS n=95	Not applicable	**NSAID early treatment** 43 acute neuropsychiatric deteriorations **Difference in duration of acute neuropsychiatric deterioration compared to *No NSAID*** 2.56 fewer weeks compared to placebo (95% CI: 0.43 to 4.68 fewer weeks), P=0.018 **NSAIDs prophylaxis** 76 acute neuropsychiatric deteriorations **Difference in duration of acute neuropsychiatric deterioration compared to *No NSAID*** 4.05 fewer weeks compared to placebo (95% CI: 1.85 to 6.24 fewer weeks), P<0.0001	**No NSAID** 271 acute neuropsychiatric deteriorations **Duration of acute neuropsychiatric deterioration** 12.2 weeks (95% CI: 9.3 to 15.1)	Doses: Naproxen 10 mg/kg x 2 (max 500 mg/dose) Ibuprofen 10 mg/kg x 3-4 (max 600 mg/dose) Celecoxib max 50–100 mg x 2 Multilevel linear model accounting for within-subject correlation, with the covariates: age, gender, weeks of PANS, other treatments	?	-	?

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.2
Outcome variable: Symptom change (reported by patients, caregivers and care staff)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Antibiotic treatment versus no antibiotic treatment									
Garvey 1999 USA	Randomized cross over study	PANDAS n=37	5 dropouts	**Penicillin V** **CY-BOCS** mean (SD) Obsessions: Baseline: 4.40 (3.93) 4 months: 3.27 (4.11) Between-groups comparison at 4 months: P=0.16 Compulsions: Baseline: 3.91 (4.46) 4 months: 2.52 (3.90) Between-groups comparison at 4 months: P= 0.08 **YGTSS** mean (SD) Baseline: 15.36 (9.03) 4 months: 13.39 (10.65) Between-groups comparison at 4 months: P=0.28	**Placebo** **CY-BOCS** mean (SD) Obsessions: Baseline: 4.40 (3.93) 4 months: 3.96 (5.08) Compulsions: Baseline: 3.91 (4.46) 4 months: 2.96 (4.93) **YGTSS** mean (SD) Baseline: 15.36 (9.03) 4 months: 12.97 (9.49)	19 randomised to penicillin followed by placebo; 18 randomised to placebo followed by penicillin Dose: Penicillin V 250 mg x 2 during 4 months No significant difference in the number of streptococcal infections between treatment periods During the first two years of the study, throat culture was evaluated monthly, and open label antibiotics provided irrespective of treatment group if found positive. During the third year, physicians and parents were blinded to the results of the routine culture. No significant difference in the number of streptococcal infections was found between the treatment periods	-	-	-

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.2
Outcome variable: Symptom change (reported by patients, caregivers and care staff)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Murphy 2017 USA	RCT	PANS n=32 I=18 C=14	One in the intervention group was removed from the analysis due to food refusal as primary presentation One in the placebo group did not complete week 4	**Azithromycin** **CGI-S** mean (SE) Baseline: 5.24 (0.23) Week 4: 4.06 (0.23) Between-groups comparison at week 4: P<0.01 **CY-BOCS** mean (SE) Baseline: 29.47 (1.85) Week 4: 20.53 (1.85) Between-groups comparison at week 4: NS **YGTSS** mean (SE) Baseline: 10.88 (1.98) Week 4: 6.82 (1.98) Between-groups comparison at week 4: NS	**Placebo** **CGI-S** mean (SE) Baseline: 5.00 (0.25) Week 4: 4.93 (0.25) **CY-BOCS** mean (SE) Baseline: 28.43 (2.04) Week 4: 23.45 (2.09) **YGTSS** mean (SE) Baseline: 13.21 (2.18) 4 weeks: 8.40 (2.23)	Primary outcome: CGI-S, CY-BOCS Secondary outcome: YGTSS Dose: Azithromycin 10 mg/kg (max 500 mg/day) Parent-rated scales were used in this study (SNAP-IV, CALS, SCARED), none of these with a significant difference between the treatment groups	?	-	-
Snider 2005 USA	Before/after study (using data from an RCT comparing penicillin V versus azitromycin)	PANDAS n=23	One dropout at month 3 excluded in the analysis	**Penicillin V** **Neuropsychiatric exacerbations** mean number (SD) Study year: 0.5 (0.5) Before/after comparison: P<0.01 **Azithromycin** **Neuropsychiatric exacerbations** mean number (SD) Study year: 0.9 (0.5) Before/after comparison: P<0.01	**No penicillin V** **Neuropsychiatric exacerbations** mean number (SD) Baseline year: 2.1 (1.0) **No azithromycin** **Neuropsychiatric exacerbations** mean number (SD) Baseline year: 1.8 (0.6)	Prospectively collected data during 12 months of prophylactic treatment with either penicillin V or azithromycin, compared with retrospectively collected data from the preceding “baseline” year Dose: Penicillin V 250 mg x 2 Azithromycin 250 mg x 2 on one day of the week Significant decrease in streptococcal infections in the study year for both groups	?	-	-

