

Celiac disease: a comprehensive current review

The calendar edition



Monday

1 January

When the body's natural defense system can't tell the difference between your own cells and foreign cells, causing the body to mistakenly attack normal cells

Celiac disease (CD) is an autoimmune condition
CD is characterized by a specific



&

profile



triggered by gluten ingestion in genetically predisposed individuals.

Tuesday

2 January

Gluten is the general term for alcohol-soluble proteins present in various cereals, including



rye spelt
kamut
barley wheat

Wednesday



3 January

In recent years, there have been significant changes in the

DIAGNOSIS

pathogenesis

and natural history

of celiac disease

Thursday

4 January



There has been a greater availability of sensitive and specific screening tests

Which allows identification of the **risk groups** for CD



This led to a significant raise in diagnoses worldwide.

Friday

5 januari

HYPOTHESIS 1

of raise in diagnosis



Spread of versions of the Mediterranean diet including the consumption of very high quantities of gluten (up to 20 g/day)



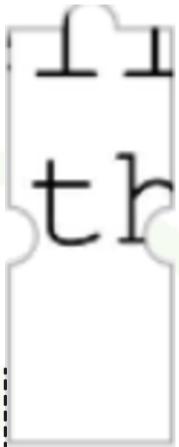
Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

6
7

january

1



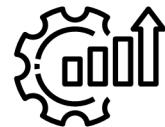
Monday

8 January

HYPOTHESIS 2

of raise in diagnosis

The production of new grain variants
due to technological rather than
nutritional reasons



Tuesday

9 January

spread of
mediterranean
diet

new grain
variants

These hypotheses have

not

been confirmed and the

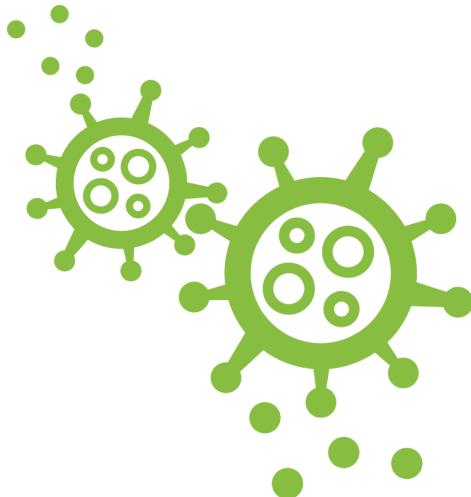
REAL CAUSE

of the risk in CD diagnoses remains

unknown

Wednesday

10 January



Similar 'epidemics' are reported for other autoimmune diseases in the Western hemisphere

CAN ENVIRONMENTAL
FACTORS OTHER THAN
GLUTEN CAN BE AT
PLAY?

Thursday
11 January

CD is one of the **most common autoimmune disorders.**

1%

With a reported prevalence of 0.5–1% of the general population.

Friday

12 January

Most CD cases remain undetected
in the absence of
serological screening
due to



HETEROGENEOUS SYMPTOMS

POOR DISEASE AWARENESS

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

13
14

January

2



Monday

15 January

CD prevalence is increasing in Western countries.

Between the years 1975 and 2000, CD prevalence increased **5-fold** in the US, for reasons that are currently unknown.

1975



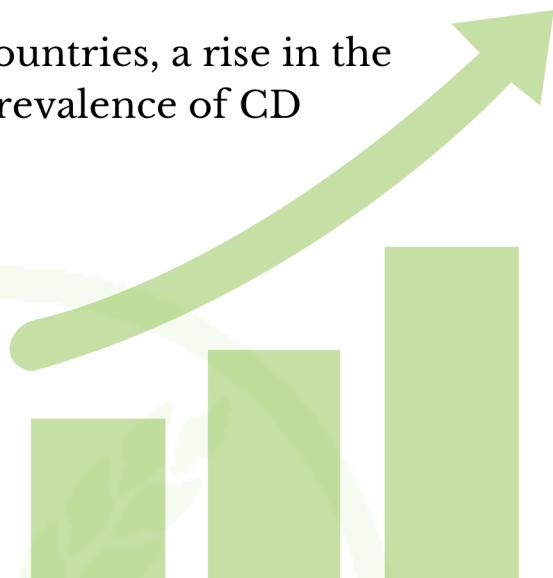
2000



Tuesday

16 January

In Western countries, a rise in the overall prevalence of CD



has been well documented, but the reason of this is **not known**

Wednesday

PREVALENCE OF CD IS
HIGHER IN

17 January



First-degree CD relatives

And other at-risk groups, particularly patients with

Down syndrome



Type 1 diabetes

IgA deficiency



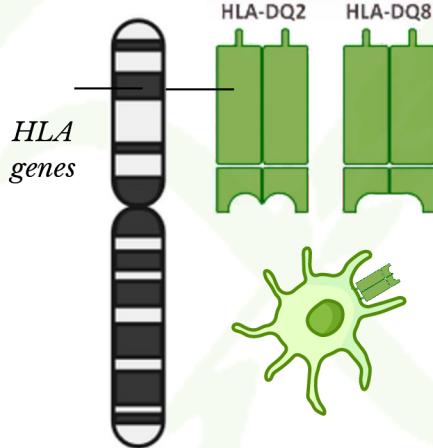
Thursday

18 January

CD is a unique autoimmune disease because of its well defined key genetic elements and environmental trigger (gluten).

KEY GENETIC ELEMENTS

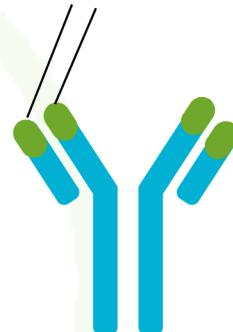
Human leukocyte antigens
(HLA-DQ2 and HLA DQ8)



Chromosome 6

&

Auto-antigen: tissue trans-glutaminase (tTG)



Antibody

Friday
19 January

A major **drawback** in CD research

has been

THE LACK

of a

reliable and reproducible



animal model

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

20
21 January

3



We
have
witnessed
an
epidemic
of
CD



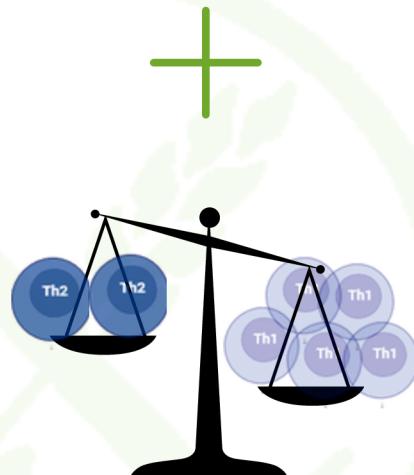
Monday 22 January

questioning
the previous
paradigm that
gluten is the
**only key
element**
dictating the
onset of the
disease in
genetically at-
risk subjects.

Tuesday 23 January

KEY ELEMENTS of the pathogenesis of the autoimmune process

adaptive immunity



imbalance between T helper 1 and 2 cell responses

Wednesday

24 January

KEY 'INGREDIENTS' OF THE CD AUTOIMMUNITY RECIPE:

- Genetic predisposition
- A pro-inflammatory innate immune response triggered by gluten
- An imbalanced gut microbiome
- Inappropriate adaptive immune response
- Loss of intestinal barrier function
- Exposure to gluten

Thursday

25 January

CD has a strong hereditary component

High familial recurrence (~10–15%)



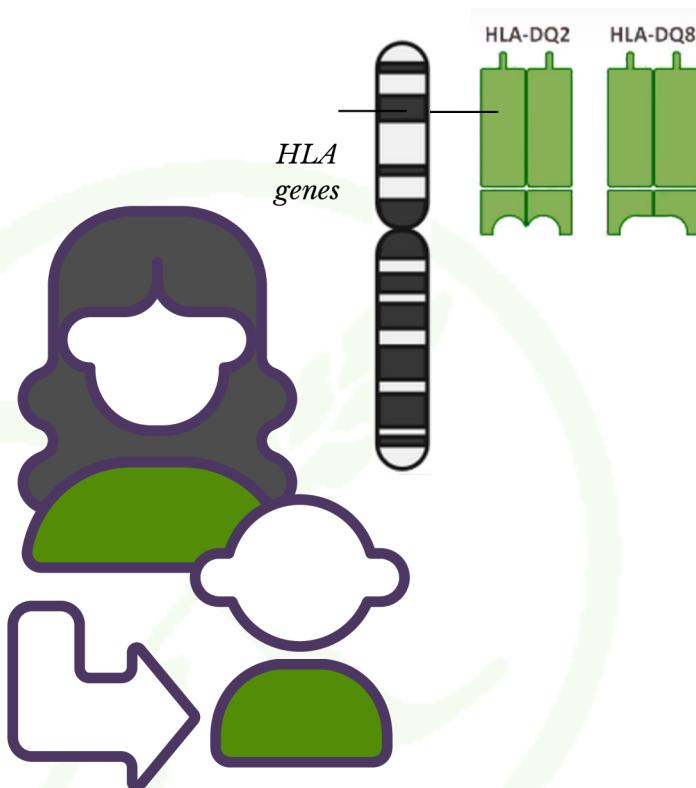
High concordance of the disease among monozygotic twins (75–80%).



Friday

26 January

There is a relevant role of HLA class II heterodimers, specifically DQ2 and DQ8, in the **heritability of CD**



WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

27
28

January

4



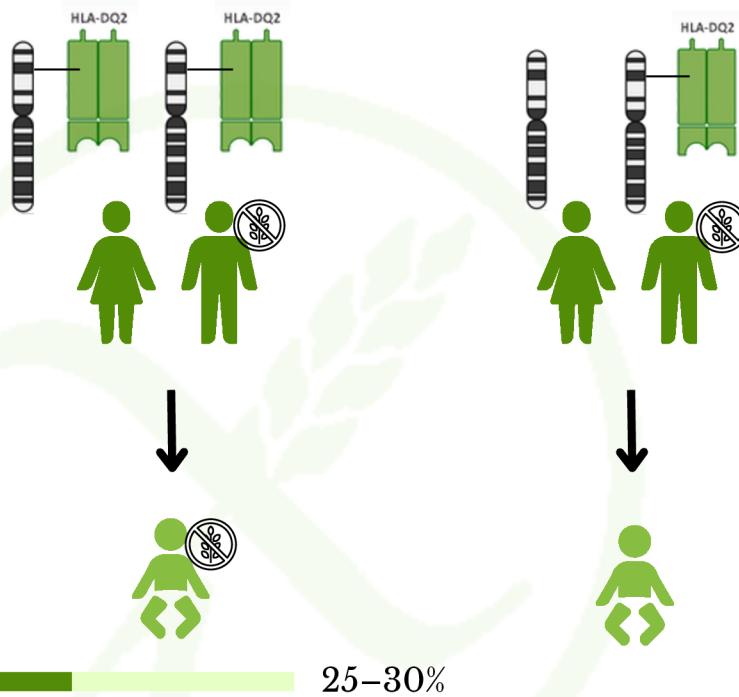
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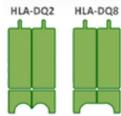
29 January

When inherited a gene from both parents

HLA-DQ2 HOMOZYGOsis

confers a much higher risk of developing **early-onset CD** in infants with a first-degree family member is affected by the disease.





Tuesday

30 January

HLA- DQ2/HLA-DQ8 is frequent among the general population (25–35%)



Only 3% of these **HLA- compatible individuals** will go on to develop CD

3%



Wednesday

31 January

10,000 YEARS AGO



During the
transition from a
nomadic lifestyle to
agricultural
settlements



Gluten-containing grains are a recent
addition to the human diet.



Thursday

1 February

These two characteristics are breaking the tolerance to this food antigen, when the immune system is activated during a bowel infection



1

Gluten is one of the few digestion-resistant proteins consumed chronically in significant quantities

2

Gluten is constituted by several non-digestible immunogenic peptides.

Friday

2 February

HYGIENE HYPOTHESIS



Improved hygiene and lack of exposure to various microorganisms

have been linked with a **steep increase** in autoimmune disorders in industrialized countries during the past

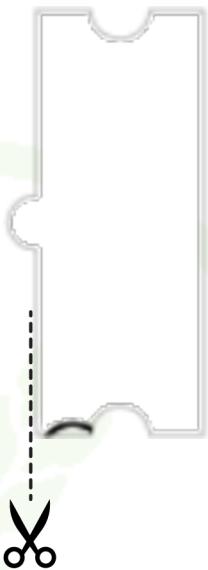
40 years

Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

3
4 February

5



Monday

THE HYGIENE HYPOTHESIS
ARGUES:

5 February

Our

LIFESTYLE

&

environmental

changes

may have

reduced

our

exposure

to

pathogens



Tuesday

6 February

The hygiene hypothesis concept can be
misleading,

while an

**'ENVIRONMENT-DEPENDENT
DYSBIOSIS HYPOTHESIS'**

would more closely reflect the **interplay**
between **host** and **environmental** pressure
dictating the balance between health and
disease

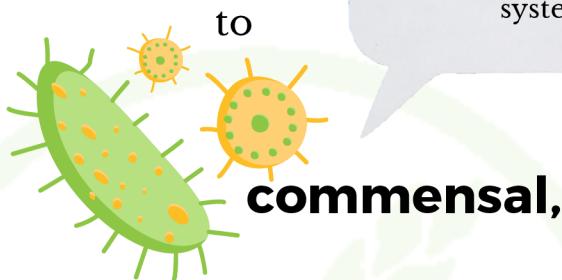


Wednesday

Broad exposure

7

February



Commensals are bacteria
that live on the waste
products on the outside of
our tissues (the digestive
system)

non-pathogenic microorganisms

early in life

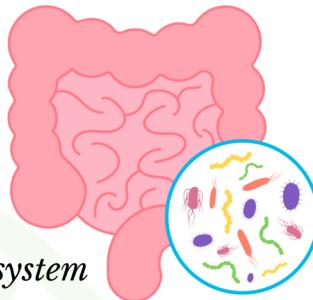
are associated with protection
against CD

Thursday

8 February



With breakthroughs in the role of the



gut microbiological ecosystem

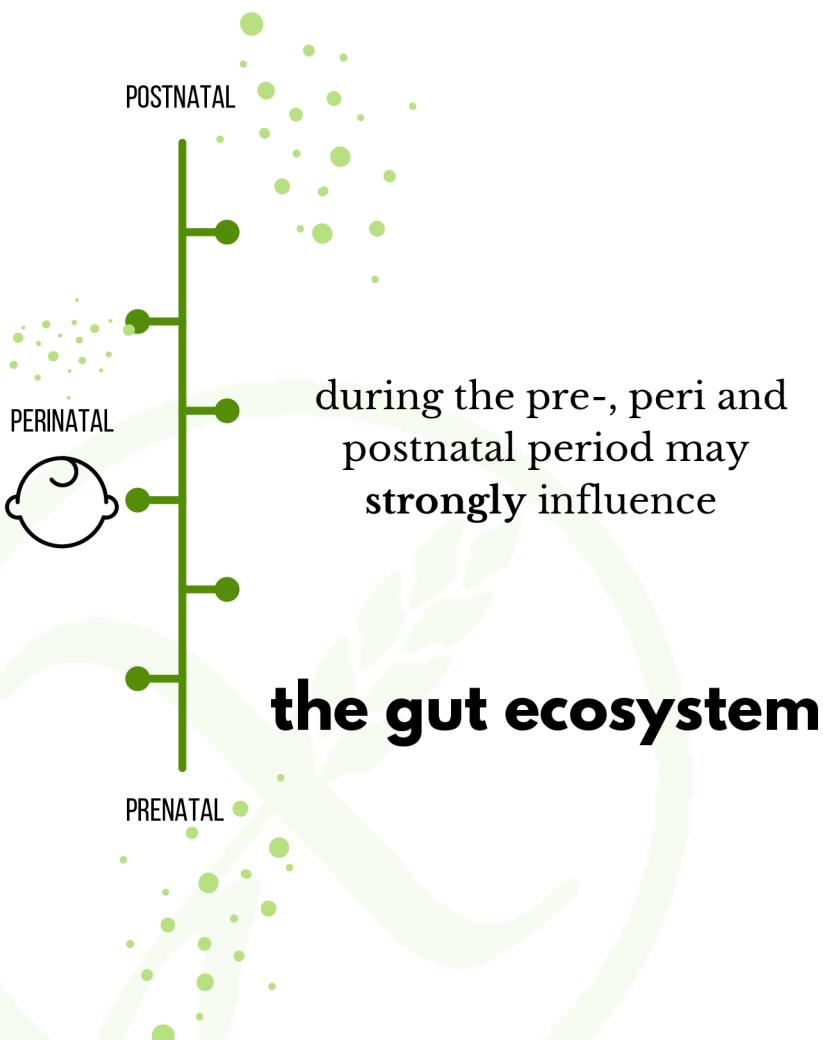
in dictating the balance between **tolerance** and
immune response leading to autoimmunity

the hygiene hypothesis is under
scrutiny...

Friday

9 February

Environmental factors

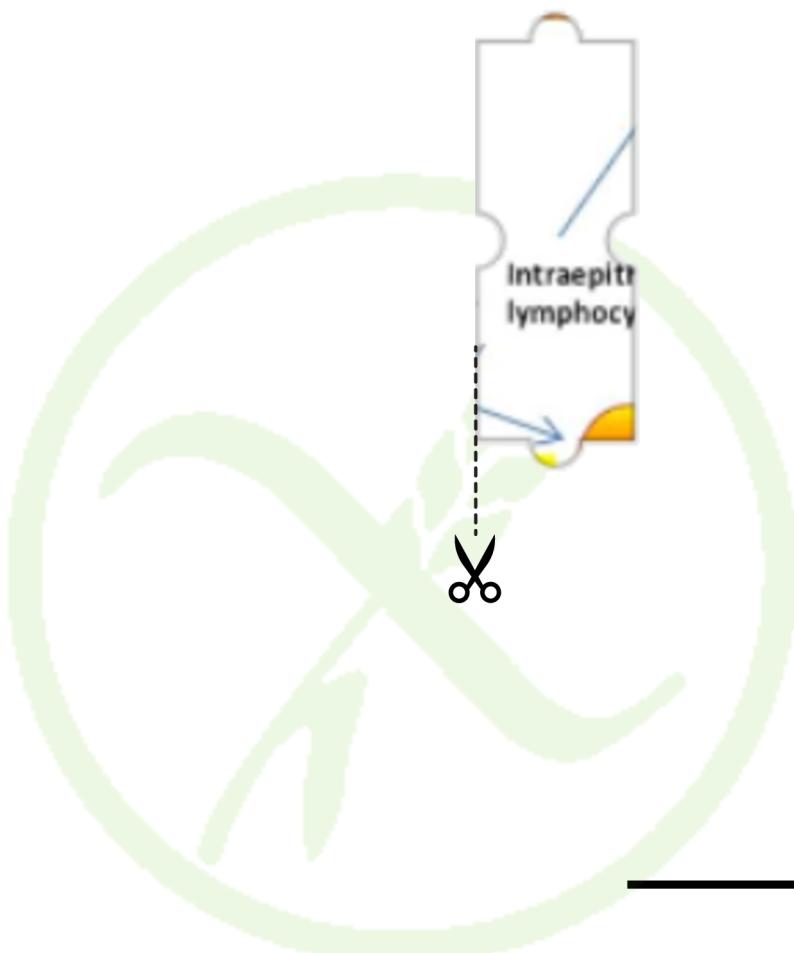


WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

10
11 February

6



Monday

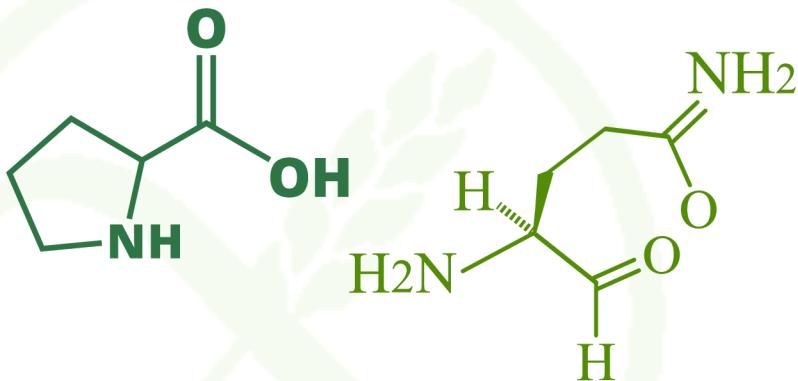
12 February

Gliadins



are key components of gluten.

