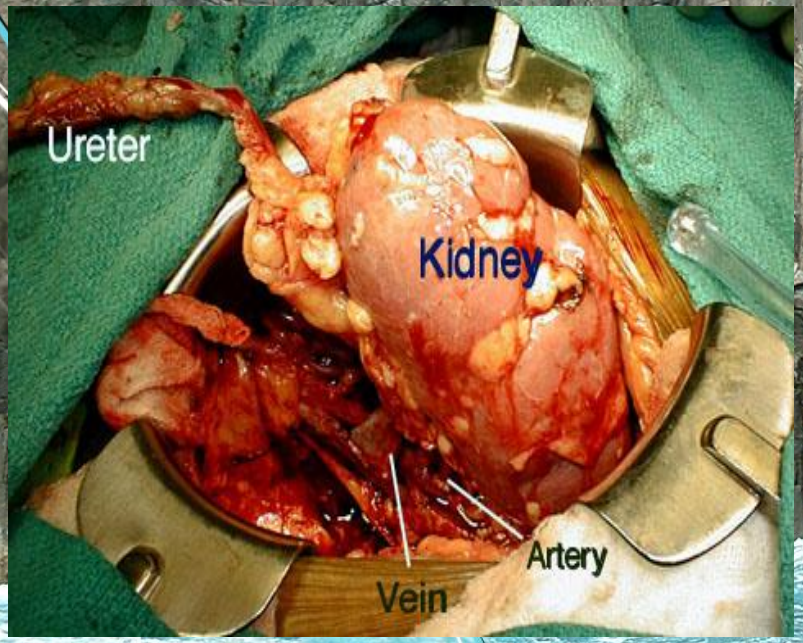
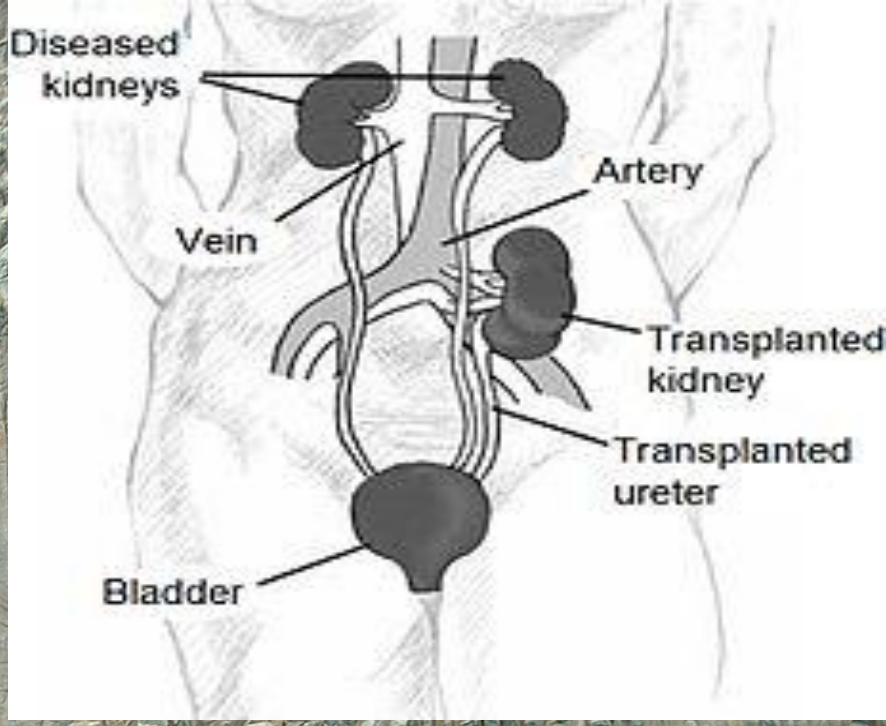
Renal Transplantation; where do we stand today?



Ioannis Griveas


Diseased kidneys
Artery
Vein
Transplanted kidney
Transplanted ureter
Bladder


www.vesalius.com

Key Issues in Organ Transplantation

- Organ shortage
- Chronic rejection
- Long-term complications of permanent immunosuppression:
  malignancies, infections, organ toxicities

Factors influencing long- term outcome

Pre - Tx		Post - Tx
DONOR	**RECIPIENT**	
• age	• age	• specific diseases
• source	• preformed Ab	• calcineurin-inhibitors
• HLA match	• immune reactivity	• factors progression
	• waiting time	• tx glomerulopathy
	• viral status	• chronic rejection

Background History

Haemagglutination was the technique first used – and that continues to be used.

1910 – shown to have inherited characteristics

1950s represented oligosaccharides

1990 the gene encoding the enzymes responsible for synthesis of ABO antigen was cloned.