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.2
Outcome variable: Symptom change (reported by patients, caregivers and care staff)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Immunomodulating versus no immunomodulating treatment									
Perlmutter 1999 USA	RCT	PANDAS n=30 I: n=10 (IVIG); n=10 (plasma exchange) C: n=10	1 dropout and 2 lost to follow-up	**IVIG** **CY-BOCS** mean (SD) Baseline: 26.7 (5.9) 1 month: 14.7 (10.8) Change from baseline: P<0.05 **TSURS** mean (SD) Baseline: 6.8 (9.2) 1 month: 5.5 (7.7) Change from baseline: NS **Global impairment** mean (SD); scale not described Baseline: 8.7 (1.0) 1 month: 5.8 (1.9) Change from baseline: P<0.05 **Global severity** mean (SD); scale not described Baseline: 4.7 (0.8) 1 month: 3.4 (1.2) Change from baseline: P<0.05 Between-groups comparisons not reported **Plasma exchange** **CY-BOCS** mean (SD) Baseline: 22.5 (13.4) 1 month: 9.5 (10.1) Change from baseline: P<0.05 **TSURS** mean (SD) Baseline: 21.7 (14.7) 1 month: 11.0 (9.2)	**Placebo** **CY-BOCS** mean (SD) Baseline: 23.0 (13.6) 1 month: 22.1 (13.1) Change from baseline: NS **TSURS** mean (SD) Baseline: 11.0 (9.5) 1 month: 9.7 (9.1) Change from baseline: NS **Global impairment** mean (SD); scale not described Baseline: 7.7 (1.6) 1 month: 7.7 (1.6) Change from baseline: NS **Global severity** mean (SD); scale not described Baseline: 4.8 (0.4) 1 month: 4.8 (0.5) Change from baseline: NS	Dose given in the study: IVIG 2 g/kg Plasma exchange: 5-6 times Placebo given as sham IVIG Plasma exchange group not blinded After the placebo period, patients were offered active treatment About 70% of patients had concomitant psychotropic drugs	?	-	-

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.2
Outcome variable: Symptom change (reported by patients, caregivers and care staff)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
				Change from baseline: P<0.05 **Global impairment** (mean (SD), scale not described) Baseline: 8.0 (2.7) 1 month: 5.2 (2.3) Change from baseline: P<0.05 **Global severity** mean (SD), scale not described) Baseline: 5.0 (0.9) 1 month: 3.2 (1.0) Change from baseline: P<0.05 Between-groups comparisons not reported					
Williams 2016 USA	RCT	PANS/ PANDAS n=35 I=17 C=18	None during the double blind phase	**IVIG** **CY-BOCS** mean (SD) Baseline: 26.47 (5.14) Week 6: 20.59 (10.12) Between-group comparison at week 6: P=0.44 **CGI-I** mean (SD) Week 6: 2.88 (1.20) Between group comparison at week 6: P=0.12	**Placebo** **CY-BOCS** mean (SD) Baseline: 28.78 (3.98) Week 6: 25.67 (8.65) **CGI-I** mean (SD) Week 6: 3.53 (1.62)	Dose given in the study: IVIG: 2 g/kg Non-responders at 6 weeks (n=24) were offered IVIG All patients received prophylactic antibiotics during the study	?	-	?