They are **complex proteins** unusually rich in prolines and glutamines



and are **not** completely digestible by
intestinal enzymes

Tuesday
13 February

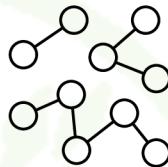
The final product



of a partial digestion of gliadins



is a mix of peptides that can trigger host responses



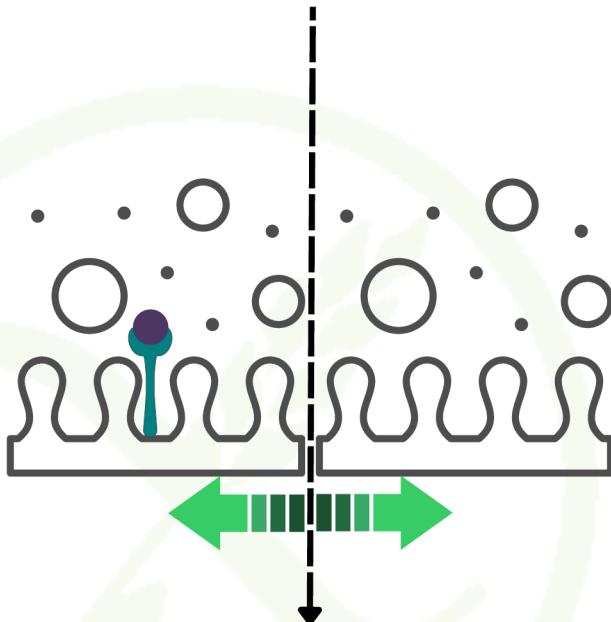
- increased gut permeability
- innate and adaptive immune response

Wednesday

14 February

Gliadin

can cause an **immediate** and transient increase
in intercellular tight junction permeability of
intestinal epithelial cells

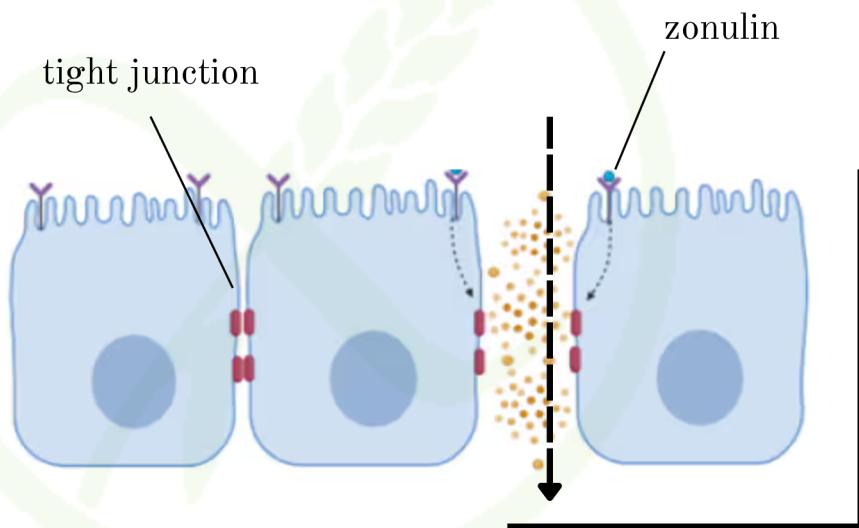


Thursday 15 February

The increased permeability effect of gliadin has been linked to the release of

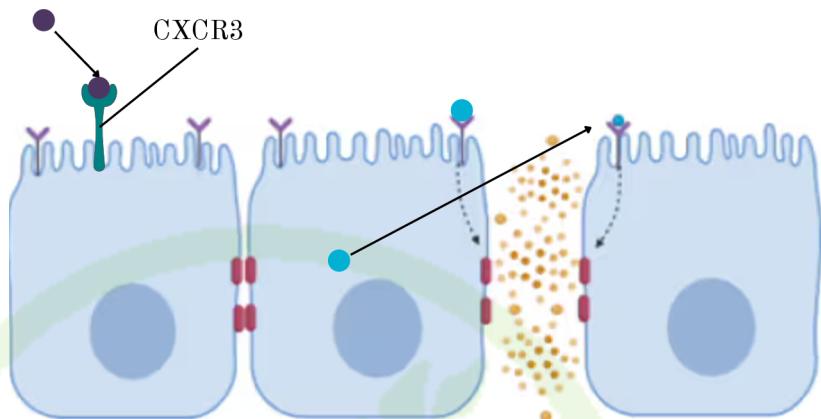
ZONULIN

a family of molecules that increases paracellular permeability by causing tight junction disassembly.



Friday
16 February

Gliadin binds to chemokine 3
receptor (CXCR3)



with subsequent zonulin release

Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

17
18

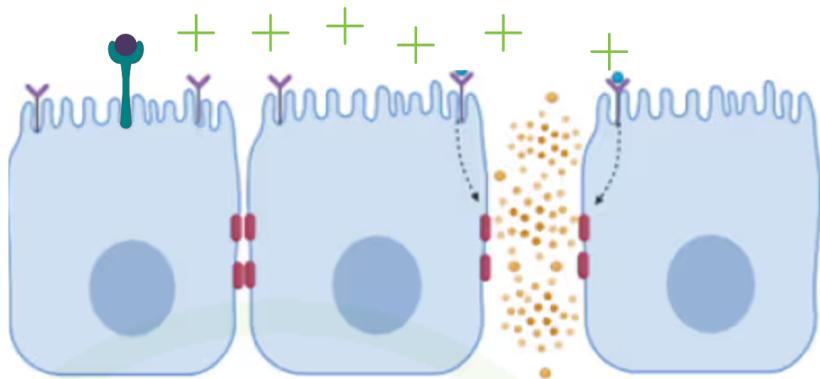
February

7



Monday

19 February

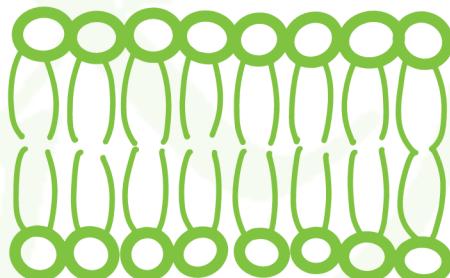
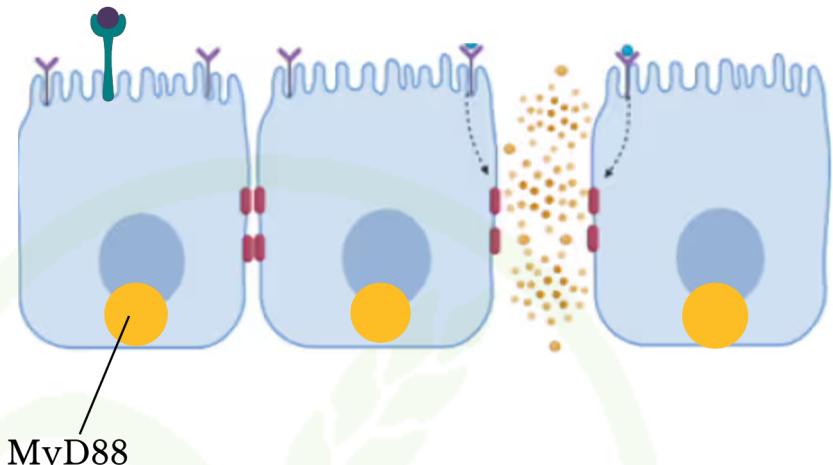


Gliadin enhances zonulin-dependent increased gut paracellular permeability

irrespective of disease status

Tuesday 20 February

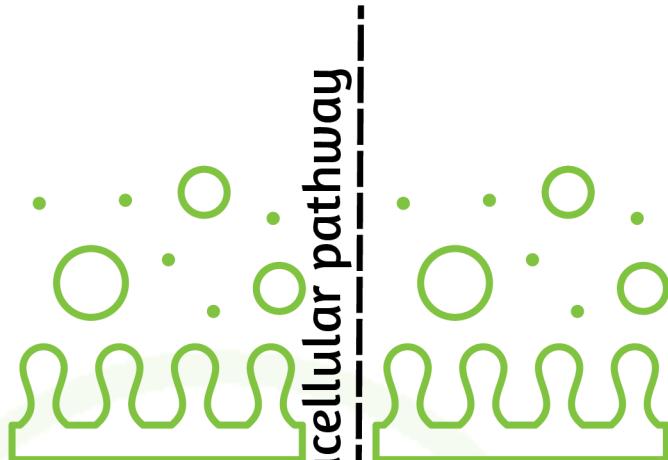
Gliadin caused a *myeloid differentiation primary response 88-dependent* (MyD88) increase



Wednesday

21 February

The involvement of the



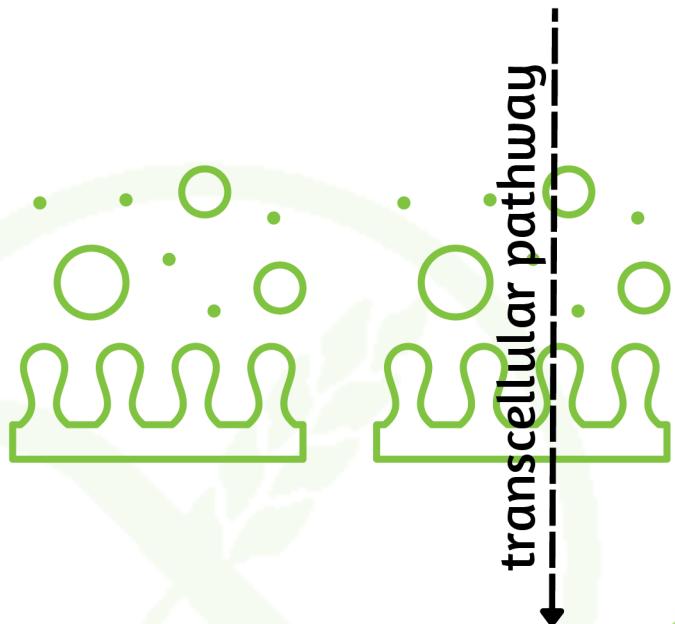
for gluten
trafficking in the

LAMINA PROPRIA

has also been linked to an association of some
tight junction genes with CD

Thursday
22 February

Gluten can also cross the intestinal barrier through the transcellular pathway



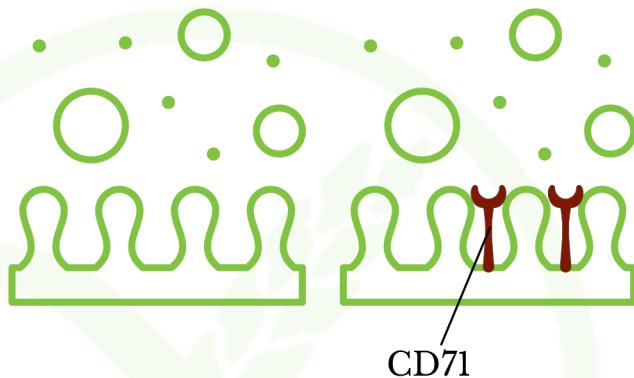
once tolerance to gluten has been *broken*.

Friday

23 February

The transferrin receptor CD71 is overexpressed on the

LUMINAL SIDE



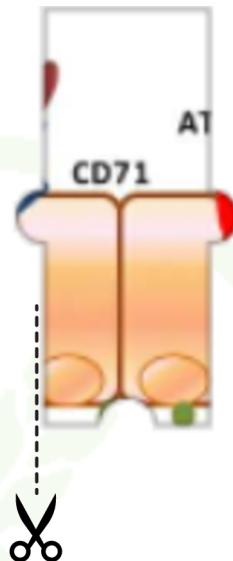
in CD patients during the acute phase of the disease

Sat + Sun

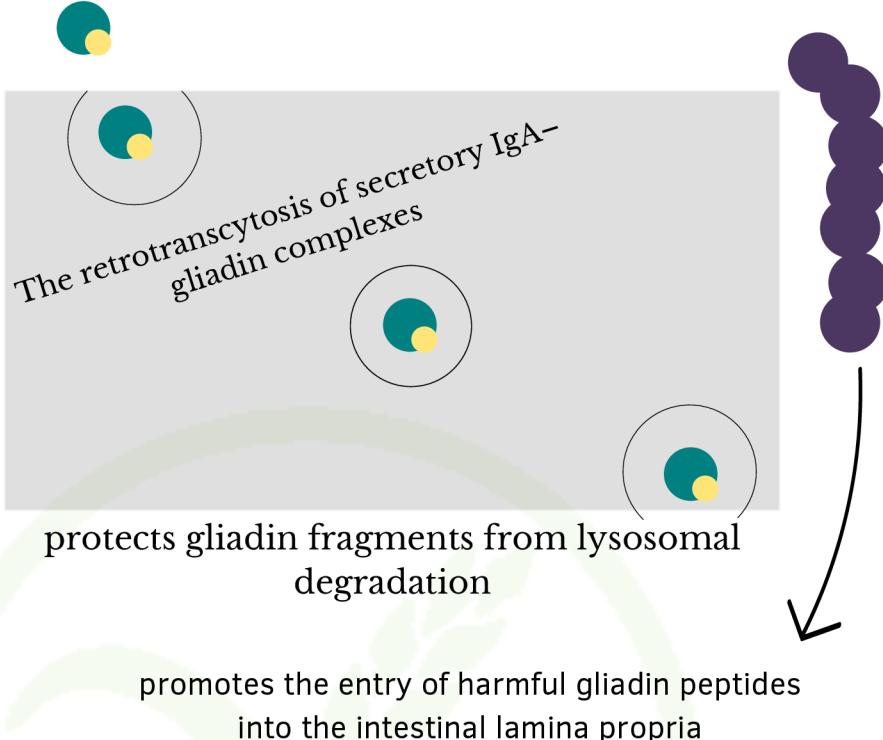
24
25

February

8



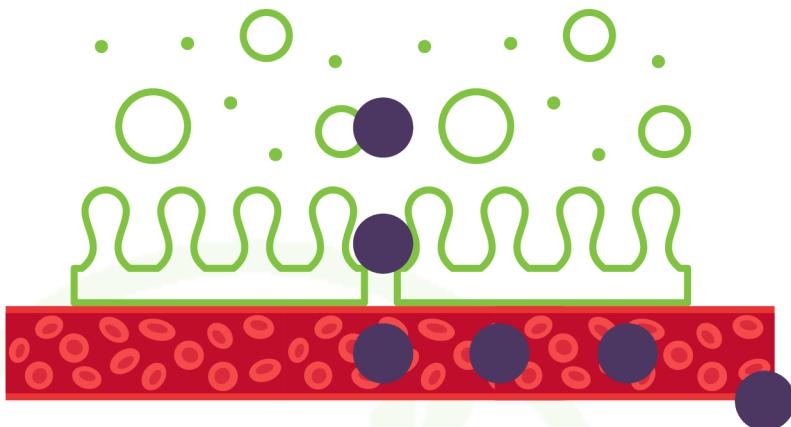
Monday 26 February



Thereby perpetuating **intestinal inflammation** initiated by the paracellular passage of these peptides.

Tuesday 27 February

Because of their resistance, the gluten immunogenic peptides (GIP) can cross the defective epithelial lining,



reach the blood stream (thus extending the inflammatory process),

and finally be excreted with the urine.



Wednesday

INNATE IMMUNITY

28 February

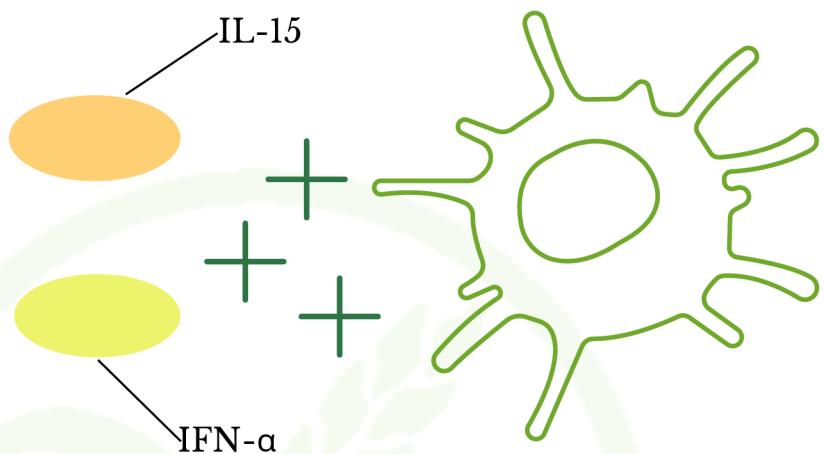


PLAYS A CRITICAL ROLE

in initiating CD

Thursday 29 February

Cytokines such as
interleukin (IL)-15 and
interferon α



can prime the innate immune response by polarizing dendritic cells and intraepithelial lymphocyte function.

Friday

1

March

GLIADIN PEPTIDES MAY INDUCE:

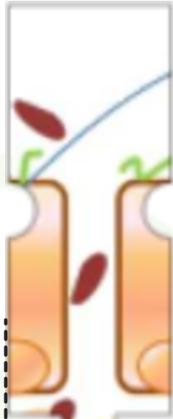
- Epithelial growth factor
- IL-15- dependent proliferation of enterocytes
- Structural modifications
- Vesicular trafficking alterations
- Signalling and proliferation
- Stress/innate immunity activation.