ABOi therapy

ANTIBODY REMOVAL

Plasma exchange

Double Filtration Plasma Exchange

Immunoadsorption

ANTIBODY SUPPRESSION

Splenectomy

Anti-CD20

Anti-CD52

IVIg

TABLE 4. Patient and graft survival among 60 ABOi kidney transplant recipients transplanted at the Johns Hopkins Hospital between 1999 and 2007

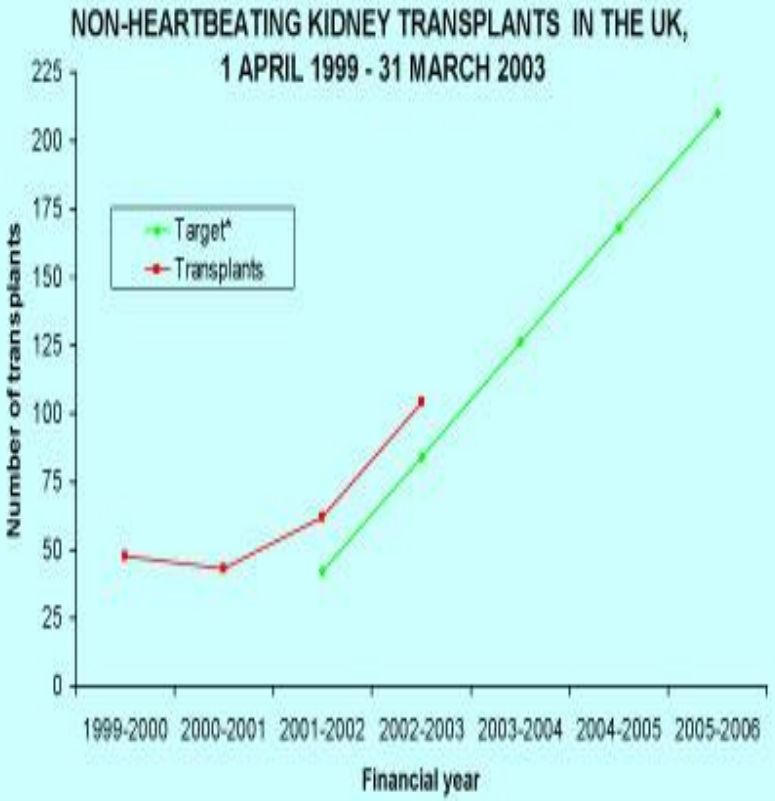
	ABOi cohort	
Years posttransplant	Graft survival[a] (%)	Patient survival[b] (%)
1 yr	98.3	96.3
3 yr	92.9	96.3
5 yr	88.7	89.4

Reported survival was determined using Kaplan-Meier estimation.

[a] Death-censored graft survival; 4 graft losses occurred in the first era cohort and were secondary to non-compliance (n=1), recurrent disease (n=2), and thrombotic microangiopathy (n=1).

[b] All 3 patients died with a functioning graft; 3 patient deaths were secondary to West Nile virus, sudden cardiac death, and metastatic liver cancer.

ABOi, ABO incompatible.



Maastricht classification

- Category I- dead on arrival-uncont.
- Category II- Failed resuscitation-uncont.
- Category III- Awaiting cardiac arrest-controlled
- Category IV-Cardiac arrest, brain dead-controlled
- Category V- Unexpected cardiac arrest in ITU

WOULD I BE WILLING TO DONATE A KIDNEY?

NO!

YES to my child - parent - sibling – relative - partner or even friend

FEARS:

- risks of pre-op testing
- potential surgical complications, all: 12.2% -. 63% (13 centers)
  - complications, severe : 0% - 13% (18 centers)
- risks of anesthesia: complications: 1 in 10,000 – 30,000
- jeopardize my own long term health
- physical stress (pain)
- psychological stress due to high expectations
  1) unsuccessful result?
  2) Do I even want to know exactly how (un)healthy I am?
  3) change in relationship
  4) paternity?
- economic and time factors

MOTIVES:

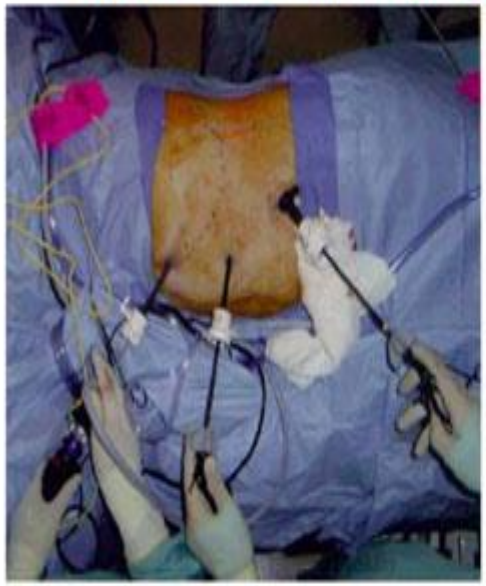
- social pressures (family, society, associates)
- it´s not fair, I´m healthy, you´re not - bad conscience
- good reputation, raise your self esteem (I´m a hero!)
- improve my own quality of life (healthy partner)

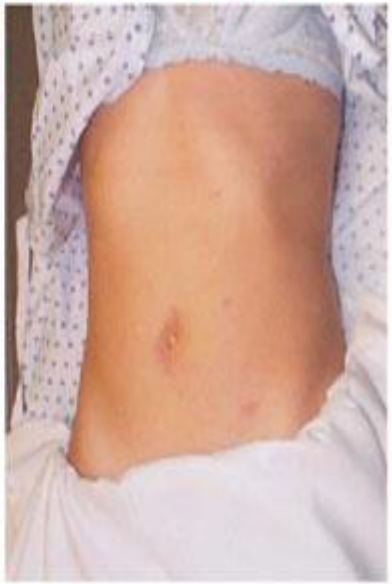
Guidelines for living kidney-donors

1) Check the health of the donor including BMI
2) Consider any alternative treatment available for the recipient (Transplantation vs Dialysis)
3) Make the risks clear
4) Elucidate the motivation

Laparoscopic Living Donor Nephrectomy For Kidney Transplantation

Stephen T. Bartlett, M.D., Eugene J. Schweitzer, M.D.





less pain, shorter hospitalisation, rapid return to normal activity, improved cosmetic result

Risks associated with donation

Possible long term complications:

- Hypertension/proteinuria
- Quality of life compromised
- Long term mortality increased?