C = comparison, CALS = Children's Affective Lability Scale, CGAS= Children's Global Assessment Scale, CGI-I = Clinical Global Impression Improvement Scale (Score 1-7 where 1 is very much improved and 7 is very much worse), CGI-S = Clinical Global Impression Severity Scale (Score 1-7 where 1 is normal and 7 is the worst), CI = confidence interval, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale (Score 0-40; higher score reflects more symptoms), I = intervention, IVIG = Intravenous immunoglobulin, NIMH= National institute of mental health, NS = not significant (P-value not provided in publication), NSAID = non-steroid anti-inflammatory drug, PANDAS = Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections, PANS = Pediatric Acute-onset Neuropsychiatric Syndrome, RCT = randomised controlled trial, SCARED = Screen for Childhood Anxiety-Related Emotional Disorders, SD = standard deviation, SE = standard error of the mean, SNAP-IV = Swanson, Nolan, and Pelham-IV Parent Scale, TSURS = Tourette syndrome unified rating scale (Minimum and maximum values are missing), YGTSS = Yale Global Tic Severity Scale (Tic severity score 0-50. Higher score=more symptoms)

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.3
Outcome variable: Complications

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments
				Intervention	Control	
Anti-inflammatory versus no anti-inflammatory treatment						
Brown 2017a USA	Cohort study	PANS/ PANDAS n=98 85 flares with cortico-steroids	Not applicable	Temporary side effects in 45 out of 102 (44%) courses of steroids: Increase in obsessive-compulsive symptom (n=10), anxiety (n=16), emotional lability/moodiness (n=12), irritability/agitation (n=15), sleep disturbance (n=10), tics (n=7), aggression (n=4), urinary symptoms (n=5), mania (n=3), sensory amplification (n=3), hyperactivity (n=2), hallucinations (n=2), vision abnormalities (n=2), behavior regression (n=2), and flat affect (n=1). Of 15 patients who received >5 days or multiple courses of corticosteroids within 1 month, eight (53%) had either weight gain and/or Cushingoid features.	Not reported	AEs based on review of medical records Course doses: 1–2 mg/kg orally for 5 days (max dose 60 mg x 2)
Brown 2017b USA	Cohort study	PANS/ PANDAS n=95 57 patients with NSAID ≥1 flare In all, 119 flares with NSAID	Not applicable	19% (11/57 with NSAID ≥1 flare) had transient AEs: abdominal pain (n=5), skin rash (n=1), bruising (n=1), proteinuria (n=3), clinically insignificant transaminitis (n=1)	Not reported	AEs based on review of medical records Only patients who tolerated NSAIDs for a minimum of 7 days were included, thus excluding patients who may have had side effects in the first week of NSAID therapy Doses: Naproxen 10 mg/kg x 2 (max 500 mg/dose) Ibuprofen 10 mg/kg x 3-4 (max 600 mg/dose) Celecoxib max 50–100 mg x 2

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.3
Outcome variable: Complications

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments
				Intervention	Control	
Antibiotic treatment versus no antibiotic treatment						
Garvey 1999 USA	Randomised cross-over study	PANDAS n=37	5 dropouts	One case with discoloration of teeth reported by parent		No systematic reporting of AEs Dose: Penicillin V 250 mg x 2 during 4 months
Murphy 2017 USA	RCT	PANS n=32 I=18 C=14	One in the intervention group was removed from the analysis due to food refusal as primary presentation One in the placebo group did not complete week 4	**Azithromycin** Loose stools: 53% Increased QT in ECG: Four patients with borderline QTc (440–46(ms) at end of week 4 (two of which had borderline QTc at baseline). Within group comparison: P=0.007 Between group comparison: P=0.060	**Placebo** Loose stools: 7% Increased QT in ECG: One patient with borderline QTc at end of week 4 (also borderline QTc at baseline).	AEs collected by parent/patient report and physical examinations Dose: Azithromycin 10 mg/kg (max 500 mg/day)
Snider 2005 USA	Before/after study (using data from an RCT comparing penicillin V versus azitromycin)	PANDAS n=23	One dropout at month 3 excluded in the analysis			Prospectively collected data during 12 months of prophylactic treatment with either penicillin V or azithromycin, compared with retrospectively collected data from the preceding “baseline” year AEs were collected but not published Dose: Penicillin V 250 mg x 2 Azithromycin 250 mg x 2 on one day of the week