Sat + Sun

2
3

March

9

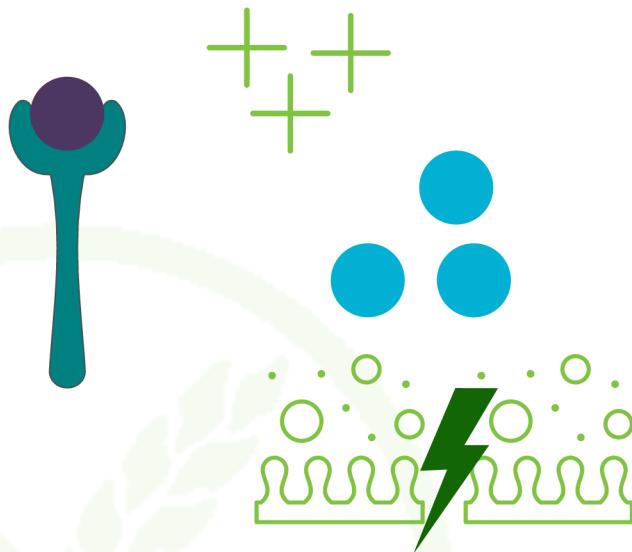


Monday

4

March

INITIATING CD ENTEROPATHY



- 1 Mucosal events, along with the functional breach of epithelial barrier function secondary to the gliadin-mediated zonulin release

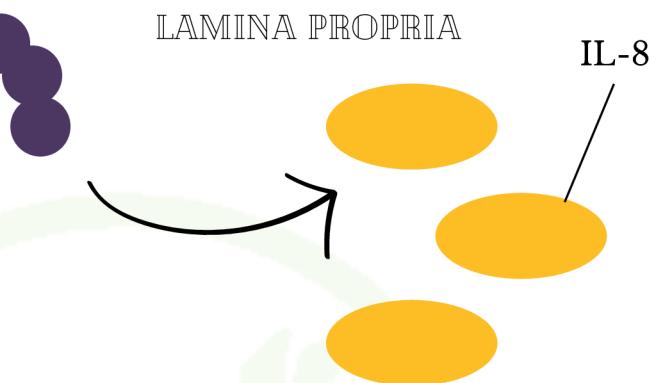
Tuesday

5

March

INITIATING CD ENTEROPATHY

2



The subsequent access of toxic peptides in the lamina propria, and gliadin-induced production of high levels of the neutrophil-activating and chemoattractant chemokine IL-8

GLIADIN

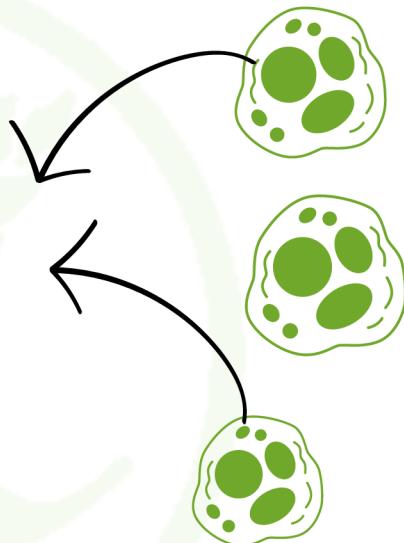
Wednesday

6

March

exerts a direct neutrophil chemoattractant effect by interacting with

fMet-Leu-Phe receptor 1



Thursday

7

March

The false adaptive immune response
consequence

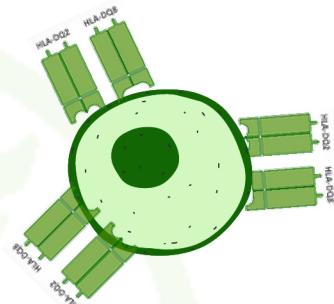
of a

highly specific interplay between

selected gluten peptides



and



major histocompatibility complex
class II HLA-DQ2/8-antigen
restricted T cells

plays a paramount role in CD pathogenesis

Friday

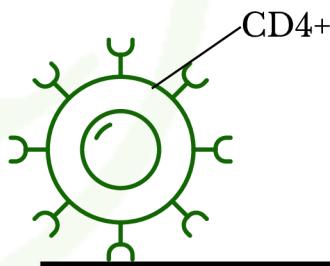
8

March



Dependent on the post-translational deamidation of gluten peptides by transglutaminase 2 (TG2), .

the interplay between gluten peptides and HLA complexes is influenced by the initial imprinting of the innate immune system through IL-15 upregulation that promotes the CD4+ T cell adaptive immune response



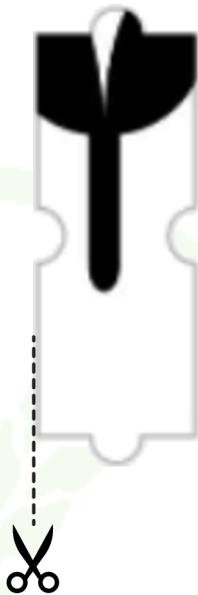
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

9
10

March

10

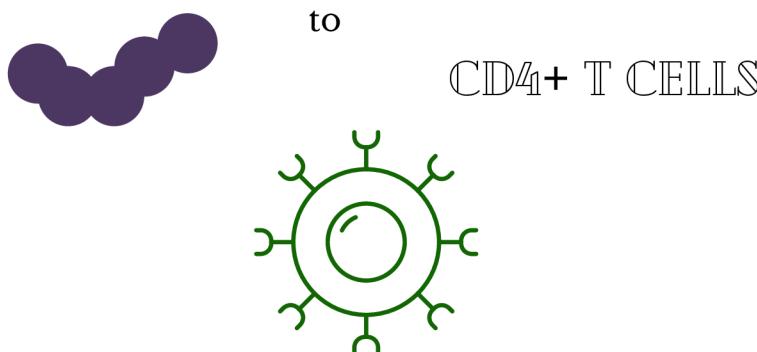


Monday

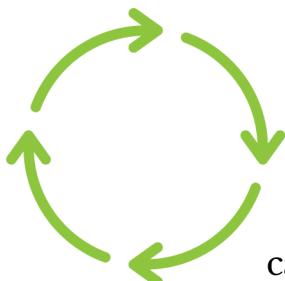
11 March

Presentation of

GLUTEN



carried out by **dendritic cells** as well as **macrophages, B cells, and even enterocytes** expressing *HLA class II*,



can cause their recirculation in the lamina propria.

Tuesday

12 March

The contact of CD4+ T cells in the lamina propria with gluten



induces their activation and proliferation

with production of

PROINFLAMMATORY CYTOKINES

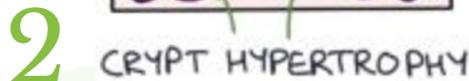
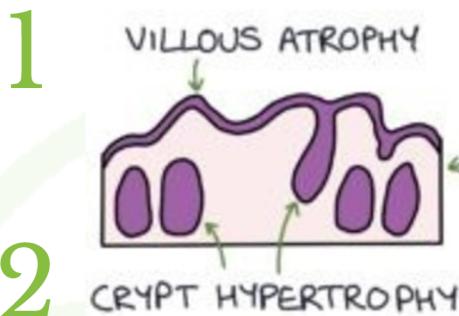
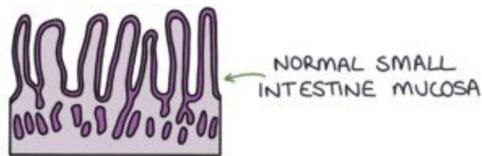
METALLOPROTEASES

AND KERATINOCYTE GROWTH FACTOR BY
STROMAL CELLS

Wednesday

Production
by stromal cells
induces

13 March



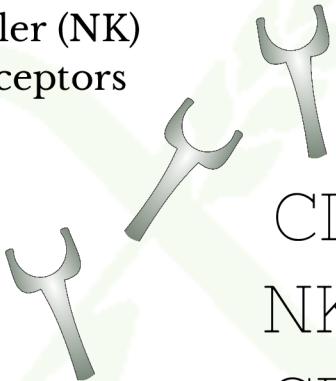
3 intestinal epithelial cell death induced
by intraepithelial lymphocytes (IELs)

Thursday

14 March

There is an overexpression of membrane-bound IL-15 on enterocytes in active CD

causing
over-
expression
of the
natural
killer (NK)
receptors



CD94 and
NKG2D by
CD3+ IELs

Friday

15 March

CD crypt hyperplasia has been hypothesized to be the consequence of an imbalance between

continuous
tissue
damage due
to the
mucosal
autoimmune
insult

inability of the
stem cells to
compensate



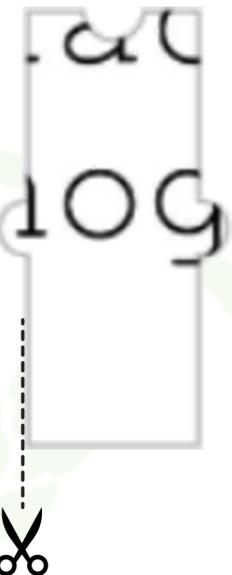
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

16
17

March

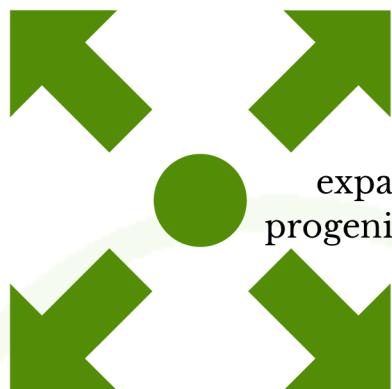
11



Monday

18 March

CELIAC HYPERPLASTIC CRYPT IS CHARACTERIZED BY



expansion of the immature
progenitor cell compartment and

downregulation of the Hedgehog signaling cascade.



CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

(complete the puzzle for the corresponding figure)

Tuesday

19 March

1

Partially digested gliadin
fragments interact with
chemokine receptor 3 on
the apical side of
epithelium

Wednesday

CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

20 March

(complete the puzzle for the corresponding figure)

2

This is inducing a myeloid differentiation primary response 88-dependent release of zonulin

Thursday

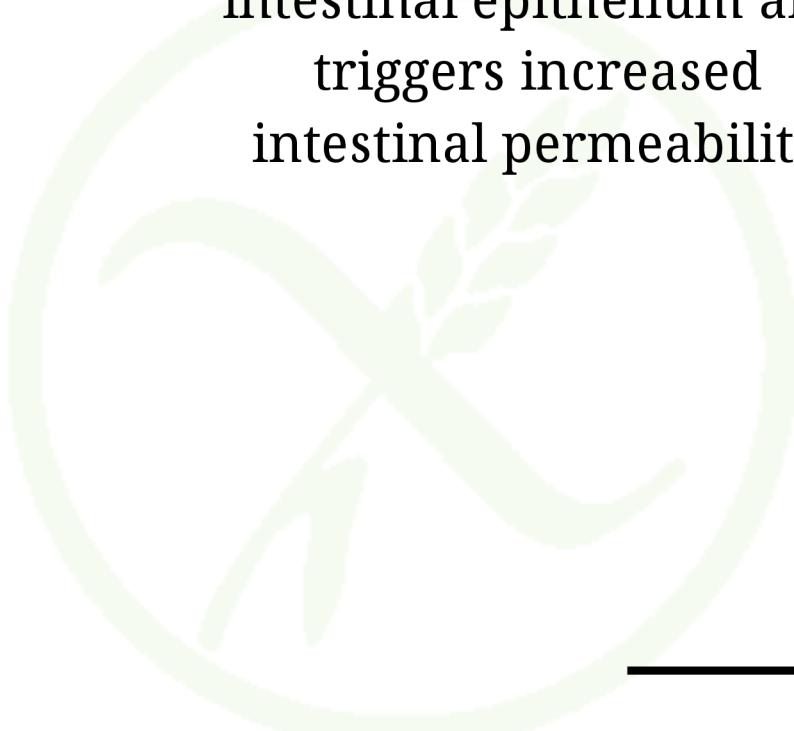
CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

(complete the puzzle for the corresponding figure)

21 March

3

Zonulin interacts with the
intestinal epithelium and
triggers increased
intestinal permeability



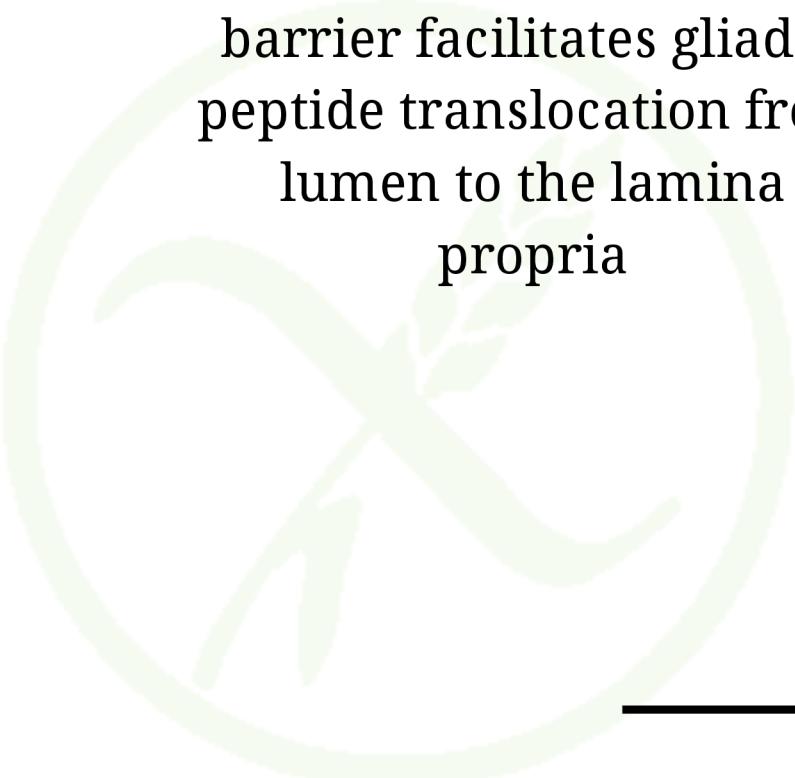
CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

(complete the puzzle for the corresponding figure)

Friday
22 March

4

Functional loss of the gut
barrier facilitates gliadin
peptide translocation from
lumen to the lamina
propria



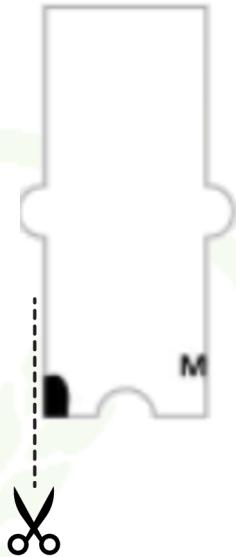
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

23
24

March

12



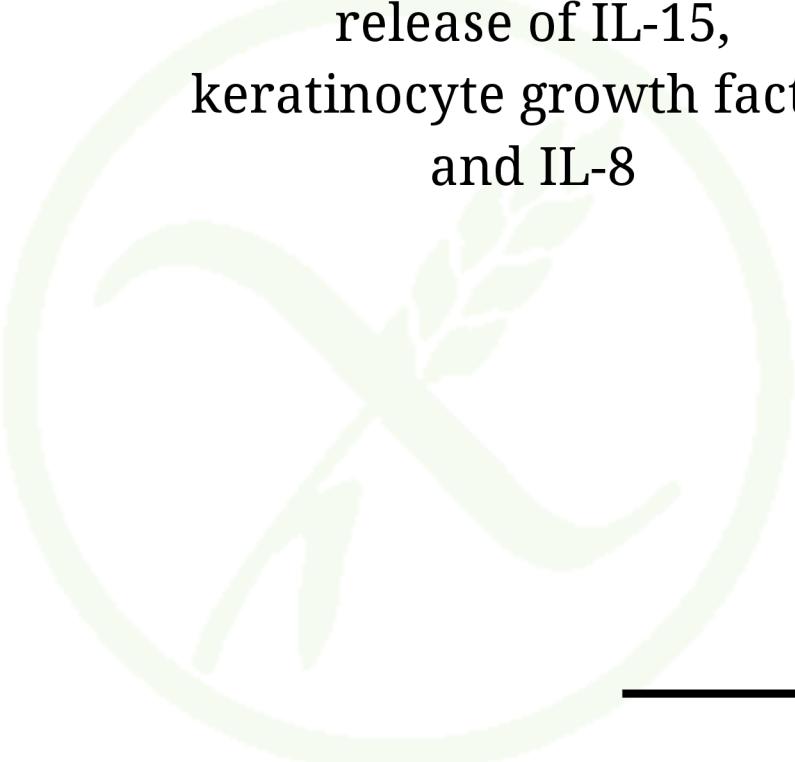
CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

(complete the puzzle for the corresponding figure)

Monday
25 March

5

Gliadin peptides trigger
release of IL-15,
keratinocyte growth factor,
and IL-8



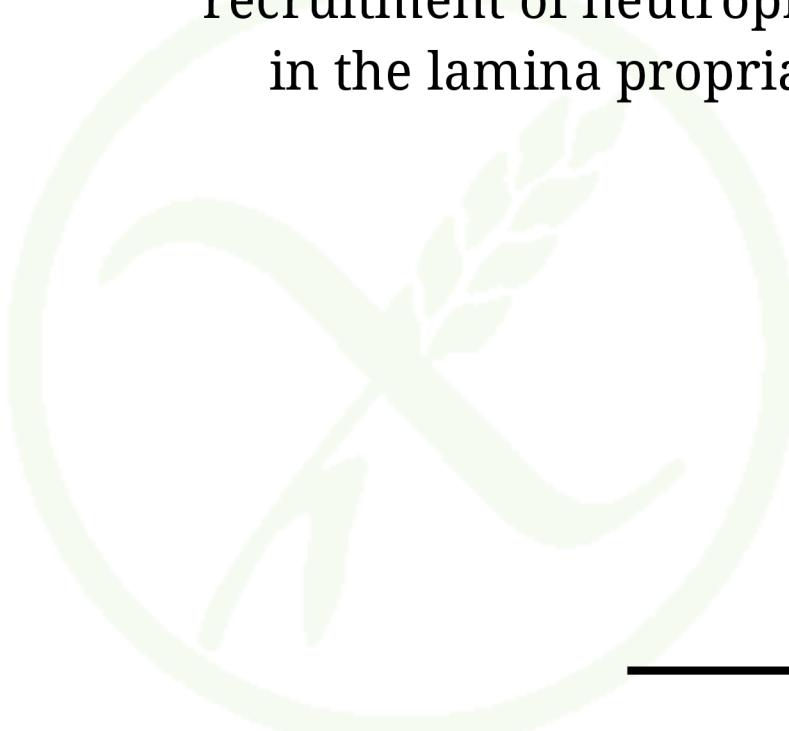
CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

(complete the puzzle for the corresponding figure)

Tuesday
26 March

6

with consequent
recruitment of neutrophils
in the lamina propria



Wednesday

CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

27 March

(complete the puzzle for the corresponding figure)

7

Simultaneously, alpha-amylase/trypsin inhibitors engage the Toll like receptor 4–MD2–CD14 complex with subsequent up-regulation of maturation markers and release of proinflammatory cytokines

Thursday

CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

28 March

(complete the puzzle for the corresponding figure)

8

Following innate immune-mediated apoptosis of intestinal cells with subsequent release of intracellular tissue transglutaminase, gliadin peptides are partially deamidated

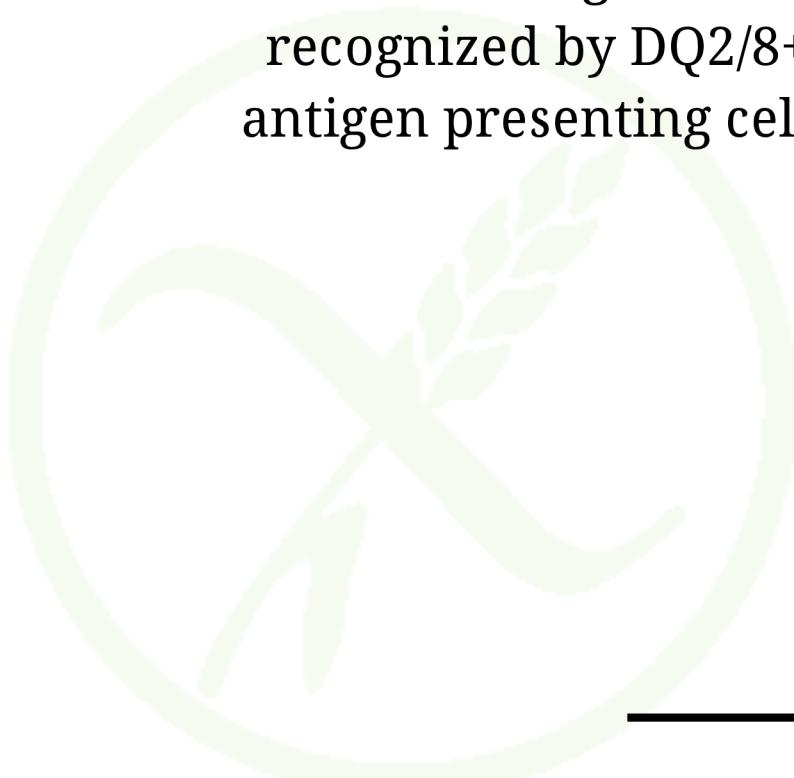
CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

(complete the puzzle for the corresponding figure)

Friday
29 March

9

Deamidated gliadin is
recognized by DQ2/8+
antigen presenting cells



WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

30
31

March

13



Monday

CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

1

April

(complete the puzzle for the corresponding figure)

10

Deamidated gliadin is
presented to T helper cells



Tuesday

2

April

CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

(complete the puzzle for the corresponding figure)

11

T helper cells trigger activation and maturation of B cells, producing IgM, IgG, and IgA antibodies against tissue transglutaminase

Wednesday

CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

3

April

(complete the puzzle for the corresponding figure)

12

T helper cells also produce pro-inflammatory cytokines (interferon γ and tumor necrosis factor α), which in turn further increase gut permeability and, together with T killer cells, initiate the enteropathy.

Thursday

CELIAC DISEASE
PATHOGENESIS IN 14 STEPS!

4

April

(complete the puzzle for the corresponding figure)

13

Damaged enterocytes express CD71 transporter also on their apical side, resulting in retrotranscytosis of secretory IgA-gliadin complexes, thus potentiating gluten trafficking from gut lumen to lamina propria.

Ultimately, the interaction between CD4+ T cells in the lamina propria with gliadin induces their activation and proliferation, with production of proinflammatory cytokines, metalloproteases, and keratinocyte growth factor by stromal cells, which induces crypt hyperplasia and villous blunting secondary to intestinal epithelial cell death induced by intraepithelial lymphocytes.

Friday

CELIAC DISEASE PATHOGENESIS IN 14 STEPS!

(complete the puzzle for the corresponding figure)

5

April

14

The hyperplastic crypts are characterized by an expansion of the immature progenitor cells compartment (WNT) and downregulation of the Hedgehog signaling cascade.