Risk for proteinuria

Follow-up of 63 donors for about 20 years

	Baseline	Present	Controls=50 donor sibling
Proteinuria	0%	8%	9%

- Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living kidney donors. Lancet 1992, 340: 807

Risk for hypertension

Follow-up of 63 donors for about 20 years

	Baseline	Present	Controls=50 donor sibling
BP	118/76	134*/80	130/80
BP medication	0%	32%	44%

- Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living kidney donors. Lancet 1992, 340: 807

Results from the metanalysis

- GFR reduction 17 ml/min
  - Tendency for improvement with time, 1.3 ml/min for each 10 years
- Proteinuria- marginal increase
- Blood pressure increase of 2,7 mm Hg
  - Subsequently one mm Hg up/decade
  - Incidence of hypertensjon - not increased

Quality of life assessment of previous kidney donors

Investigation of 478 kidney donors

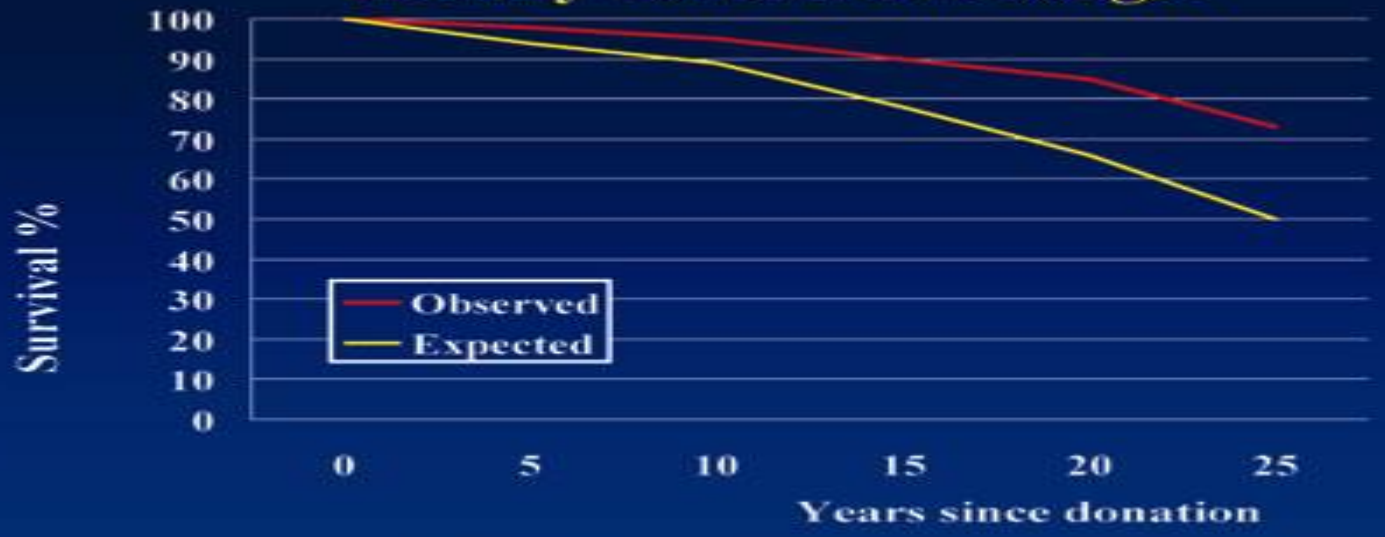
Has the donation impaired your health?

Not at all	446	(93,3%)
A little	29	(6,1%)
Significantly	3	(0,6.%)

Conclusions from mortality studies

- Observed mortality is less than expected in the general population
- Observed mortality is equal to what is seen in healthy people beeing accepted for life insurance

Kidney donors live longer



Fehrman-Ekholm et al. Transplantation 1997

Clinical work-up in aged transplant recipients

- Maximize cardiovascular investigation
- Intensive research of hidden malignancy
- Nutrition state
- Rehabilitation degree

How did it start?

Lindberg and Carrel
1935:

Normothermic, pulsatile

Future

- Betteroxygen delivery: perfluorocarbons
- Long term preservation
- Reversing ischaemic damage
- Immunological manipulation

Machine preservation: pulsatile, non pulsatile and cold

- 'Home made'
- Waters
- Organ Recovery Systems

European trial

- Less DGF after machine perfusion (70 v 89, p=0.01)
- Better 1 year graft survival after machine perfusion (94 v 90% p=0.04)
- In extension study of DCDs, DGF reduced from 70 to 54%

• *Pirenne Trans Int 2009*

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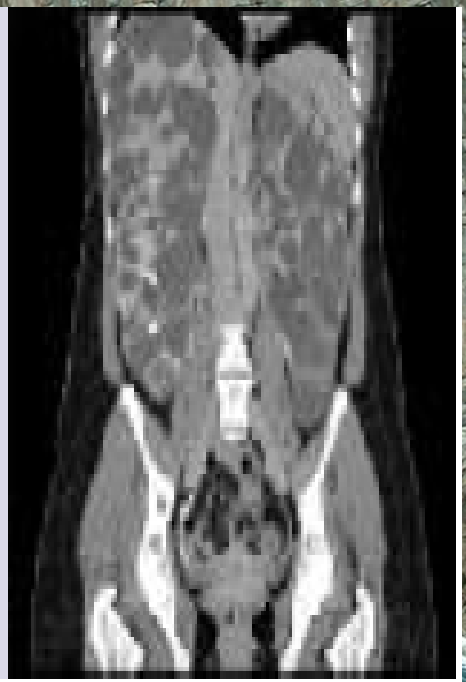
Kidney Transplantation in Patients with Autosomal Dominant Polycystic Kidney Disease