Project: Treatment within the research condition of PANS/PANDAS
Appendix 4.3
Outcome variable: Complications

Author year country	Study design	Number of patients	Withdrawals - dropouts	Results		Comments
				Intervention	Control	
Immunomodulating versus no immunomodulating treatment						
Perlmutter 1999 USA	RCT	PANDAS n=30 I: n=10 (IVIG); n=10 (plasma exchange) C: n=10	1 dropout from IVIG, 2 lost to follow-up	**IVIG** AEs of mild to moderate severity (n=6): nausea and vomiting (n=5), mild to moderately severe headache (n=3), low-grade fever (n=4) **Plasma exchange** Pallor/dizziness/nausea (n=7), vomiting (n=2), anxiety (n=3)	**Placebo** Mild AEs (n=2): stomachache (n=2), headache (n=1)	AEs collected by parent/patient report and physical examinations Dose given in the study: IVIG 2 g/kg Plasma exchange: 5-6 times Placebo given as sham IVIG
Williams 2016 USA	RCT	35 IVIG n=17 Placebo n=18	None during the double blind phase	**IVIG** One patient had a possible allergic reaction which resolved without complication Headache (n=8), sore throat (n=1), stomach or abdominal discomfort (n=3), nausea (n=4), vomiting (n=3), muscle/bone/joint pain (n=3), tiredness/fatigue (n=2), anxiety (n=2)	**Placebo** Headache (n=3), sore throat (n=2), stomach or abdominal discomfort (n=1), nausea (n=1), muscle/bone/joint pain (n=2), tiredness/fatigue (n=1), anxiety (n=2	AEs collected by parent/patient report and physical examinations Dose given in the study: IVIG: 2 g/kg

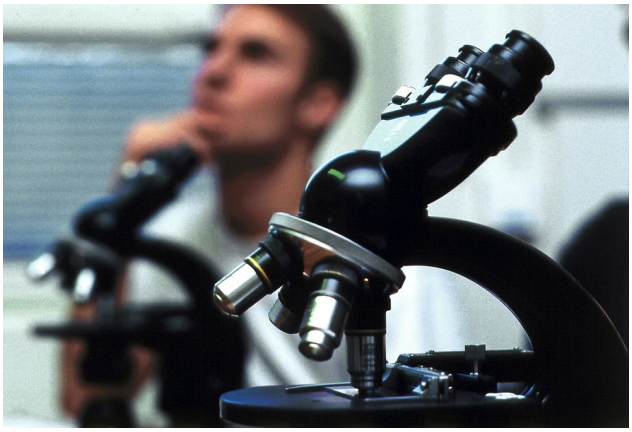
AE= adverse event, ECG = echocardiogram, IVIG = Intravenous immunoglobulin, NSAID = non-steroid anti-inflammatory drug, RCT = randomised controlled trial

Components of this Health Technology Assessment

- ☑ Description of methods
- ☑ PICO
- ☑ Full literature search
- ☑ Flowchart
- ☑ Selection based on relevance
- ☑ Quality assessment
- ☑ Data tabulation
- ☑ Evidence synthesis
- ☐ Meta-analysis
- ☑ Certainty of evidence by GRADE
- ☑ Summary
- ☑ Economical aspects
- ☑ Organisational aspects
- ☑ Ethical aspects
- ☑ Ongoing studies
- ☑ Excluded articles
- ☑ Participation of experts
- ☑ External review
- ☑ Knowledge gaps identified
- ☑ Conflict of interest reported