An increased number of stromal cells known to be part of the intestinal stem cell niche and increased levels of bone morphogenetic protein antagonists, like Gremlin-1 and Gremlin-2, may further contribute to the crypt hyperplasia present in celiac disease

Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

6
7

April

14



Monday

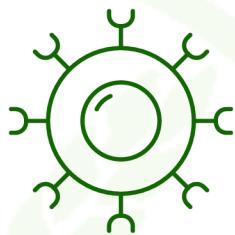
8

April



Lack of consistent CD-like enteropathy in humanized mice

supports the concept that the accelerated
disruption of enterocytes



secondary to the adaptive CD4+ T cell
insult **cannot** fully explain

CD pathogenesis

Tuesday

9

April

KEY ELEMENT OF CD ENTEROPATHY:



An intrinsic defect



of the stem cell compartment



in subjects at risk of CD

Wednesday

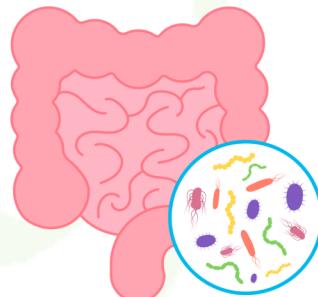
10

April

THERE IS
AN ASSOCIATION BETWEEN



and a change in
the microbiome
composition



Thursday

11

April

There is no direct causation between

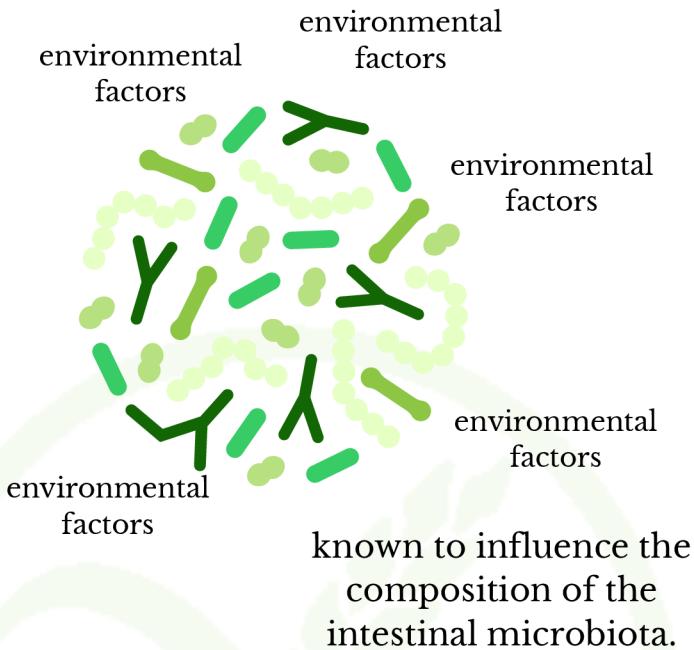
microbiota
composition

and CD pathogenesis.



Friday
12 April

Many



are also thought to play a role in the development of CD

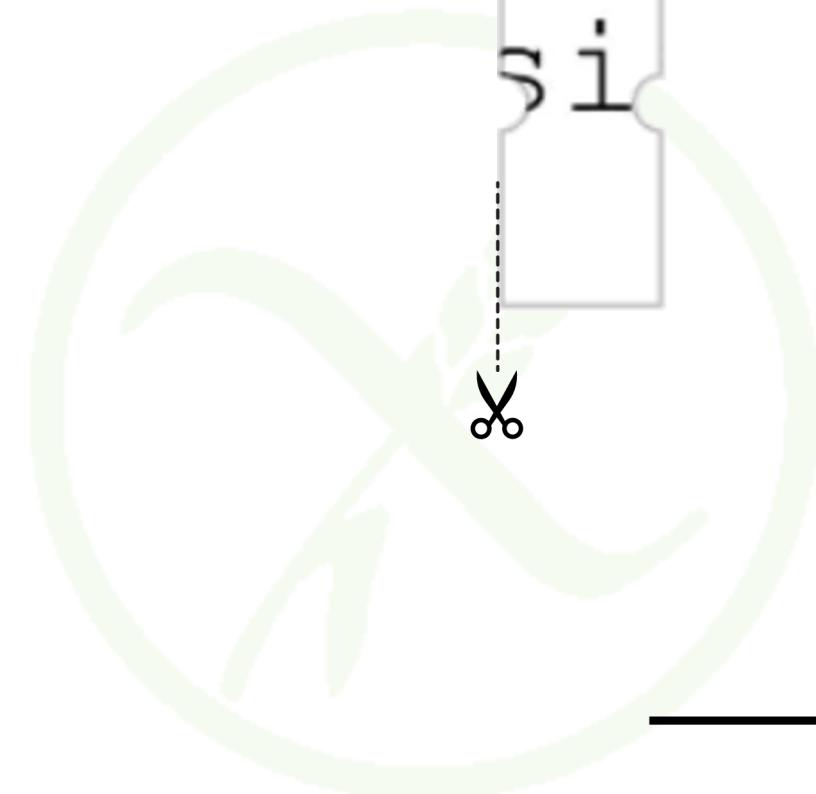
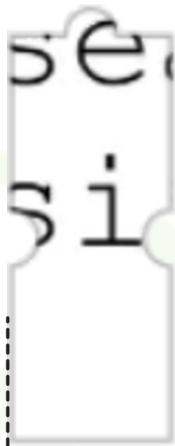
Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

13
14

April

15



Monday
15 April

NEONATES AT FAMILY RISK OF CD



had a decreased representation of Bacterioidetes and a higher abundance of Firmicutes.

Tuesday

16 April

Infants who developed autoimmunity

had decreased lactate signals in their stools ,

coincident with a diminished representation in Lactobacillus species in their microbiome

preceded the first detection of positive antibodies.



Wednesday

17

April

To move from

ASSOCIATION to CAUSATION,

large-scale,

LONGITUDINAL studies

are necessary to define if and how gut microbiota composition and metabolomic profiles may influence

the loss of gluten tolerance
and subsequent onset of CD in
genetically susceptible subjects

Thursday

18

April

CD is diagnosed more frequently in **women**



Female: male

2:1



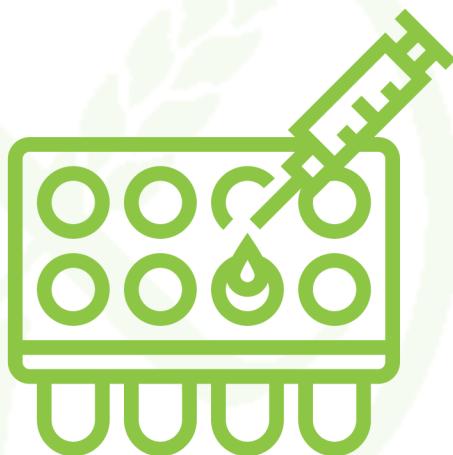
3:1

Friday
19 April

Actual female: male

1.5:1

Based on serological screening,



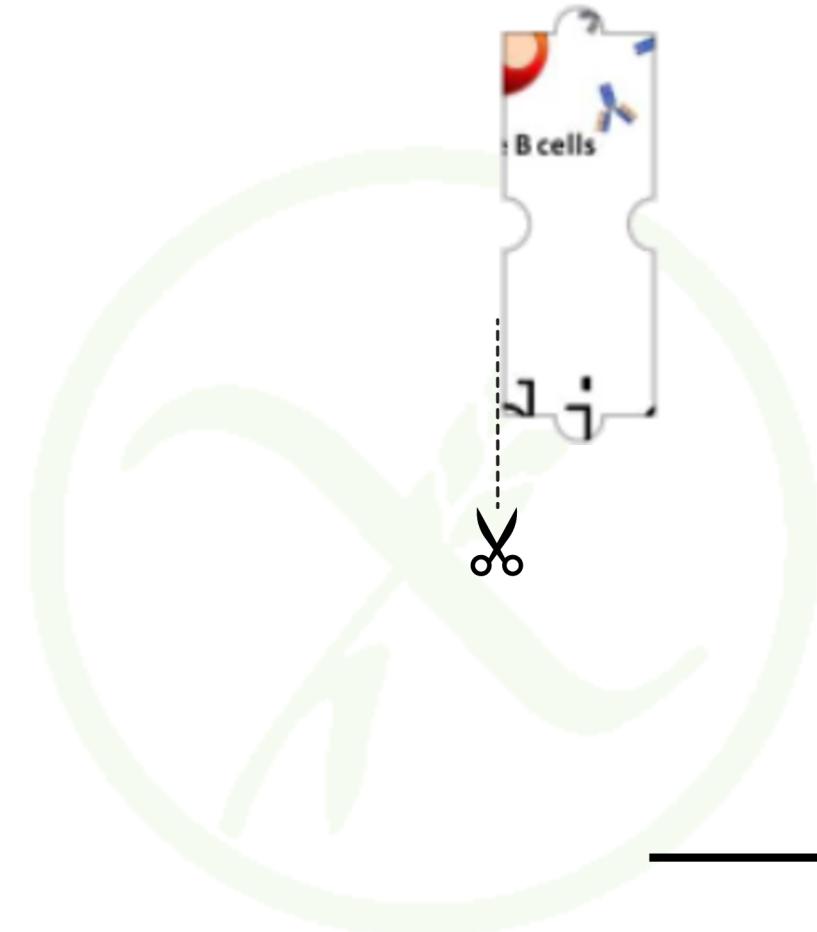
Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

20
21

April

16



Monday
22 April

elderly



The disease
can occur
at any age

early childhood

Tuesday
23 April

Occurrence comes with
2 peaks of onset



Wednesday

24 April

The diagnosis of CD can be

CHALLENGING

since **symptoms** can vary significantly



from patient to patient

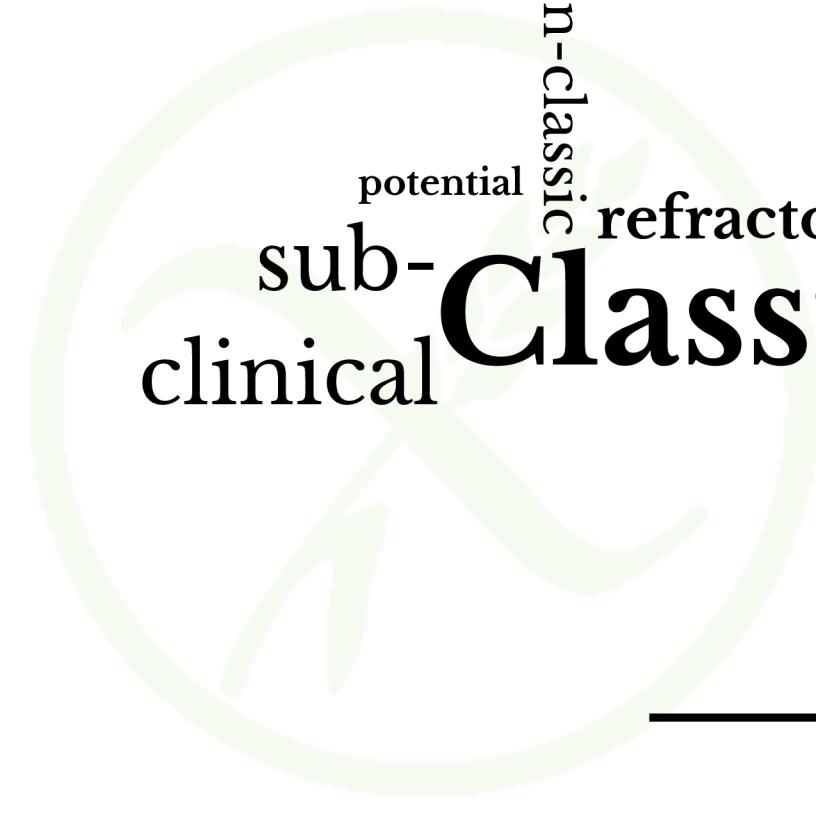


Thursday

25

April

In 2011, the *Oslo classification* of CD identified the following clinical presentations:



non-classic
refractory
Classic
sub-clinical
potential

Friday 26 April

INTESTINAL
(CLASSIC)

EXTRAINTESTINAL
(NON-CLASSIC)

better represent the **main** clinical
phenotypes
of CD

which may occur **individually**



or in **combination**

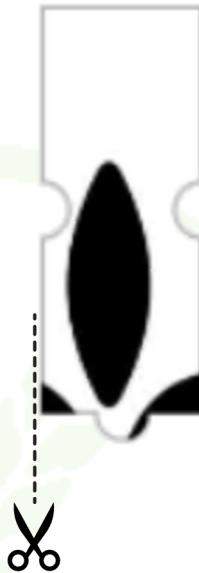
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

27
28

April

17



THE INTESTINAL FORM OF CD

Monday
29 April

is more commonly detected in



pediatric population



children younger than 3 years.

THE INTESTINAL FORM OF CD

Tuesday

30

April

is characterized by diarrhea, loss of appetite, abdominal distention, and failure to thrive.



Wednesday

THE INTESTINAL FORM OF CD

1

May

In older children and adults, they may complain of



bloating
abdominal pain
weight loss
diarrhea
constipation

Thursday

2

May

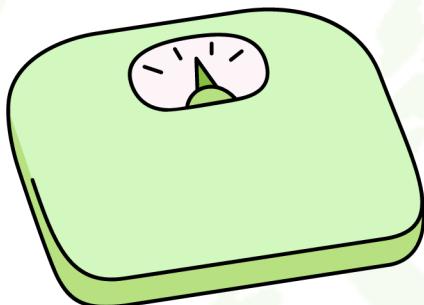
THE INTESTINAL FORM OF CD

In adults, the malabsorption syndrome with

significant asthenia

weight loss

chronic diarrhea



is quite rare

Friday

3

May

THE INTESTINAL FORM OF CD

Despite its uncommon detection, this form can cause **hospitalization** due to

cachexia

sarcopenia

significant
hypoalbuminemia

electrolyte abnormalities

Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

4
5

May

18



Monday

THE INTESTINAL FORM OF CD

6

May

More frequent:

An irritable bowel syndrome (IBS)-like presentation with

CONSTIPATION



or alternating bowel and/or dyspepsia-like symptoms, such as

NAUSEA AND
SOMETIMES VOMITING



Tuesday

7

May

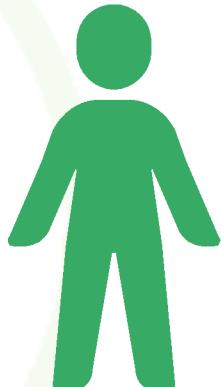
THE EXTRAINTESTINAL FORM OF CD

Symptoms are common in both

CHILDREN



ADULTS



Wednesday

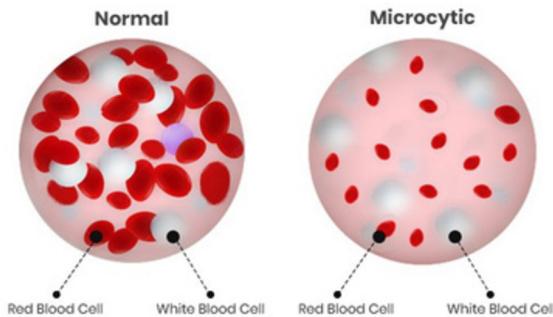
THE EXTRAINTESTINAL FORM OF CD

8

May

Symptoms include:

IRON DEFICIENCY
MICROCYTIC ANEMIA



detectable in up to 40% of cases (*by cause of iron malabsorption or chronic inflammation*)

Thursday

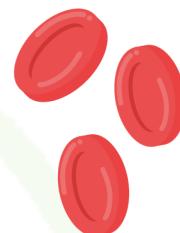
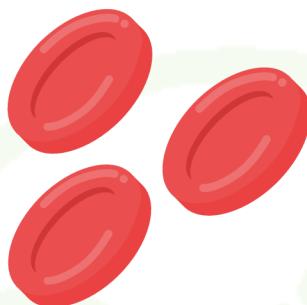
9

May

THE EXTRAINTESTINAL FORM OF CD

More rare symptoms are

MACROCYTIC ANEMIA



Normal

due to folic acid and/or vitamin B12 deficiency
(more frequent in Europe than in the US)

THE EXTRAINTESTINAL FORM OF CD

Friday
10 May

Other symptoms

CHANGES IN BONE MINERAL DENSITY, INCLUDING
OSTEOPENIA OR OSTEOPOROSIS

(affecting about

70%
of patients at diagnosis)

are related to altered absorption
of calcium and vitamin D3

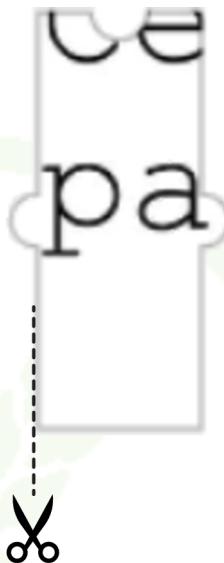
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

11
12

May

19



THE EXTRAINTESTINAL FORM OF CD

Monday
13 May

In children

GROWTH RETARDATION AND SHORT STATURE



can raise the suspect of an underlying
extraintestinal CD

Tuesday

THE EXTRAINTESTINAL FORM OF CD

14

May

Other signs include

TOOTH ENAMEL DEFECTS



APHTHOUS STOMATITIS

20%

of undiagnosed CD patients

HYPERTRANSAMINASEMIA

45%

of untreated patients

which can be ascribed to food and bacterial antigen translocation reaching the liver due to increased intestinal permeability.

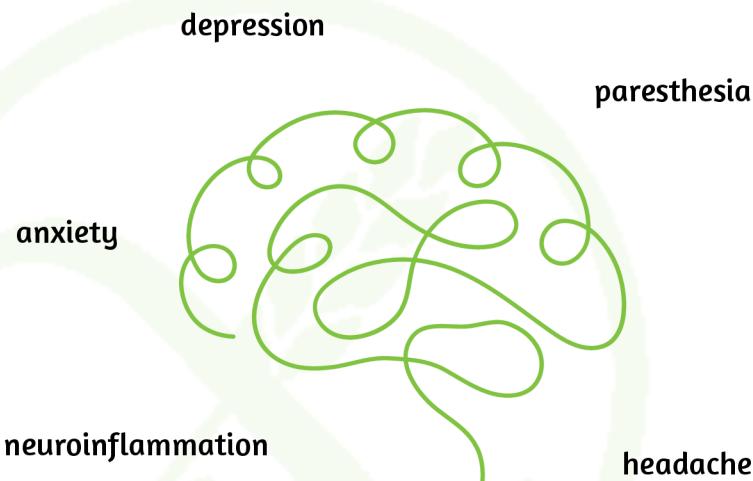
Wednesday

THE EXTRAINTESTINAL FORM
OF CD

15

May

A wide array of **neurological symptoms** can be detectable in CD patients.



Thursday

16

May

THE EXTRAINTESTINAL FORM OF CD

The clinical presentation may also include changes in reproductive function characterized by



changes in the number and mobility of spermatozoa

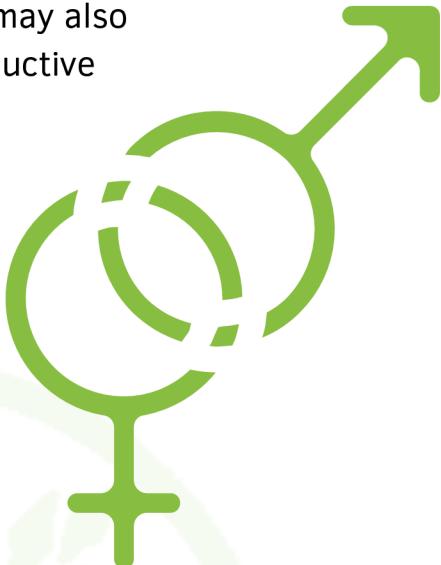
early menopause

amenorrhea

recurrent miscarriages

premature birth

late menarche



Friday
17 May



Manifestations can be reversed



when patients start a strict gluten-free diet (GFD)

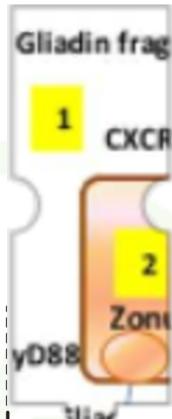
Sat + Sun

18
19

May

WEEKEND EDITION'S
PUZZLE PIECE NO.