Mr D van Dellen
Dr D Benavente
Dr I Griveas
Dr L Foggensteiner

PAGE 7



Specific diseases causing CGD

Recurrent diseases

Thrombotic microangiopathy

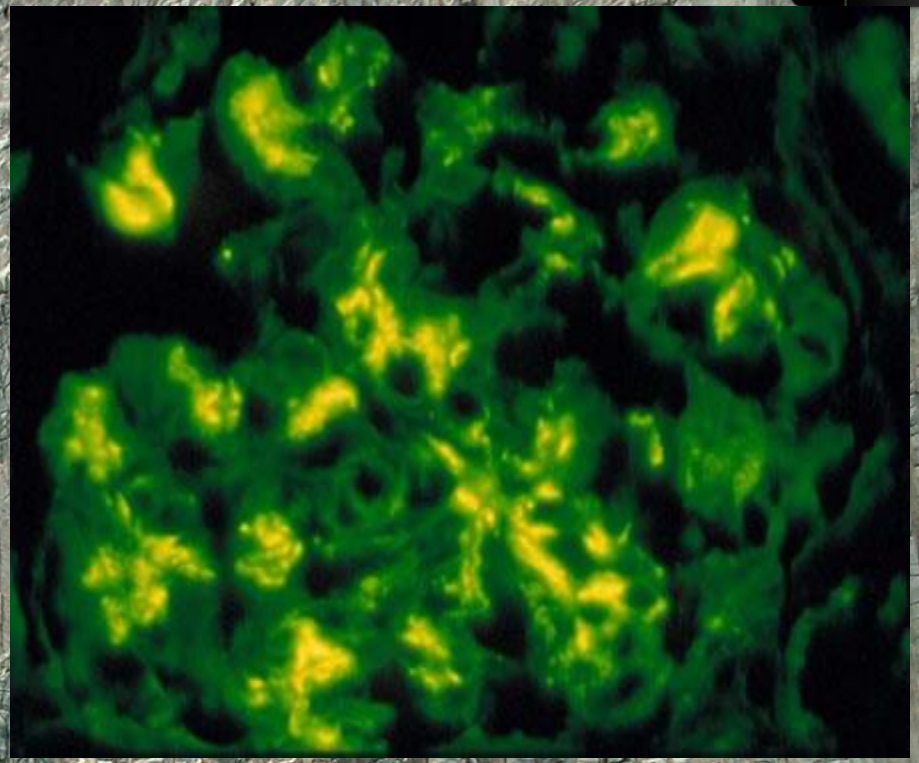
BK nephropathy

Interstitial nephritis

De novo GN

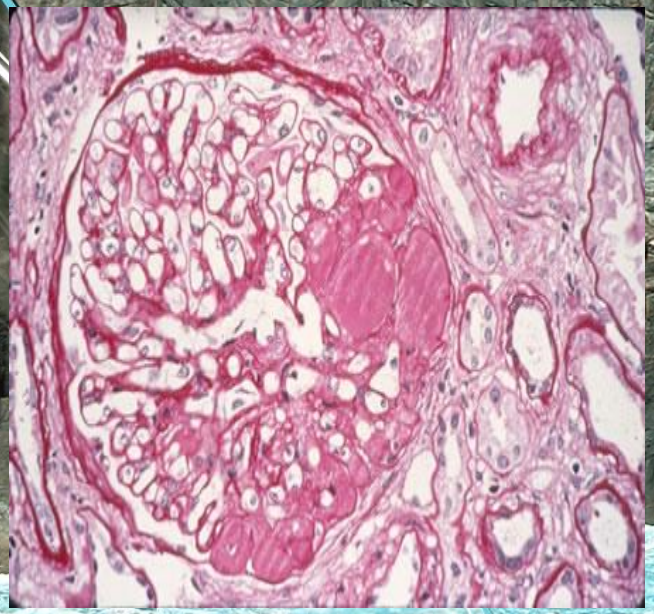
Risk of recurrence of IgA GN after renal transplantation

Author	*Pts*	*Recurrence*
Berger 1988	32	17 (53%)
Schwartz 1991	8	1 (12%)
Odum 1994	46	28 (61%)
Hartung 1995	128	47 (38%)
Kessler 1996	28	13 (46%)
Klur 1996	75	36 (30%)
Frohnert 1997	51	14 (26%)
Ohmacht 1997	61	33 (61%)
Bumgardner 1998	61	18 (29%)
Freese 1999	104	13 (12%)
Hariharan 1999	22	3 (13%)
Jain 2002	56	6 (11%)
Total	**672**	**229 (34%)**



Recurrence of FSGS after transplantation

Frequency	20-30%
	85-100% retransplants
Median time	14 days
Presentation	Proteinuria usually nephrotic



Graft outcome in pts with recurrence of FSGS

Children median survival 5 months
(Erich NDT 1992)

Adults 84% lost graft function within 32 months (1-104)