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

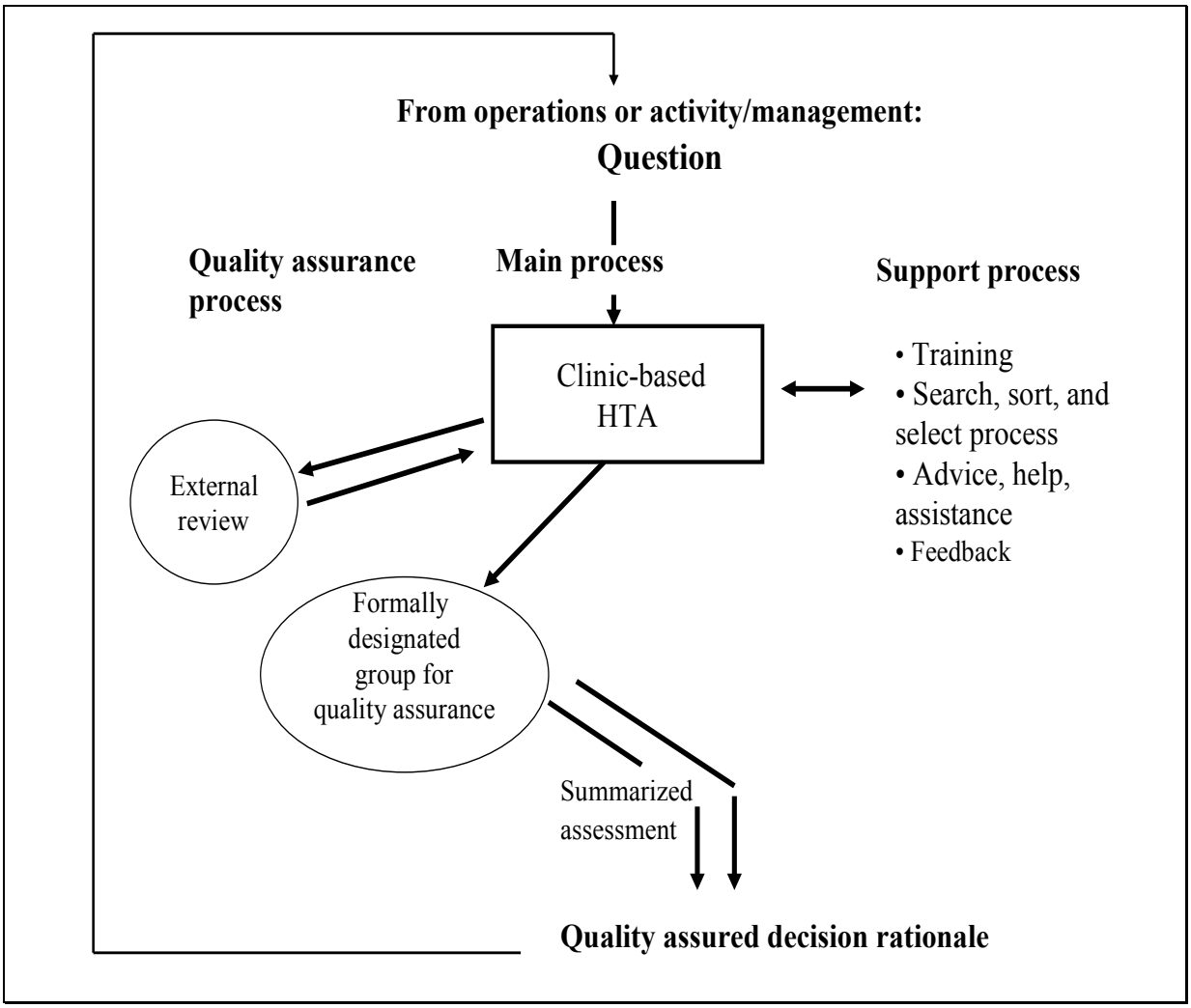
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh
Professor, MD
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset, HTA-centrum
Röda Stråket 8, 413 45 Göteborg
www.sahlgrenska.se/htacentrum