20



Monday

20 May

Fatigue and some **neurological manifestation** as well as **functional gastrointestinal (GI)** symptoms can persist for a long period in a subgroup of CD patients.

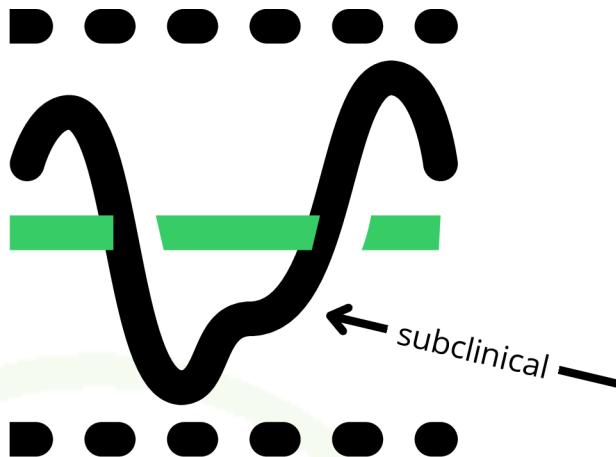


THE SUBCLINICAL FORM OF CD

Tuesday

21

May



Includes patients with symptoms/signs
below the clinical identification threshold

and are often recognizable only after the
appreciation of the beneficial effects
induced by the GFD



Wednesday

THE SUBCLINICAL FORM OF CD

22

May

A typical example of cases are those patients undergoing antibody screening



due to being **relatives** of CD patients or cases identified as a result of a **screening strategy** in the general population

THE POTENTIAL FORM OF CD

Thursday

23

May

is characterized by **positive** serological and genetic markers



with a **normal** intestinal mucosa and **minimal signs** of inflammation such an increase in IELs

THE POTENTIAL FORM OF CD

Friday

24

May

Patients with this form can manifest with

CLASSIC AND NON-
CLASSIC SYMPTOMS

or be entirely

ASYMPTOMATIC

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

25
26

May

21



THE POTENTIAL FORM OF CD

Monday
27 May

The scientific community has **not universally** agreed on whether or not a GFD should be prescribed for patients with potential CD.



THE REFRACTORY FORM OF CD
(RCD)

Tuesday

28

May

Is characterized by **persistent**
symptoms and

ATROPHY OF THE INTESTINAL VILLI



after at least 12months of a **strict GFD**

Wednesday

THE REFRACTORY FORM OF CD
(RCD)

29

May

Can lead to complications such as

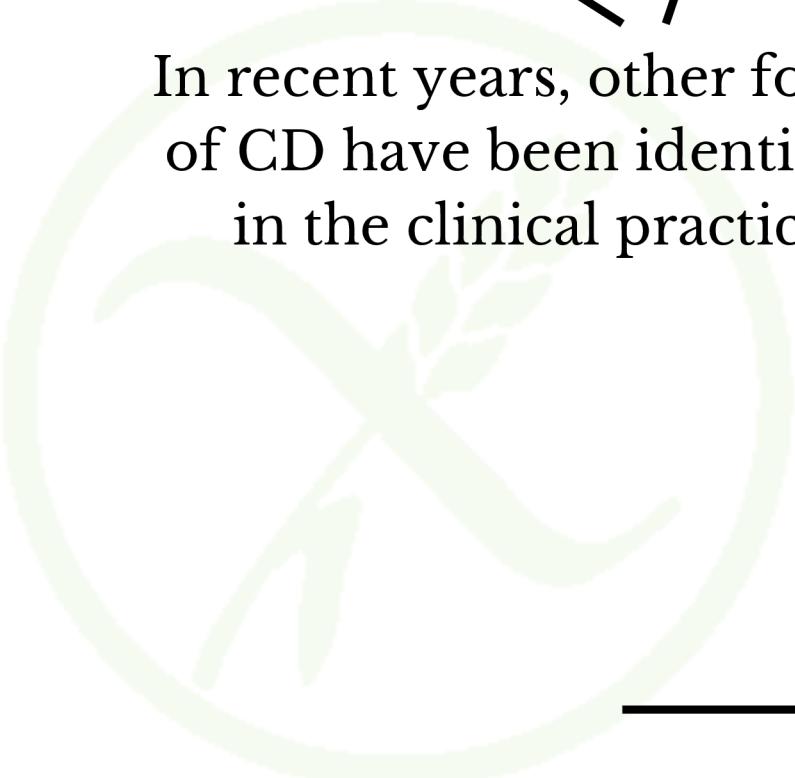
INTESTINAL LYMPHOMA

COLLAGENOUS SPRUE

ULCERATIVE JEJUNOILEITIS

Thursday
30 May

SERONEGATIVE GFD NON-RESPONSIVE CD



In recent years, other forms
of CD have been identified
in the clinical practice

THE SERONEGATIVE FORM OF CD

Friday

31

May

Is characterized by



the lack of demonstrable serological markers

along with clinical sign of severe malabsorption

and atrophy of the intestinal mucosa

Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

1
2

June

22



Antibodies



THE NON-RESPONSIVE FORM OF CD

Monday

3

June

Indicates

GI SYMPTOMS

that persist despite a GFD of
more than 12 months



Tuesday

ASSOCIATED DISEASES 1: AUTOIMMUNE DISEASES

4

June

- Type 1 diabetes mellitus
- Hashimoto's thyroiditis Graves' disease
- Autoimmune hepatitis
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Dermatitis herpetiformis
- Vitiligo
- Addison's disease
- Alopecia
- Psoriasis
- IgA deficiency
- Autoimmune atrophic gastritis
- Autoimmune hemolytic anemia
- Sjogren's syndrome Scleroderma
- Systemic erythematosus lupus
- Polymyositis
- Rheumatoid arthritis
- Myasthenia gravis
- IgA nephropathy (Berger's disease)

Wednesday

ASSOCIATED DISEASES 2:

IDIOPATHIC DISEASES

5

June

- Dilated cardiomyopathy
- Epilepsy with or without occipital calcifications
- Cerebellar ataxia
- Peripheral neuropathy
- Multiple myoclonic seizures
- Multiple sclerosis
- Cerebral atrophy
- Chronic inflammatory intestinal diseases
- Sarcoidosis
- Atopy

Thursday

ASSOCIATED DISEASES 3:
CHROMOSOMAL DISEASES

6

June

- Down syndrome
- Turner syndrome
- William's syndrome

Friday

7

June

The **importance** of diagnosing CD associated with these concomitant diseases is twofold



since a GFD is able to resolve symptoms, prevent complications, and improve some of the CD associated diseases



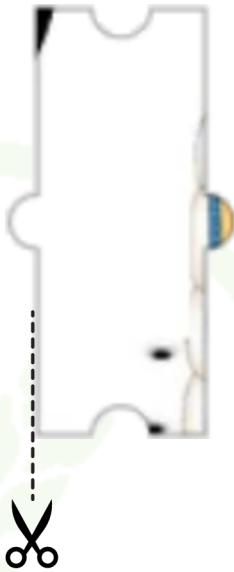
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

8
9

June

23



Monday

10

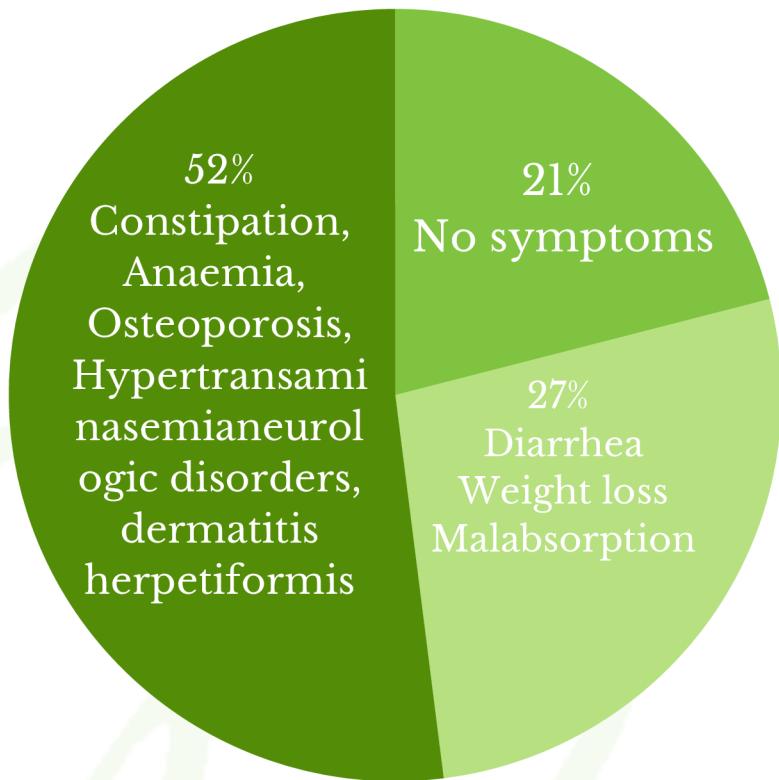
June

PREVALENCE OF CLINICAL PHENOTYPES OF ADULT CELIAC DISEASE

● Subclinical CD

● Classical CD

● Non-classical CD



Tuesday

11 June

CD diagnosis is represented by the combination of

mucosal changes (detected by duodenal biopsy)



and by

the positivity of serological tests

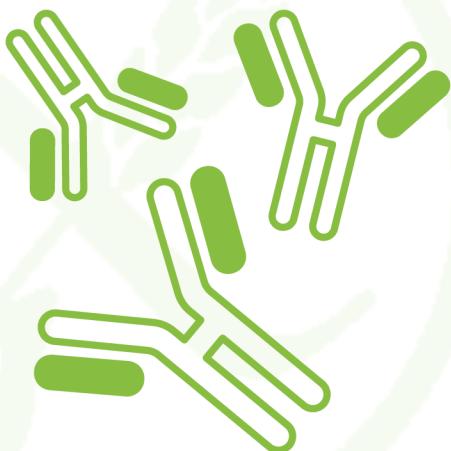
Wednesday

12

June

Serological tests for CD include

- anti-tTG antibodies
- anti-endomysium antibodies (EmA)
- deamidated gliadin peptide (DGP) antibodies.



Thursday
13 June

NO ANTIBODY TEST CURRENTLY AVAILABLE

provides a sensitivity and
specificity of

100%

Friday
14 June

PEDIATRIC PATIENTS WITH high titers of

detectable EmA
anti-tTG antibodies
HLA-DQ2/ HLA-DQ8 positivity

and signs/symptoms suggestive of CD

MAY SKIP DUODENAL BIOPSY.

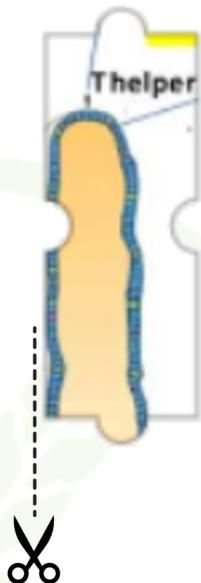
Sat + Sun

15
16

June

24

WEEKEND EDITION'S
PUZZLE PIECE NO.



Monday
17 June

Most pediatric cases,
especially those with low to medium anti-tTG2 titers,



require histopathological assessment to
confirm celiac disease diagnosis.

Tuesday
18 June

An intestinal biopsy



is a key adjunct for establishing a correct diagnosis.

Wednesday

19 June

The combination of

EmA

anti-tTG

HLA-DQ2/HLA-DQ8 positivity

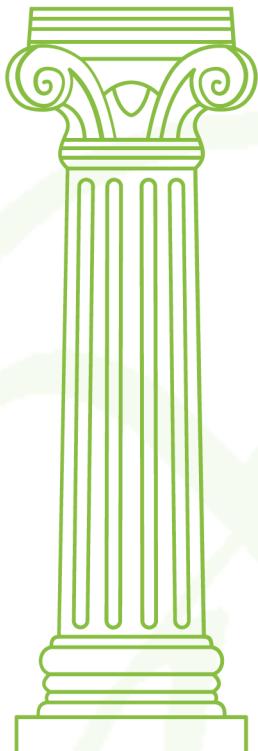
has a good accuracy across the range of
pre-test probabilities

in detecting adult patients with CD.



Thursday
20 June

Duodenal biopsy represents a pillar



in the diagnosis of
adult patients with
suspected CD.

Friday

21 June

The current standard of care is based on the
“four out of five rule”

which indicates that four out of five of the following criteria are enough to establish CD diagnosis:

- 1** Typical signs and symptoms
- 2** Antibody positivity
- 3** HLA-DQ2 and/or HLA-DQ8 positivity
- 4** Intestinal damage
- 5** Clinical response to GFD

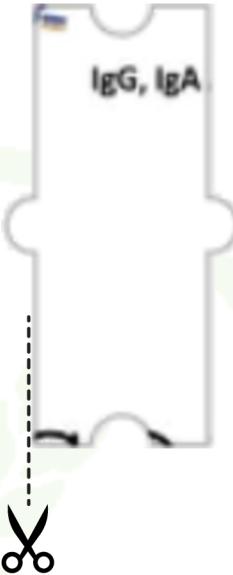
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

22
23

June

25



Monday
24 June

SERONEGATIVE CD

is identified by

the absence of antibody
positivity

[RULE 3]

Tuesday
25 June

POTENTIAL CD

is identified by



the absence of
intestinal damage

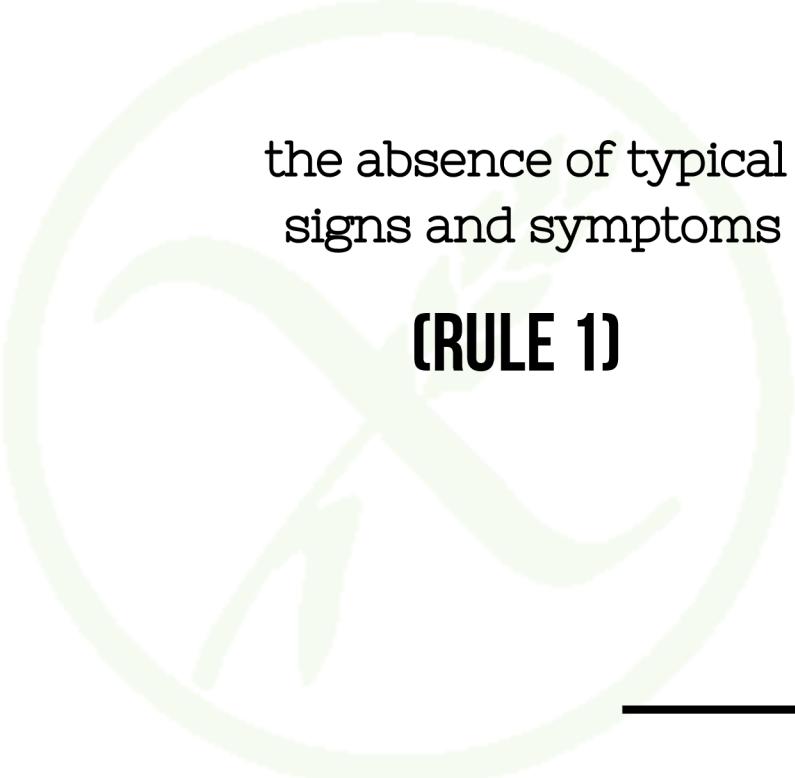
(RULE 4)

Wednesday

26 June

NON-CLASSIC CD

is identified by



the absence of typical
signs and symptoms

[RULE 1]

Thursday
27 June

NON-RESPONSIVE CD

is identified by

the absence of clinical
response to CD

(RULE 5)

Friday
28 June

Routine blood tests can lead to **suspect CD**.



WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

29
30

June

26



Monday

1

July

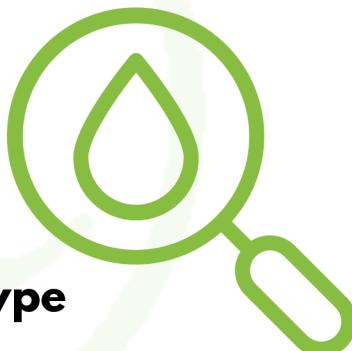
Low serum levels of hemoglobin, albumin, calcium, potassium, magnesium, and phosphorus

are more commonly detected in CD with

a classic phenotype

rather than

a non-classic phenotype



Tuesday
2 July

Most CD patients develop an **iron deficiency**

MICROCYTIC ANEMIA



Wednesday

3

July

Normocytic, macrocytic, or dimorphic anemia

due to concomitant malabsorption of folate and/or vitamin B12,



is less common in CD patients with an increased variability in the size of red blood cells



particularly in cases associated with autoimmune atrophic gastritis.



Thursday

4

July

Elevated levels of

bone-specific alkaline phosphatase

and

a significant vitamin D3 deficiency

can be found in patients
with CD and



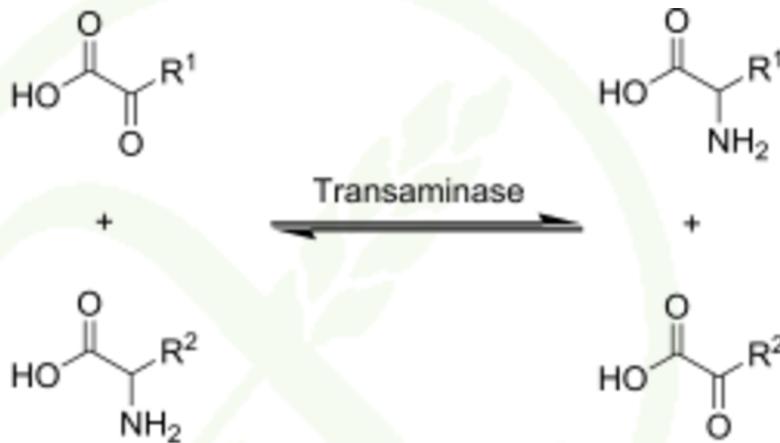
OSTEOPENIA/OSTEOPOROSIS.

Friday

5

July

A cryptogenic increase of **transaminases** may herald the presentation of CD



even in the absence of other relevant symptoms.

Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

6
7

July

27



Monday

8

July

Transaminases revert to
normal within



6-12 MONTHS

of a GFD.

Tuesday

9 July

Anatomical or **functional hyposplenism** can be identified in around **30%** of adult patients with CD,



with prevalence increasing up to **80%** in patients with complications.



Wednesday

10 July

A sign of **hyposplenism** is the detection of

a marked thrombocytosis

in association

with a small spleen

revealed by ultrasound.



Thursday
11 July

Red cell abnormalities like

Howell-Jolly bodies

& pitted red cells

suggest an
underlying hyposplenism



Friday
11 July

Howell-Jolly bodies

can be detected by



changes in the membrane and cytoplasm
of red blood cells.

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

12
13

July

28



Monday
14 July

pitted red cells
can be identified by



Nomarski phase contrast microscopy

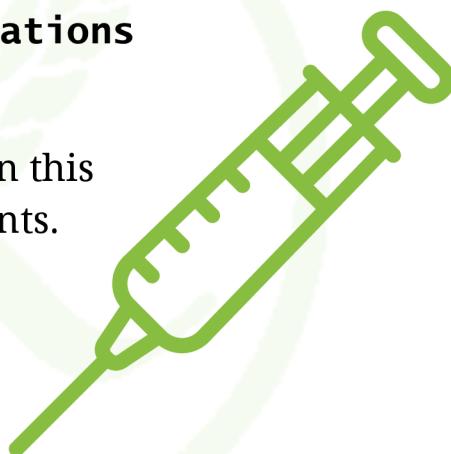
Tuesday
15 July

Hyposplenism

has a greater risk of developing infections
encapsulated bacteria

**anti-pneumococcal and
anti-meningococcal
vaccinations**

are recommended in this
subgroup of patients.



Wednesday
16 July

HYPOSPLENISM

is associated with autoimmune diseases and complications such as

ULCERATIVE JEJUNOILEITIS

LYMPHOMA

RCD

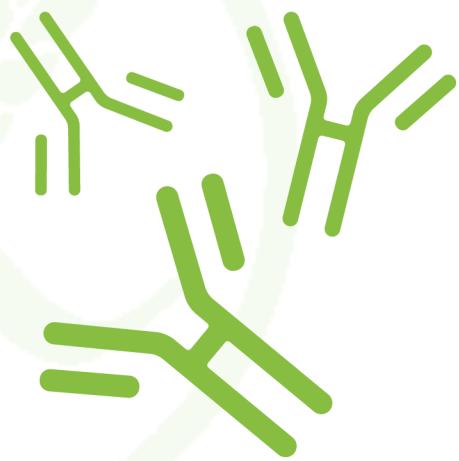


Thursday
17 July

CD-related antibodies

can identify patients with suspected CD, including

EmA
anti- tTG
DGP



Friday
18 July

Anti-gliadin antibodies

were the

1ST serological marker used to screen patients at risk for CD,

but due to their low specificity, it is not used for diagnosis.