(Hariharan AJKD 1999)

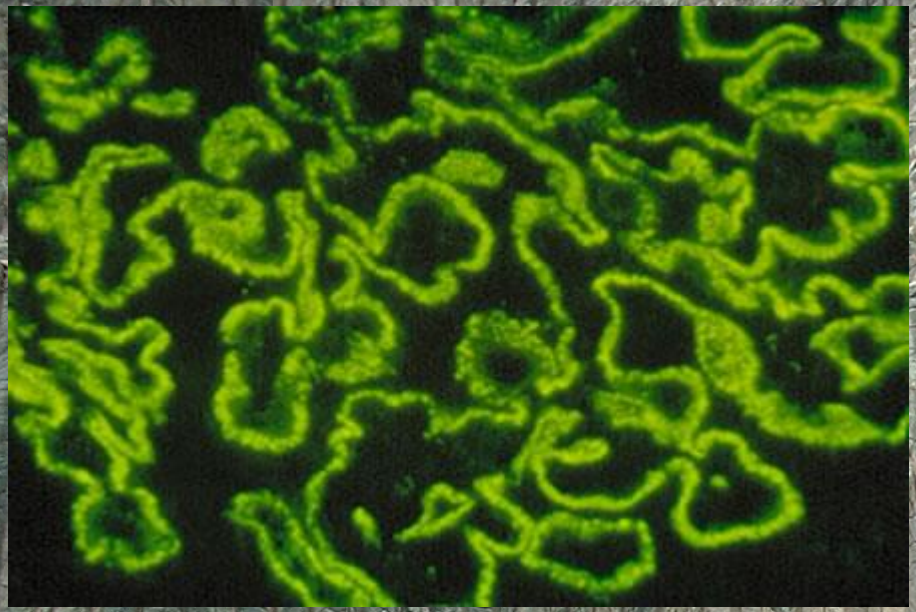
Conclusions 1

Focal and segmental glomerulosclerosis

- May recur in 20-30% of renal transplants
- Recurrence occurs early after transplantation
- Pts with recurrence have reduced graft survival
- Plasmapheresis may be helpful in several cases of recurrence

Conclusions 2

- In spite of the high risk of recurrence FSGS is not a contraindication to renal transplantation
- In case of living donation the possibility of early recurrence leading to graft loss should be clearly explained to the potential donor and recipient



Problems in defining MN recurrence

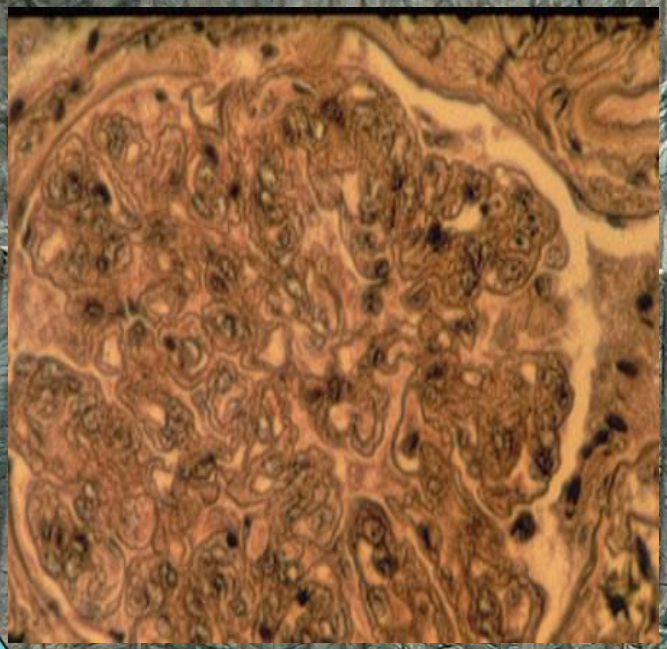
- MN is a rare cause of ESRD
- Recurrent MN and "de novo" MN are histologically indistinguishable

Recurrent MN after transplantation

Author	Pts		Recurr.	%
Morzycka	7		4	57
Berger	25		1	4
Montagnino	9		3	33
Lustig	11		4	36
Couchoud	19		5	26
Marcen	6		3	50
Odorico	64		13	20
Cosyns	12	27?	3?	25
Total	153		36	24%

CONCLUSIONS

- MN may recur in 20-30% of adults
- No predictive factor for recurrence is identifiable
- Spontaneous remission is rare
- Most patients progress to ESRD, but in many cases graft failure is caused by rejection rather than recurrence



Risk of recurrence in type 1 MPGN

Children	64% (Habib 1987)
	7% (Alexander 1990)
Adults	48% (Andresdottir 1997)
	3% (Shimizu 1998)
Median time	20 months, 1-45 (Andresdottir 1997)

Risk factors for recurrent MPGN 1

No risk factor has been identified

Prognosis for recurrent MPGN type 1

2-year graft survival 86%
(Briggs and Jones 1999)

Mean graft survival 40 months
(Andresdottir 1997)

Is there any effective therapy for recurrent type 1 MPGN?

Pasmapheresis
(Muczynski1995, Saxena 2000)

Cyclophospamide
(Lien 2000)

Anti-CMV therapy
(Andresdottir 2000)

Conclusions

- MPGN type 1 is not a contraindication to renal transplantation
- The risk for recurrence is poorly determined
- The impact of recurrence on graft survival is still unclear

Recurrence of dense deposit disease

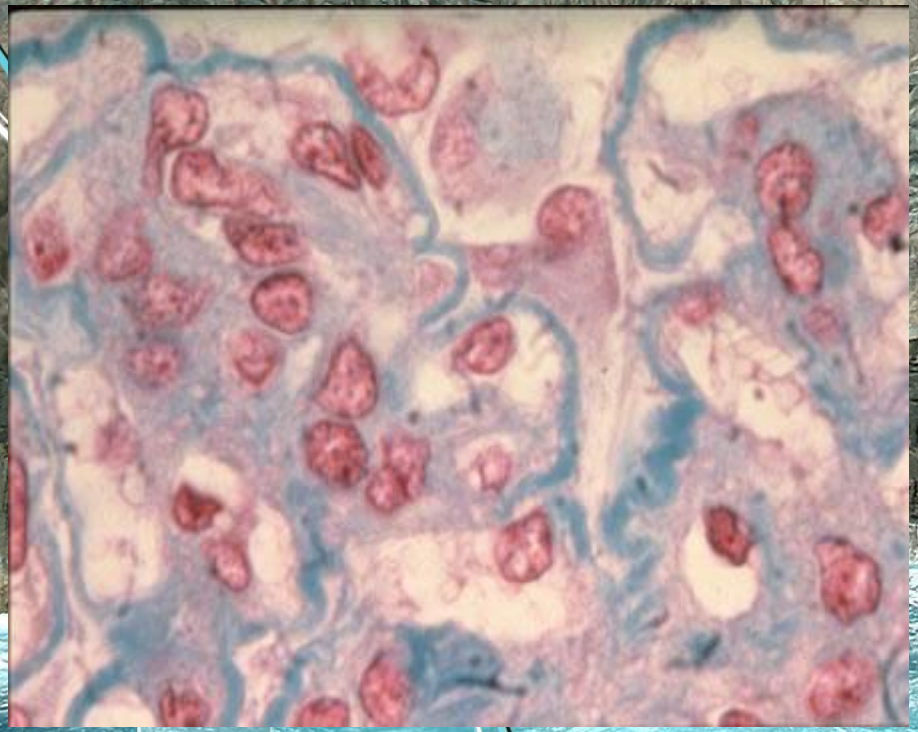
Histological: 85-100%

Clinical: ~ 10%

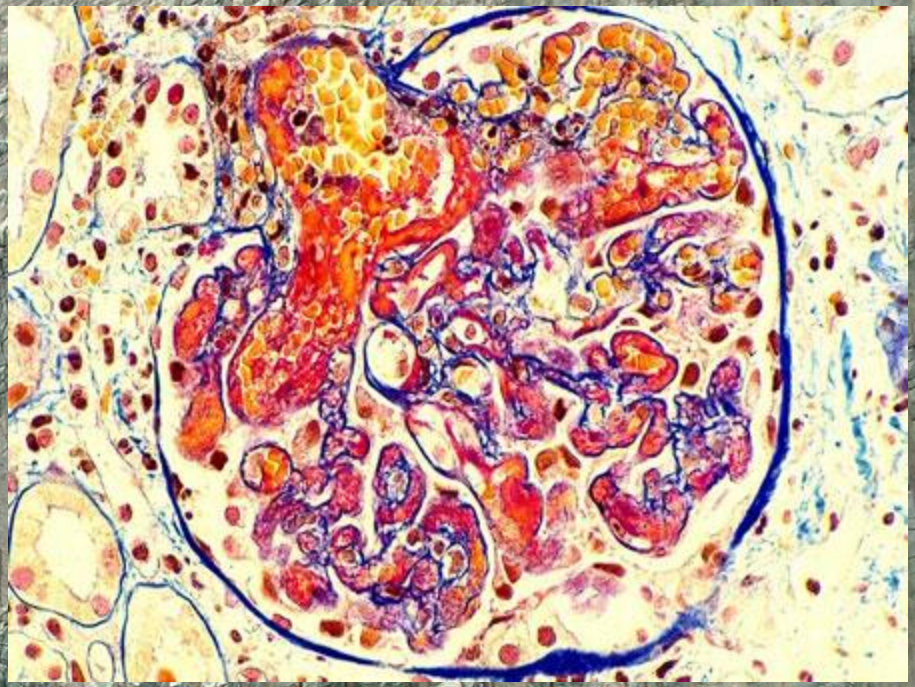
Graft failure: 28% in children

10-13% in adults

Data from: Habib (1987) Cameron (1991)
Mathew (1991) Hariharan (1998)
Andresdottir (1999)