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

19
20

July

29



Monday
21 July

Anti-gliadin antibodies

are now confined to the possible identification of
a subset of cases with

non-celiac gluten/wheat
sensitivity.



Tuesday
22 July

CD-related antibodies belong to IgA and IgG



classes,
but only those of

IGA CLASS

can be regarded as

HIGHLY SENSITIVE AND SPECIFIC FOR CD.

Wednesday

23 July

The use of IgG markers (except for DGP) is often misleading due to

the high percentage of false positives,



and their use should be limited to patients with IgA deficiency.

Thursday
26 July

EmA

is the antibody test with the

highest diagnostic accuracy

since it offers an absolute specificity if tested in third-level laboratories by expert operators.

Friday
27 July

The sensitivity of

anti-tTG IgA 97%

is higher than that of

EmA IgA 94%

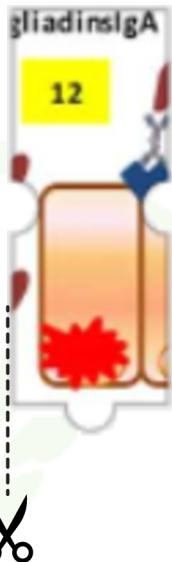
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

28
29

July

30



Monday
29 July

The specificity of

tTG IgA 91%

is certainly lower than that of

EmA 99%

Tuesday

30 July

Performance of serological markers for a diagnosis of celiac disease

	Sensitivity (%)	Specificity (%)
Anti-tTG IgA	96.8	91.0
EmA IgA	93.7	100
DGP IgG	84.4	98.5

PPV (%)	NPV (%)	Diagnostic accuracy (%)
91.2	96.8	97.7
100	94.4	96.9
98.2	86.8	91.6

Wednesday

31

July

False positives for anti-tTG

normally display a



low antibody titer

(less than twice the cut off).

Thursday

1

August

IgG DGP are particularly useful in identifying CD in

early childhood (age < 2 years)



Friday
2 August

IgA DGP

have been shown to be of

little usefulness in diagnosing CD



and therefore are

not recommended for diagnosis.

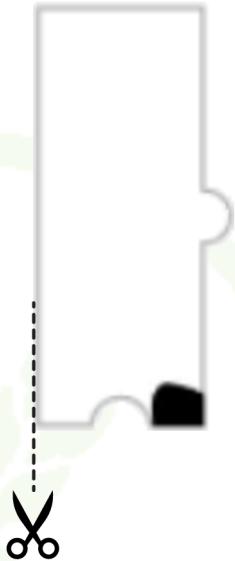
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

3
4

August

31



Monday

5

August

In **adult CD**, serology should include



TESTING ANTI-TTG IGA

along with

TOTAL IGA

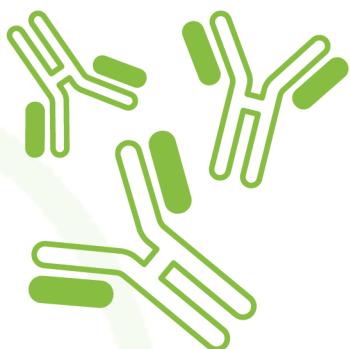


Tuesday

6

August

Should anti-tTG IgA be positive
at a high titer with normal total
IgA level,



a duodenal biopsy can be performed
without assessing EmA.



Wednesday

7

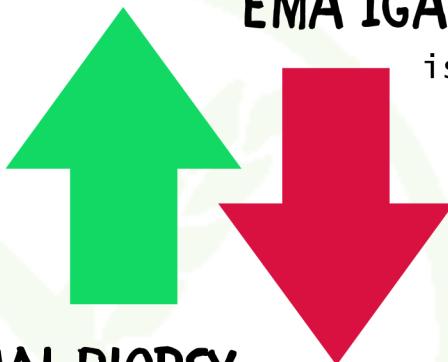
August

with a low

TITER ANTI-TTG IGA,

EMA IGA TESTING

is necessary



if positive,

A DUODENAL BIOPSY

should be recommended to confirm CD diagnosis.

Thursday

8

August

Strict compliance with a GFD
in most CD patients leads to

the disappearance or significant
decrease of antibodies within 12
months

together with

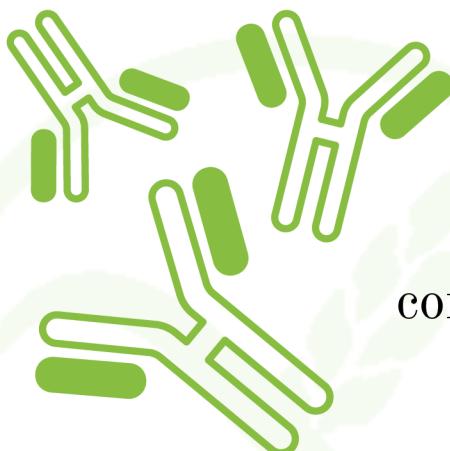
regrowth of the intestinal villi

Friday

9

August

IGA ANTI-TTG ANTIBODIES



are the most
commonly used test

TO MONITOR CD PATIENTS DURING FOLLOW-UP

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

10
11

August

32



Monday
12 August

Disappearance of IgA anti-tTG antibodies

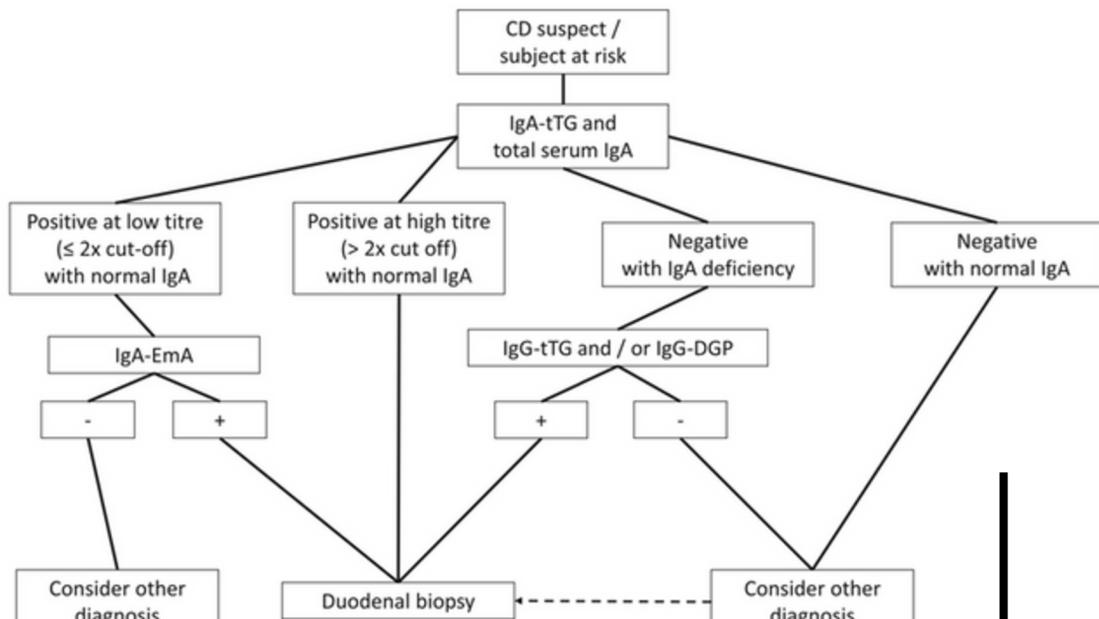


the regrowth of intestinal villi.

Tuesday

13 August

Diagnostic algorithm for celiac disease diagnosis



Wednesday

14 August

HISTOLOGY

remains the
‘gold standard’

for CD diagnosis



Thursday

15 August

Recommendations for CD diagnosis
with histology are

- 4** biopsies on the second duodenal portion
- 2** biopsies at the bulb

Friday
16 August

A fundamental principle for

the correct evaluation

is the orientation of biopsy samples using

cellulose acetate Millipore filters



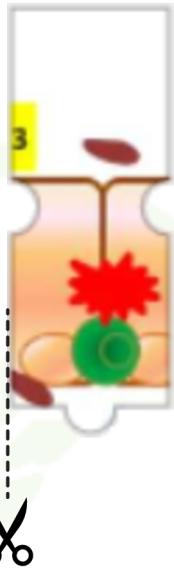
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

17
18

August

33



Monday

19 August

The different **types of CD-related lesions** of the intestinal mucosa can be categorized into five stages according to the **Marsh classification**, modified by Oberhüber.

TYPE 1 LESION

TYPE 2 LESION

TYPE 3A LESION

TYPE 3B LESION

TYPE 3C LESION

Tuesday
20 August

Type 1 and type 2 lesions
are characterized by **an increase in**



IELS
and
normal villi

Wednesday

21 August

Type 3 lesions are characterized by
an increase in



IELS
and
atrophy in villi

The normal **IEL cut-off** has been established to be
 ≥ 25 lymphocytes over 100
epithelial cells.

Thursday

22 August

Type 3 lesion of CD
shows a change in the
villi-to-crypt ratio

3:1 → 1:1

Friday
23 August

According to **Oberhüber's type 3** lesion can
be subdivided into three stages

depending on the severity of the atrophy

3A MILD

3B PARTIAL

3C SUBTOTAL ATROPHY

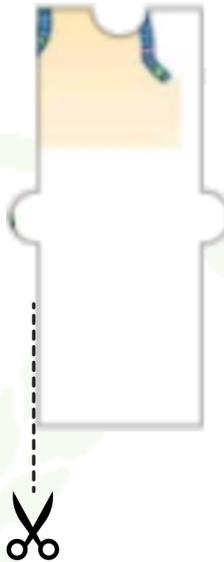
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

24
25

August

34



Monday
26 August

ACCORDING TO MARSH

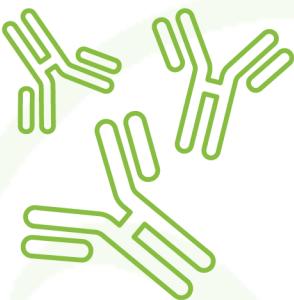
SUB-DIVISION OF TYPE 3 LESION

CAN BE CLINICALLY IRRELEVANT AND
SOMETIMES MISLEADING.

Tuesday
27 August

Together with

positive anti-tTG and EmA,



minimal intestinal lesions
indicate **potential CD**.

Wednesday

28 August

In most cases, minimal lesions are attributable to other causes, including

Food allergies

Crohn's disease

Lymphocytic colitis

Bacterial and parasitic intestinal infections, such as

- Giardia
- Common variable immunodeficiency
- Small intestinal bacterial overgrowth
- Non-steroidal anti-inflammatory drugs
- Helicobacter pylori infection.

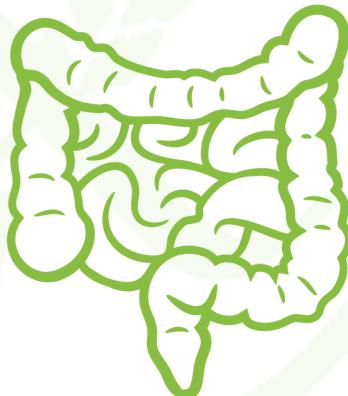
Thursday
29 August

The IEL cytometric pattern

is more accurate

than subepithelial deposits of anti-TG2 IgA

**for identifying CD in
lymphocytic enteritis**



Friday
30 August

Corazza and Villanacci divided the CD lesions into two categories:

NON-ATROPHIC (GRADE A)

ATROPHIC (GRADE B)

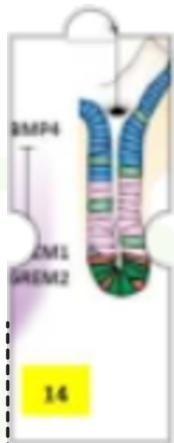
Grade B lesions can be further subcategorized into

B1 AND B2.

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun
31 August
1 September

35



Monday

2 januari

Comparison between the **two classifications** for the duodenal biopsy

Marsh-Oberhüber
Histological
classification

Corazza Villanacci
Histological
classification

Type 1
lesion

Type 2
lesion

Grade A
No
atrophy

Type 3a
lesion

Type 3b
lesion

Grade B1
Partial
atrophy

Type 3c
lesion

Grade B2
Subtotal
atrophy

Tuesday

3

januari

GRADE A LESIONS

are characterized by

INCREASE IN THE NUMBER OF IELS.



Wednesday

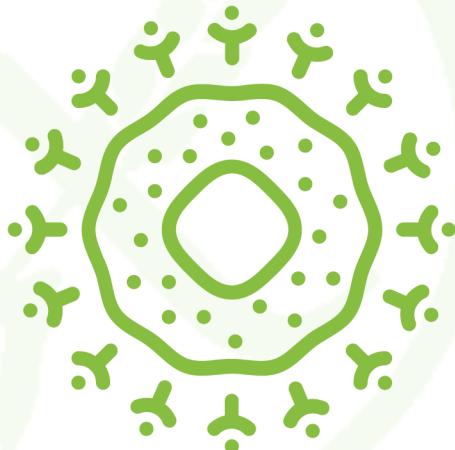
4

januari

GRADE A LESIONS

are identified by

IMMUNOHISTOCHEMICAL STAINING FOR CD3.



Thursday

5

januari

GRADE B1 LESIONS

are characterized by

A VILLI-TO-CRYPT RATIO LESS THAN

3 : 1

Friday

6

januari

GRADE B2 LESIONS

are characterized by

A diagram illustrating Grade B2 lesions. It shows a cross-section of intestinal mucosa with several prominent, rounded green structures representing villi. Below these villi is a layer of white, rounded cells representing crypts. The villi appear shorter and less densely packed than normal, which is characteristic of atrophy. A large green rectangular box highlights the text 'VILLI THAT ARE ENTIRELY ATROPHIC' located below the diagram.

VILLI THAT ARE ENTIRELY ATROPHIC

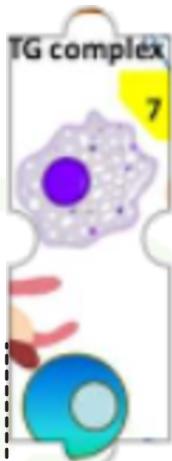
Sat + Sun

7
8

january

WEEKEND EDITION'S
PUZZLE PIECE NO.

36



Monday

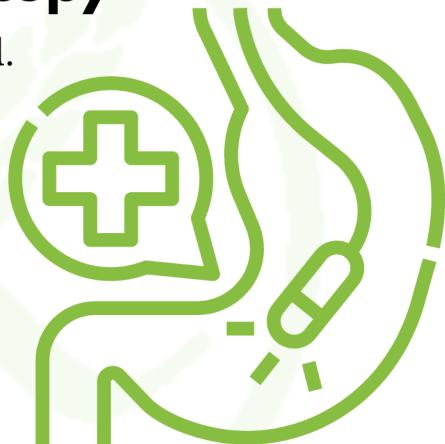
9

januari

In some patients with more **distal disease** or in those with **contraindication to biopsy**

capsule endoscopy

can be recommended.



Tuesday
10 januari

Patients who have

antibody positivity for CD with
HLA-DQ2/HLA-DQ8
(IgA EmA and anti-tTG)

and

lack of villous atrophy

have

POTENTIAL CELIAC DISEASE

Wednesday

11 januari

Patients with potential CD represent around 10% of subjects with CD.



10%

Thursday

12 januari

In patients with potential CD
the intestinal mucosa may be



normal (Marsh 0)

or

slightly inflamed

(increased number of IELs,
Marsh 1)



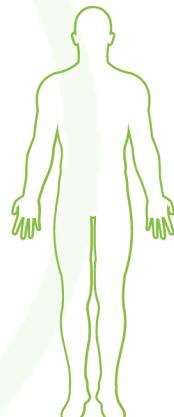
Friday 13 januari

Patients with **potential CD** may have



**INTESTINAL AND / OR
EXTRAINTESTINAL SYMPTOMS**

or be
ENTIRELY ASYMPTOMATIC



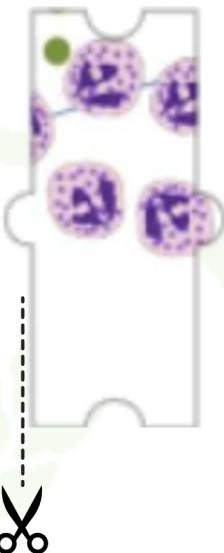
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

14
15

january

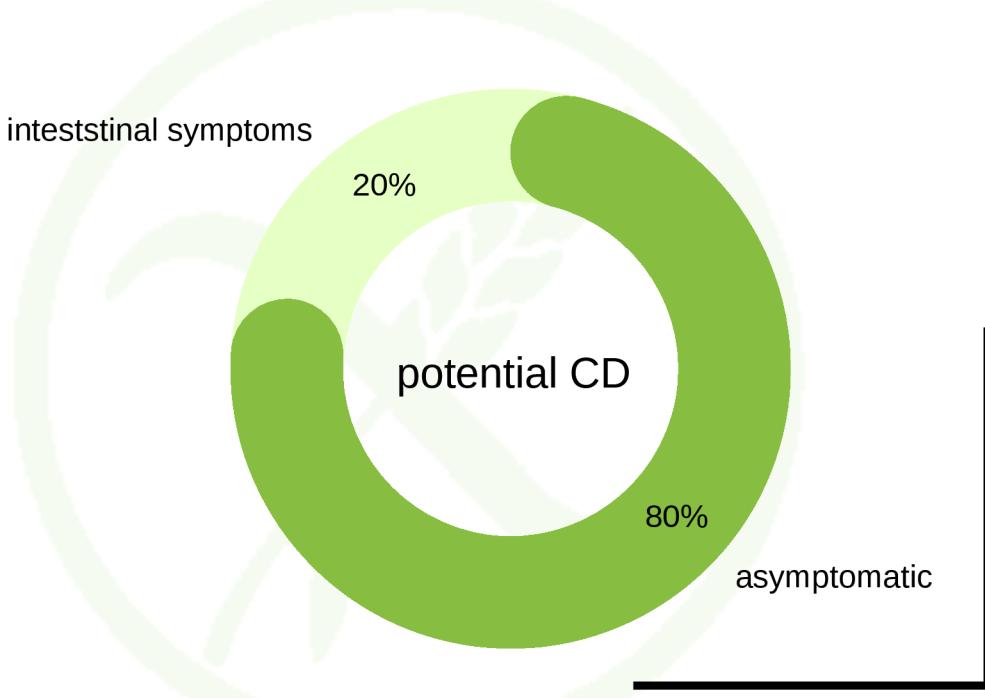
37



Monday

16 januari

In children, over **80%** of patients with potential CD are **asymptomatic** and the remaining **20%** more commonly experience **intestinal symptoms** rather than extraintestinal symptoms.



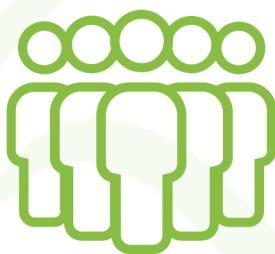
Tuesday

17

januari

The occurrence of

symptomatic features of potential CD



is much more common
in adults than in children.

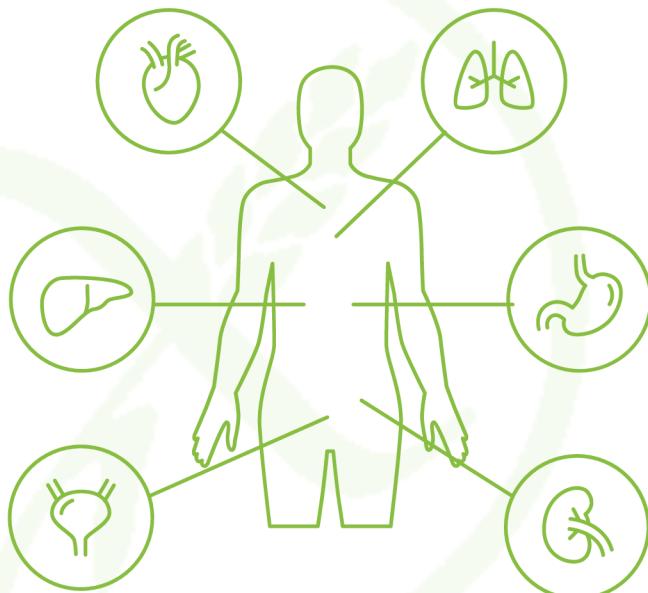


Wednesday

18 januari

The symptomatic phenotype in adult patients
with **potential CD**

is primarily characterized by
extraintestinal symptoms.