DE NOVO THROMBOTIC MICROANGIOPATHY



ETIOLOGY

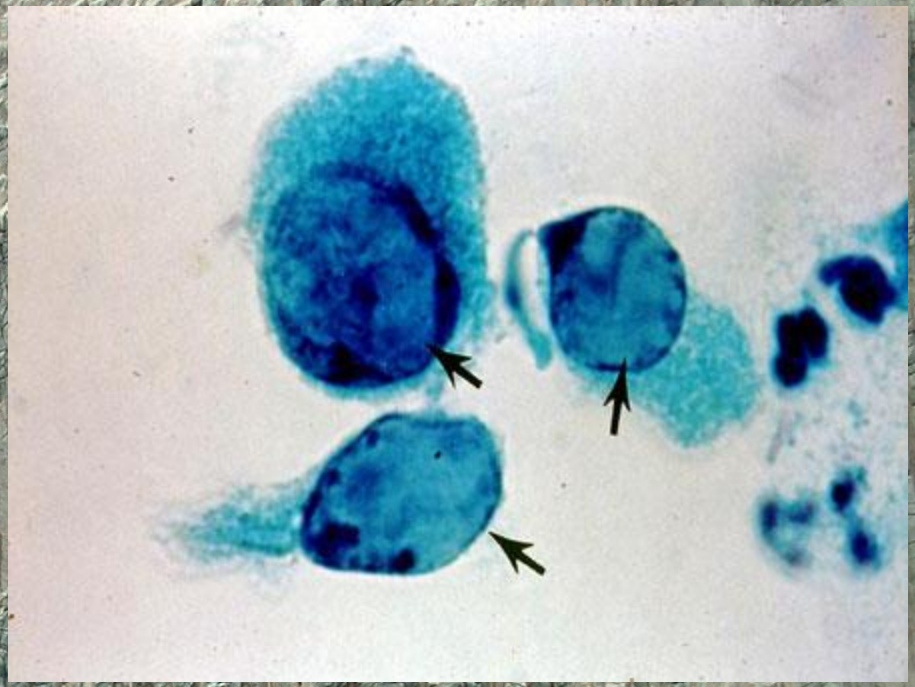
Calcineurin inhibitors;
anti-mTOR agents;
OKT3

TREATMENT

Removal offending drug
Plasmapheresis

POLYOMA BK NEPHRITIS

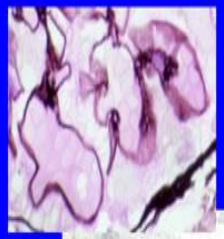
• INCIDENCE	• 5-6%
• ETIOLOGY	• Reactivation BKV
• DIAGNOSIS	• Decoy cells, cytopathic changes, simian virus MAB,PCR
• PROGNOSIS	• Severe
• TREATMENT	• Reduce IS, Leflunomide



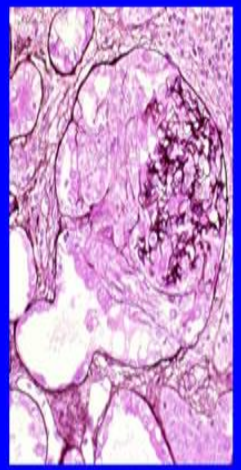
INTERSTITIAL NEPHRITIS

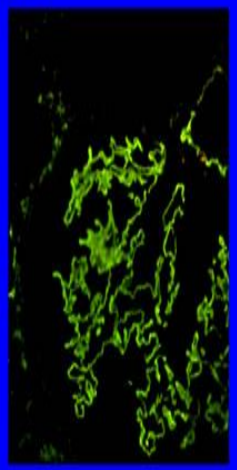
- VIRUS
  - CMV, HV 1-2, Adenovirus
- DRUGS
  - Antibiotics, Sulphonamides, Allopurinol, Diuretics, NSAID

de novo Membranous Glomerulonephritis



Cresentic glomerulonephritis in Alport patients





IgG

De novo Glomerular Disease

Membranous glomerulonephritis	*chronic transplant glomerulopathy*
Focal glomerulosclerosis	*primary*
	secondary
anti-GBM glomerulonephritis	*Alport disease*
Membranoproliferative glomerulonephritis I	*HCV, CMV, EBV*
Congenital nephrotic syndrome, Finnish type	*ab-mediated*
Transplant glomerulopathy	*acute, chronic*
Thrombotic microangiopathies	*drugs: CsA, tacrolimus, OKT3*
	virus: parvovirus, CMV, influenza A

Non specific factors of progression

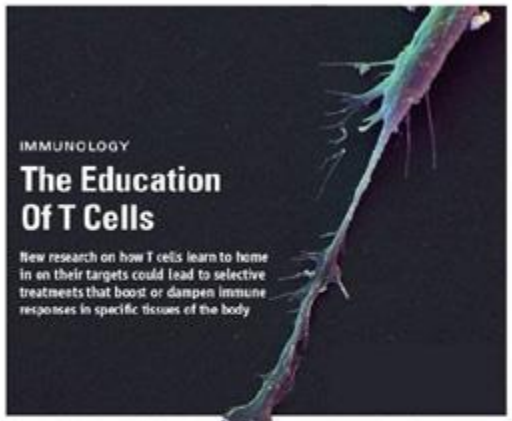
Diabetes

Arterial hypertension

Drug nephrotoxicity

Proteinuria

CMV infection



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Ferber, *Science*, 2007

How near are we to reaching the point where transplant tolerance will become a clinical reality?