Thursday 19 januari

Few patients with potential CD consuming a gluten-containing diet develop



**full-blown
villous atrophy.**



Friday
20 januari

IN AROUND

2-3% OF CD PATIENTS
test negative for serological markers,

CALLED

SERONEGATIVE CD

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

21
22

january

38



Monday

23 januari

Patients with seronegative CD

are diagnosed to the
detection of villous atrophy on

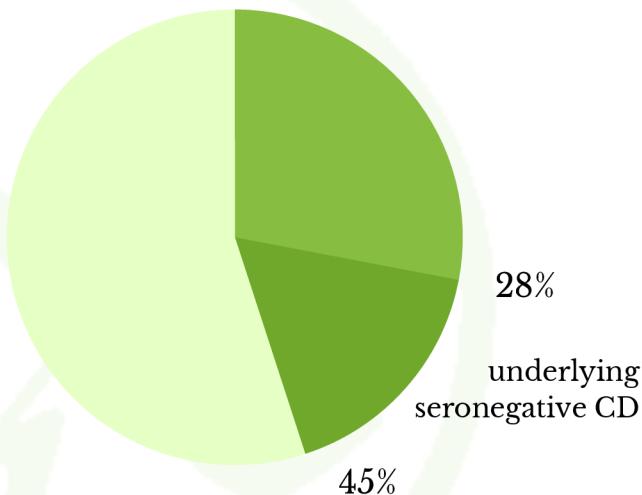
a duodenal histology and a genetic test.



Tuesday

24 januari

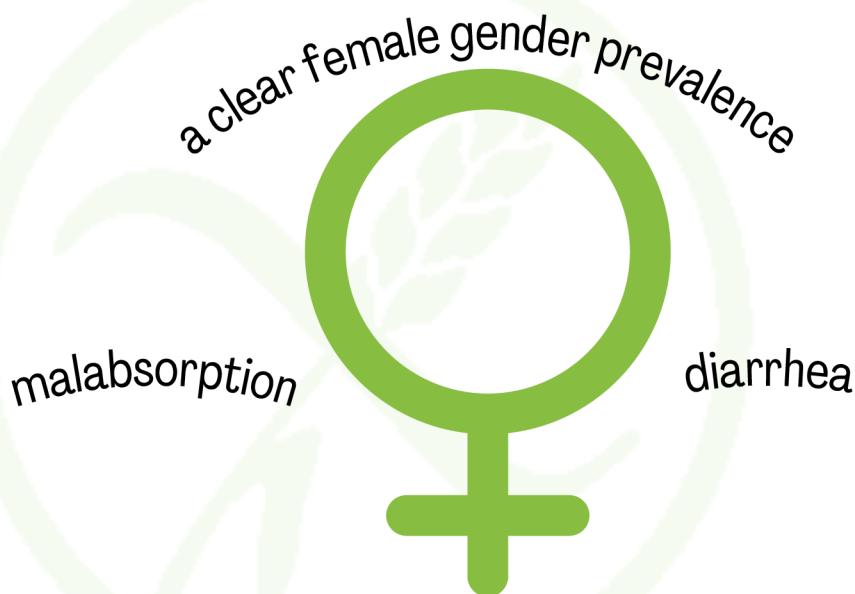
Of all **villous atrophies** lacking CD antibodies, 28–45% are due to an **underlying seronegative CD**.



Wednesday

25 januari

Seronegative CD patients display
a classic clinical phenotype,
characterized by



Thursday
26 januari

Seronegative CD patients have a



higher risk of morbidity
and mortality

compared with antibody-positive CD patients

which could be due to the late diagnosis of
this condition, which on average is around

50 years of age

Friday
27 januari

Compared to classic CD

SERONEGATIVE PATIENTS

have a greater association with
autoimmune diseases

and

a higher risk of developing
refractory disease.



WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

28
29

january

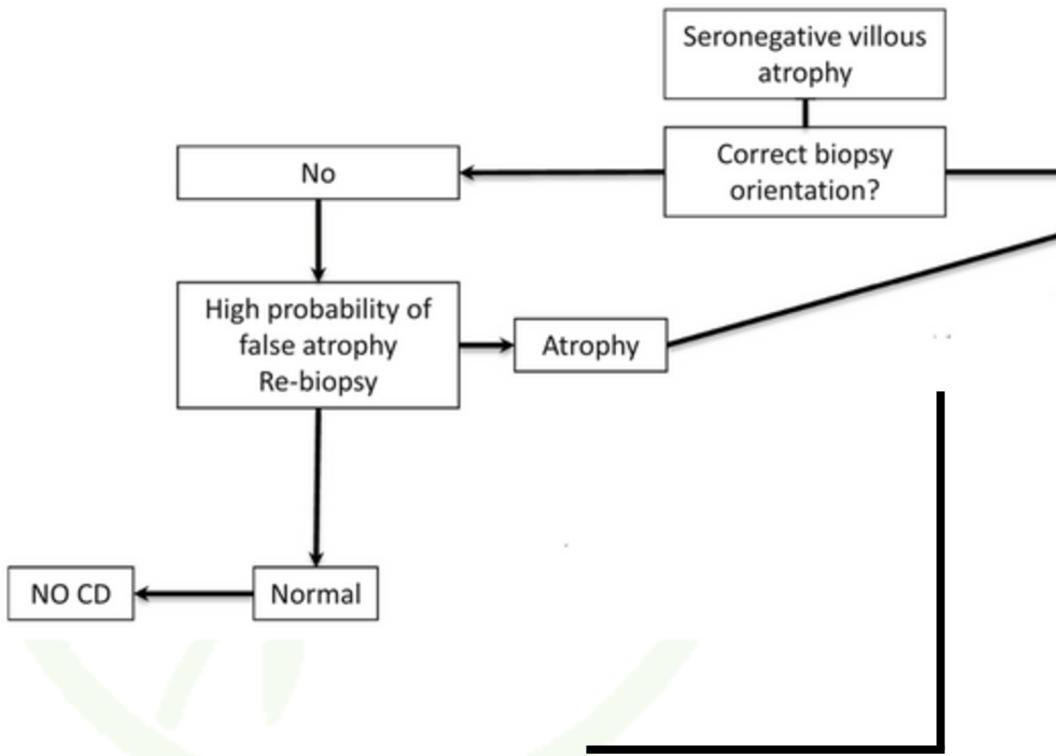
39



Monday

30 januari

Diagnostic algorithm for seronegative villous atrophy.
SIBO small intestinal bacterial overgrowth
part 1

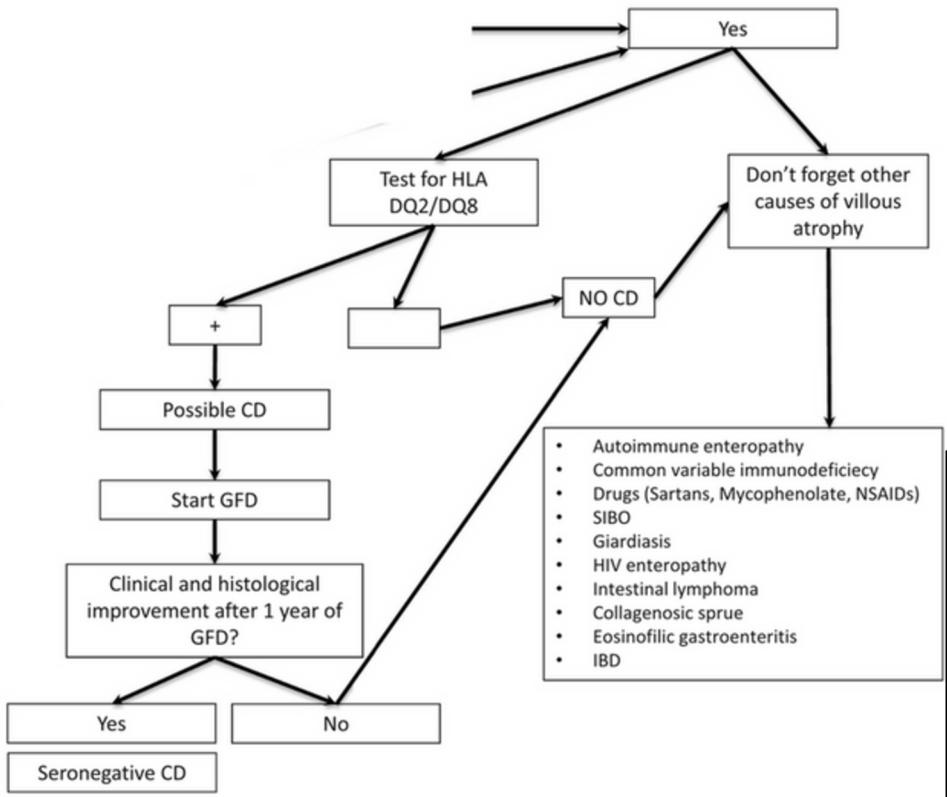


Tuesday

1

januari

Diagnostic algorithm for seronegative villous atrophy. SIBO small intestinal bacterial overgrowth part 2



Wednesday

2

januari

Non-responsive CD patients

fail to have complete control of symptoms and normalization of villous structure

despite attempted adherence to the GFD.

Thursday

3

januari

A new method to evaluate a patient with CD on a GFD and with ongoing signs or symptoms is by the differentiation between:

**ongoing active CD
(OACD)**



**the presence of
associated CD
conditions (ACDCs).**

Friday

4 januari

OACD can be seen in three scenarios

1 SLOW RESPONSE

Progressive improvement in symptoms and mucosal damage, but full remission does not occur for at least 1–2 years.

2 RCD

Ongoing severe enteropathy and malabsorptive symptoms after 6–12 months on a GFD.

3 GLUTEN EXPOSURE

Despite adequate understanding of the GFD and attempted adherence, gluten avoidance is insufficient to result in symptomatic or histologic remission.

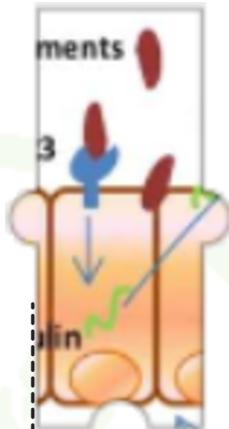
Sat + Sun

5
6

january

WEEKEND EDITION'S
PUZZLE PIECE NO.

40



Monday

7

januari

ACDCs include:

IBS

SMALL INTESTINAL BACTERIAL OVERGROWTH

MISCRYSCOPIC COLITIS

CROHN'S DISEASE

PANCREATIC INSUFFICIENCY

DIVERTICULAR DISEASE

AUTOIMMUNE ENTEROPATHY

LACTOSE INTOLERANCE

DRUG-INDUCED ENTEROPATHY

FRUCTOSE INTOLERANCE

Tuesday

8

januari

A late diagnosis of CD

(after the age of 50)

or

NOT FOLLOWING A STRICT GFD

can lead to



A HIGHER MORTALITY

compared to that of the general population.

Wednesday

9 januari

COMPLICATIONS

in around 1% of patients diagnosed with CD include

- Hyposplenism
- RCD
- Intestinal lymphoma
- Small bowel adenocarcinoma
- Ulcerative jejunoileitis

Thursday

10 januari

Complications can occur in all patients who complain of an unexplained persistence or re-exacerbation of symptoms like

diarrhea

weight loss

intestinal sub-occlusion

fever

abdominal pain

severe asthenia

Friday

11 januari

Complications occur more commonly when

a diagnosis of CD was established in elderly patients



or in those who are homozygous for DQ2 not observing a strict GFD.

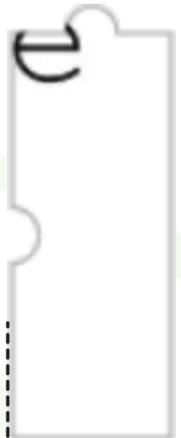
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

12
13

january

41



Monday

14 januari

RCD represents

10%

of all OACD cases

1-1.5%

of total cases of CD.

Tuesday
15 januari

RCD IS

characterized by
symptoms of malabsorption,
weight loss, and diarrhea

associated with
persistent villous atrophy after at
least 1 year on a strict GFD,

confirmed by
negative CD serology.

Wednesday

16 januari

Refractory CD
is subdivided
into two
categories

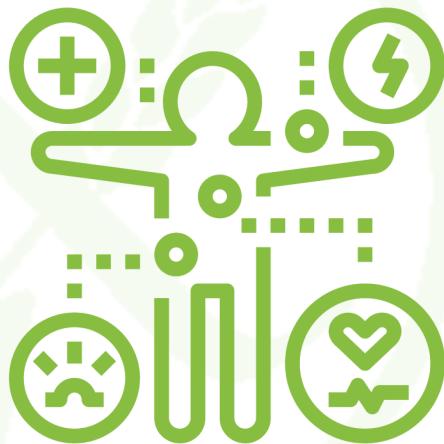
P
R
I
M
A
R
Y

SECONDARY RCD

Thursday

17 januari

Patients with **primary RCD** have a
symptomatic response
since the **beginning** of GFD.



Friday 18 januari

Patients with **secondary RDC** have

a recurrence of symptoms



after a more or less **long period** of improvement.

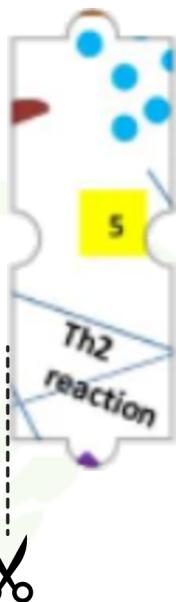
Sat + Sun

19
20

january

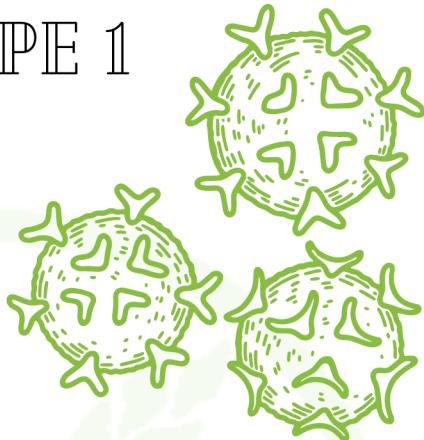
WEEKEND EDITION'S
PUZZLE PIECE NO.

42



Monday
21 januari

RCD TYPE 1

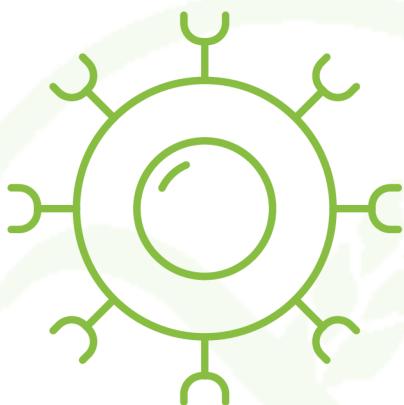


has a normal CD3+CD8+
phenotype of the IEL population.

Tuesday
22 januari

RCD TYPE 2

has a clonal presentation of **surface CD3 /intra-cytoplasmic CD3+ IELs**

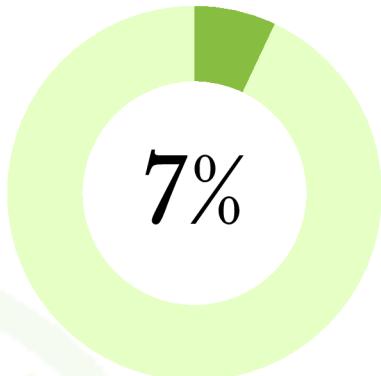


along with **monoclonal re-arrangement of the gamma-chain of the T cell receptor.**

Wednesday

23 januari

RCD type 1 has a 5-year mortality rate of 7%.



RCD type 2 has a 5-year mortality rate of 55%

Thursday

24 januari

The mortality of patients with type 2 RCD
is primarily due to

the development of intestinal lymphoma

which appears to occur
more often in

male patients

Friday 25 januari

In all cases of **type 2 RCD**
it is essential at diagnosis to perform,

a computed tomography (CT)

or

magnetic resonance (MR) enterography

followed by

**positron emission tomography (PET),
capsule endoscopy, and enteroscopy**

to rule out the progression to intestinal lymphoma.

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

26
27

january

43



Monday
28 januari

A **capsule endoscopy** has been recommended once a year at the follow-up.



for patients with a diagnosis of
type 2 RCD

Tuesday

29 januari

Type 1 therapy is based on
immunosuppressive therapy, containing

steroids

azathioprine

6-mercaptopurine

methotrexate

Wednesday

30 januari

Type 2 therapy is based on additional medications, including

cyclosporine

and

chemotherapy

such as cladribine and fludarabine associated with anti-CD52 monoclonal antibodies (alemtuzumab).

Thursday
31 januari

A delayed diagnosis of CD may

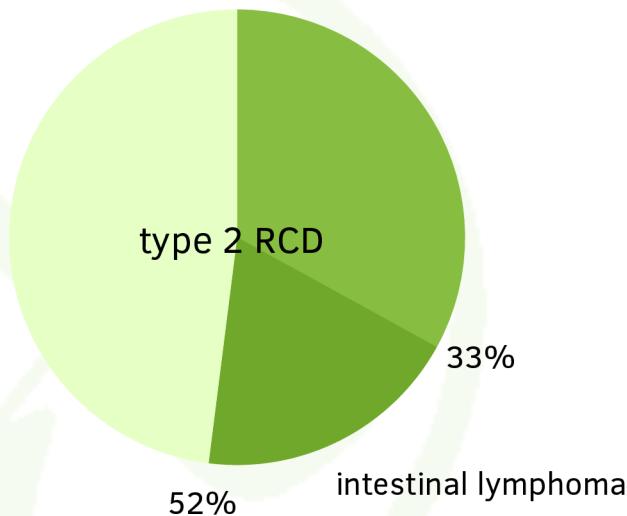


the risk of developing
neoplastic diseases.

Friday

1 November

In most cases, the development of **intestinal lymphoma** is preceded by type 2 RCD and develops into a **malignant disease in 33–52%** of cases within 5 years from diagnosis.

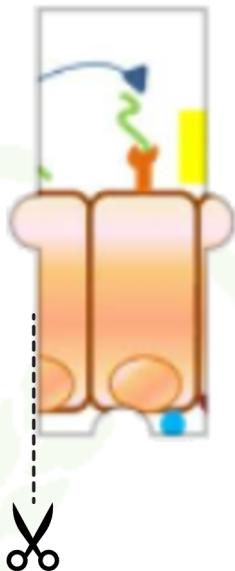


Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

2
3 November

44



Monday

4 November

Intestinal lymphoma may develop from type 1 RCD,



WITH A RATE OF 14% OVER 5 YEARS.

14%

Tuesday

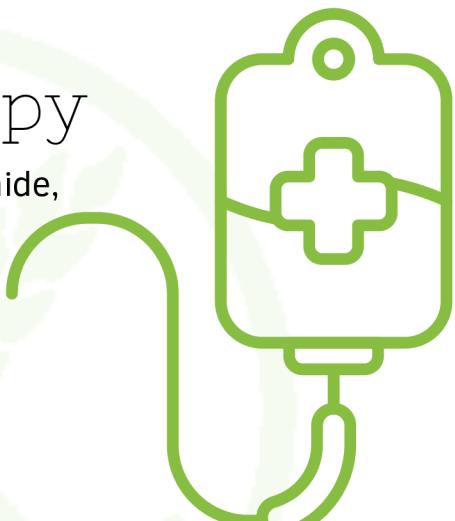
5 November

Treatment

in cases of CD-related **intestinal lymphoma** involves

chemotherapy

such as high-dose ifosfamide,
epirubicin, and etoposide
methotrexate



followed by autologous
stem cell transplantation

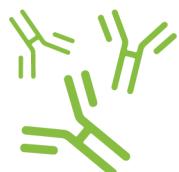
Wednesday

6 November

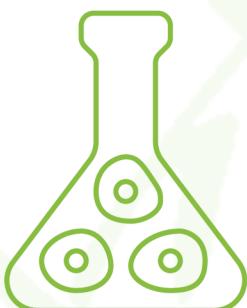
If **intestinal lymphoma** includes an elevated expression of CD30 (> 80% of the neoplasm)

80%

it is possible to use **biologic therapy** with anti-CD30 associated with monomethyl auristatin E (brentuximab vedotin)



and a **chemotherapy regimen** containing cyclophosphamide– doxorubicin– prednisone



followed by autologous **stem cell transplantation**.

Thursday

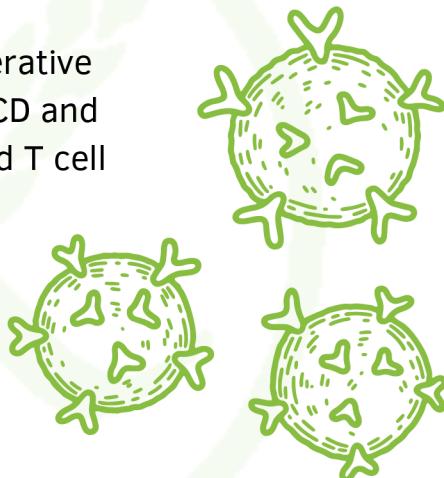
7

November

NKp46, a NK receptor expressed by lymphocytes,

can be a biomarker as well as a possible therapeutic target

for T cell lymphoproliferative diseases, like type 2 RCD and enteropathy-associated T cell lymphoma.



Friday

8 November

SMALL BOWEL ADENOCARCINOMA

is an extremely rare cancer
in the general population (5.7
cases/1,000,000 people per
year)



but it is much more common
in patients with CD.

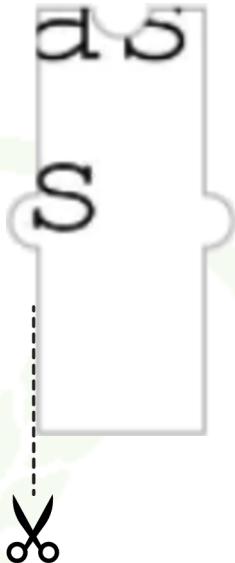


WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

9
10 November

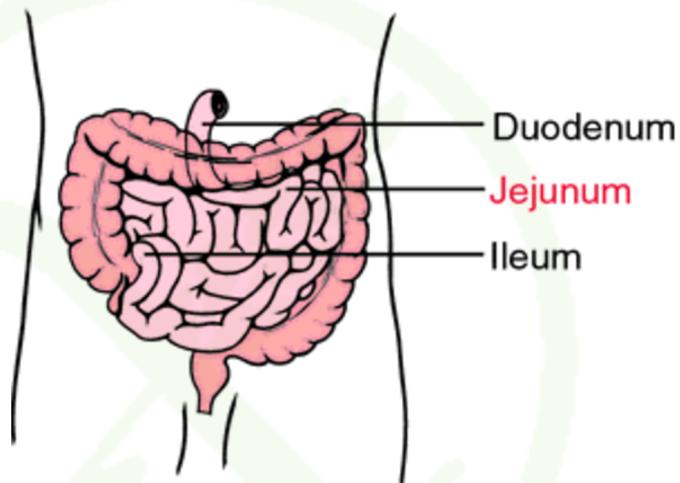
45



Monday

11 November

Small bowel adenocarcinoma is usually detected in
the jejunum.



Tuesday
12 November

Small bowel adenocarcinoma

is not preceded by RCD

and occurs
more commonly in



female
patients

Wednesday

13 November

The onset of a sudden
intestinal (sub)/occlusion or anemia

are suggestive
clinical features



of an underlying
small bowel adenocarcinoma.

Thursday

14 November

For **small bowel adenocarcinoma**, a thorough diagnostic work-up is mandatory and requires a wide array of imaging tests including:

- CT/MR-enterography
- PET
- Capsule endoscopy
- Enteroscopy



Friday
15 November

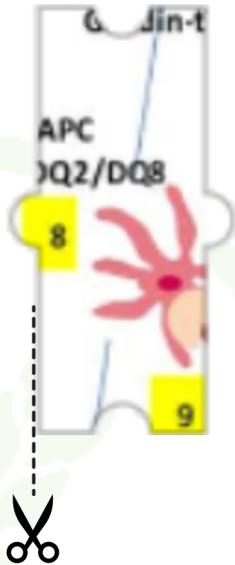
FOLLOW-UP VISITS ARE NEEDED TO

- Allow for the early diagnosis of any complications.
- Confirm compliance with the GFD
- Rule out the onset of autoimmune diseases and metabolic changes.

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun
16
17 November

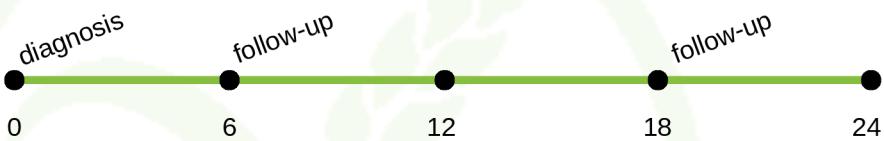
46



Monday

18 November

Usually, the **first follow-up visit** is planned within **6 months** from diagnosis and then every 12–24 months.



Should a CD-related complication occur follow up visits should be more frequent, every 3–6 months.

Tuesday

19 November

Follow up visits include:

a consultation with a dietician

blood tests including



folate
ferritin
vitamin D3
transaminases
metabolic profile
anti-thyroglobulin
complete blood count
anti- thyroidperoxidase
thyroid stimulating hormone
anti-tTG IgA (or IgG in case of IgA deficiency)

Wednesday

20 November

The first follow-up should include a screening of



ANTINUCLEAR

antibodies

NON-ORGAN-SPECIFIC

autoantibodies

to rule out the presence of markers predictive of autoimmune diseases associated with CD.

Thursday
21 November

If a CD-related complication occurs

FOLLOWING-UP TESTS

in addition to standard test

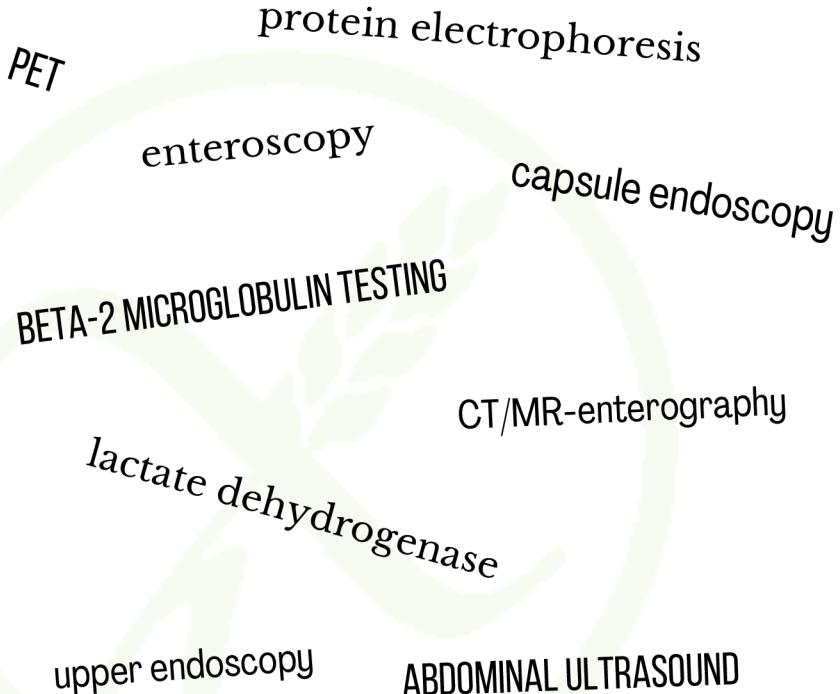
should be performed.



Friday

22 November

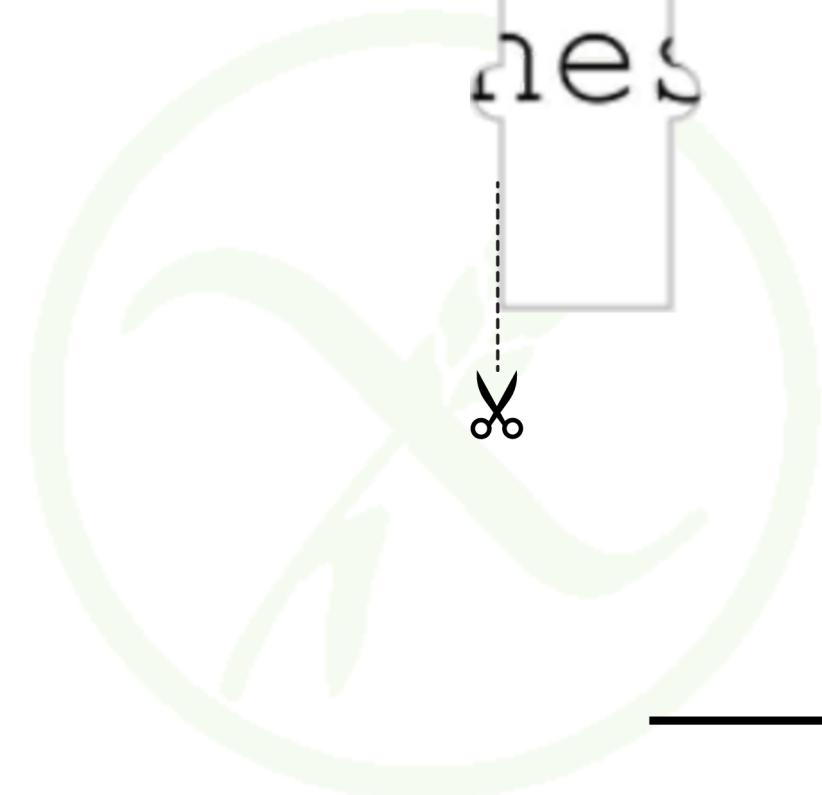
Follow-up tests for complications include:



WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun
23
24 November

47



Monday

25 November

After 12-18 months of a GFD for adults

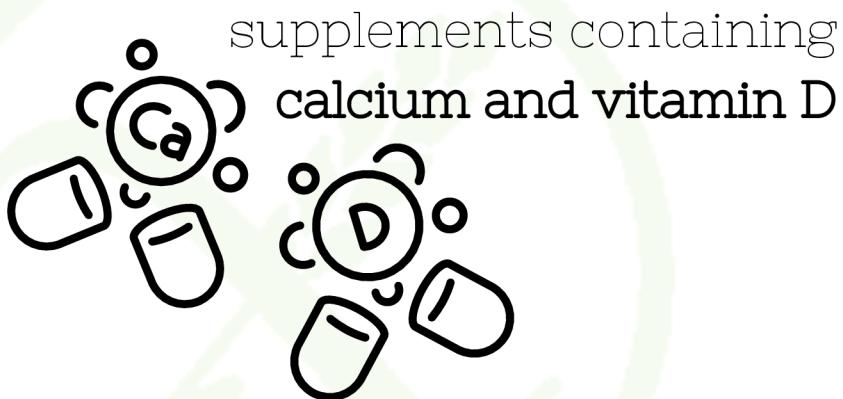


BONE DENSITY SCANS

should be performed and repeated regularly only if abnormal or in case of other indications.

Tuesday
26 November

Patients with **osteopenia**
should be treated with



Wednesday

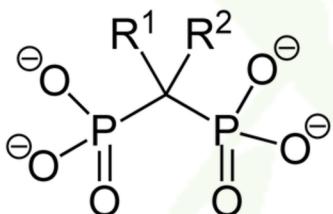
27 November



CD patients with

OSTEOPOROSIS

should be treated with



BISPHOSPHONATES

Thursday
28 November



Friday
29 November

AN ABDOMINAL ULTRASOUND

can be used to test patients for

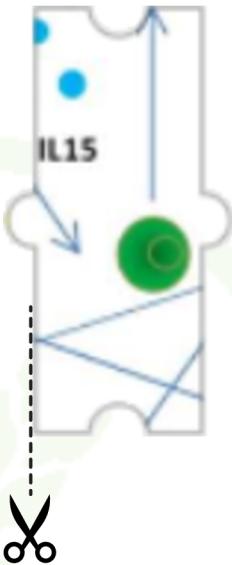
SPLEEN ABNORMALITY



WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun
30 November
1 December

48



Monday

2 December



BODY WEIGHT INCREASE

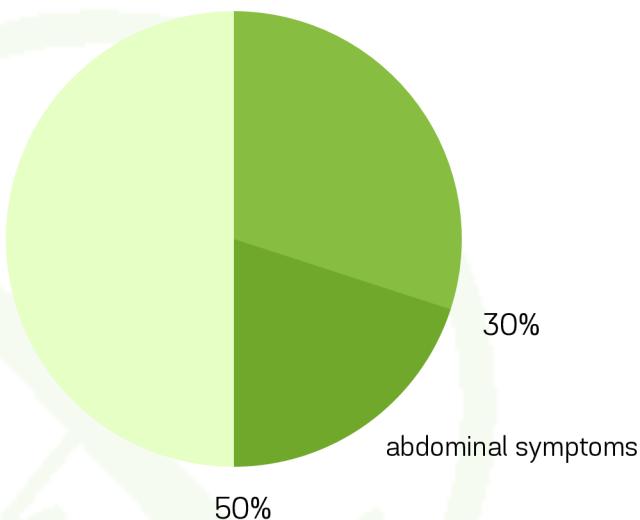
may occur as a consequence of

an excessive consumption of dietary
products high in vegetable fats
commonly present in GFD.

Tuesday

3 December

Although a strict GFD, CD patients may experience **abdominal symptoms** due to IBS in 30– 50% of cases.



Wednesday

4 December

Abdominal symptoms may respond to:

dietary recommendations

as well as

symptomatic drug therapy.



Thursday

5 December

A SELF-ADAPTED GFD

without the support of a nutritionist

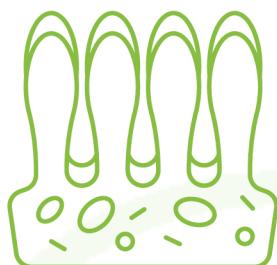
CAN CAUSE VITAMIN AND TRACE METAL
DEFICIENCY



and should be supplemented
if needed.

Friday

6 December



To check the **regrowth of villi** in adult patients on a GFD,

physicians may consider performing a follow-up **duodenal biopsy**.



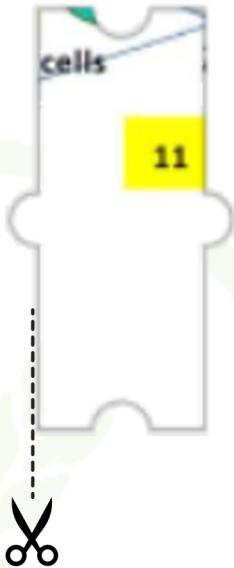
Sat + Sun

WEEKEND EDITION'S
PUZZLE PIECE NO.

7
8

December

49



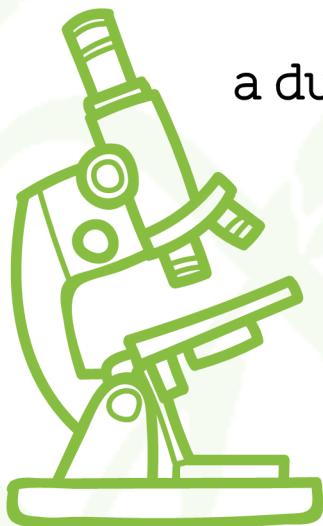
Monday

9 December

For patients with

no or partial clinical response to gluten withdrawal,

a duodenal histopathology is advisable.



Tuesday
10 December

The average time to regrow the villi
could take up to

3 YEARS

Wednesday

11 December

GIP ASSESSMENT

can be performed on stool samples

and may be useful
for monitoring
the adherence
to a GFD.



Thursday
12 December

Autoimmune thyroiditis

as a complication should always be screened for both adults and children.



Friday
13 December



CHILDREN WITH CD HARDLY EVER DEVELOP
COMPLICATIONS, UNLIKE ADULTS.

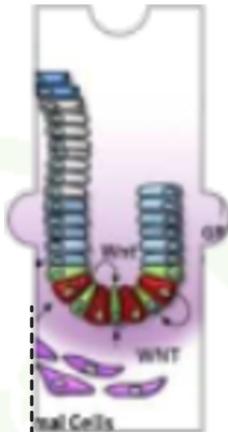
WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

14
15

December

50



Monday

16 December

CHILDREN WITH CD SHOULD BE

followed up after 6 months

from diagnosis and then every year to check:

- Symptomatic improvement
- Adherence to GFD
- Quality of life
- Progressive normalization of CD-related antibodies

Tuesday
17 December

Currently

the only effective treatment

available for CD is

a strict GFD for life



Wednesday

18 December

CRUCIAL ADVANTAGES OF GFD:

- Leads to the resolution of intestinal and extraintestinal symptoms
- Negativity of autoantibodies
- Regrowth of the intestinal villi
- The diet offers a partial protective effect towards several complications.

Thursday
19 December

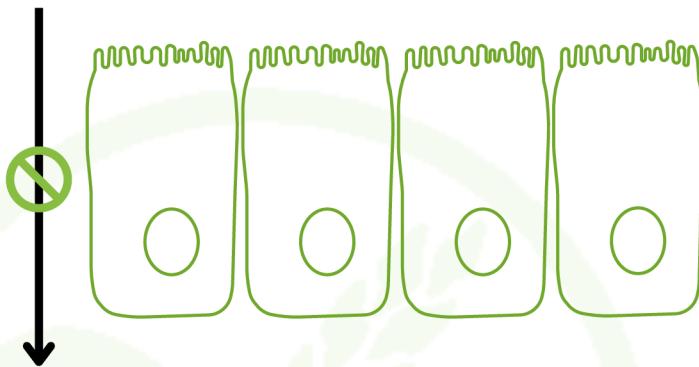
POSSIBLE DISADVANTAGES OF GFD:

- Negative impact on quality of life
- Psychological problems
- Fear of involuntary contamination with gluten
- Possible vitamin and mineral deficiencies
- Metabolic syndrome
- Increased cardiovascular risk
- Severe constipation

Friday

20 December

Larazotide acetate is a zonulin antagonist which can block tight junction disassembly,



thereby limiting gluten crossing a permeable intestinal mucosal barrier

and has shown efficacy in gluten-related symptom control.

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

21
22

December

51



Monday
23 December

A POSSIBLE TREATMENT FOR CD IS

ALV003

which targets gluten and

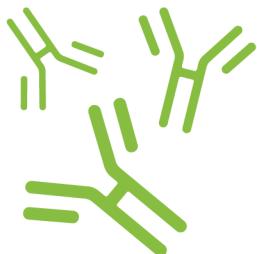
DEGRADES IT INTO SMALL FRAGMENTS IN THE STOMACH

before they pass into the duodenum.

Tuesday

24 December

IL-15 monoclonal antibodies
(AMG 714) are being investigated
in both gluten challenge and RCD
type II patients.



Additional safety studies are needed
for the acquisition and competition of
the license.

Wednesday

25 December



vaccination (Nexvax2)

is a possible therapeutic strategy aimed at desensitizing patients with CD.

to gliadin peptides.



Thursday
26 December

BREAST-FEEDING,

MODALITY OF DELIVERY,

time of gluten introduction

in the diet of infants at risk for CD
may **affect the incidence** of the disease.



Friday
27 December

Rotavirus vaccination



seems to significantly

decrease the risk of CD

in particular among children (before 6 months of age) with early gluten exposure.

WEEKEND EDITION'S
PUZZLE PIECE NO.

Sat + Sun

28
29

December

52



Monday
30 December

Reference Article

Caio, G., Volta, U., Sapone, A., Leffler, D. A.,
De Giorgio, R., Catassi, C., & Fasano, A.
(2019). Celiac disease: a comprehensive current
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doi:10.1186/s12916-019-1380-z

Tuesday

31 December

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