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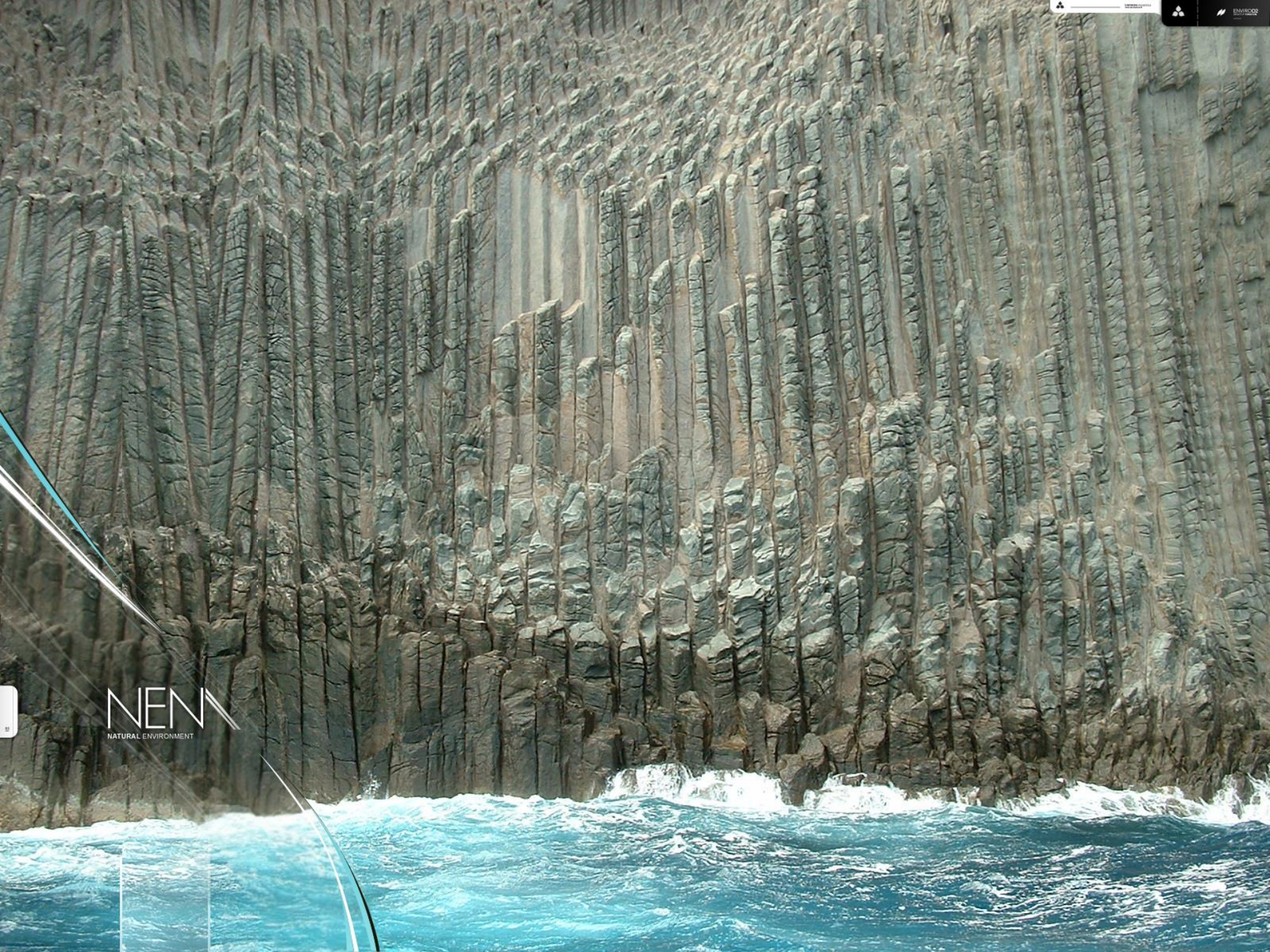
Transplantation Tolerance:
- Elements of Definition -

- Long-term acceptance of grafted tissue in absence of continuous immunosuppression

- Donor-specific immune unresponsiveness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Renal Transplantation; where to we stand today?

Pre-transplant factors

FACTOR	OPTIMAL	REAL
HLA	Identical	Mismatch
Donor source	Living	15 % (2001)
Donor age	Young adult	Older and older
Recipient age	Young adult	Older and older
Anti-HLA Ab	Absent	Variable
Dialysis duration	No dialysis	Longer and longer


Renal Transplantation; where to we stand today?
Ioannis Griveas
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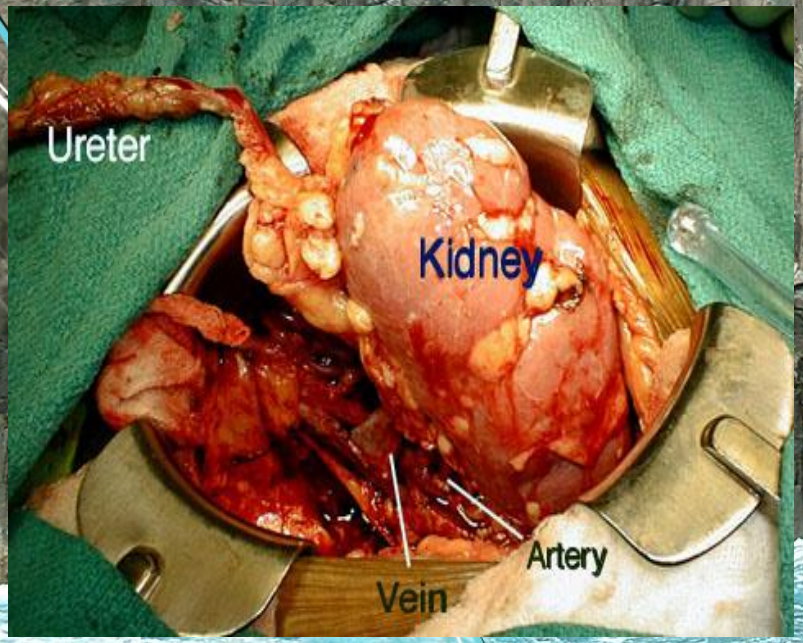
Renal Transplantation; where to we stand today?



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Renal Transplantation; where to we stand today?
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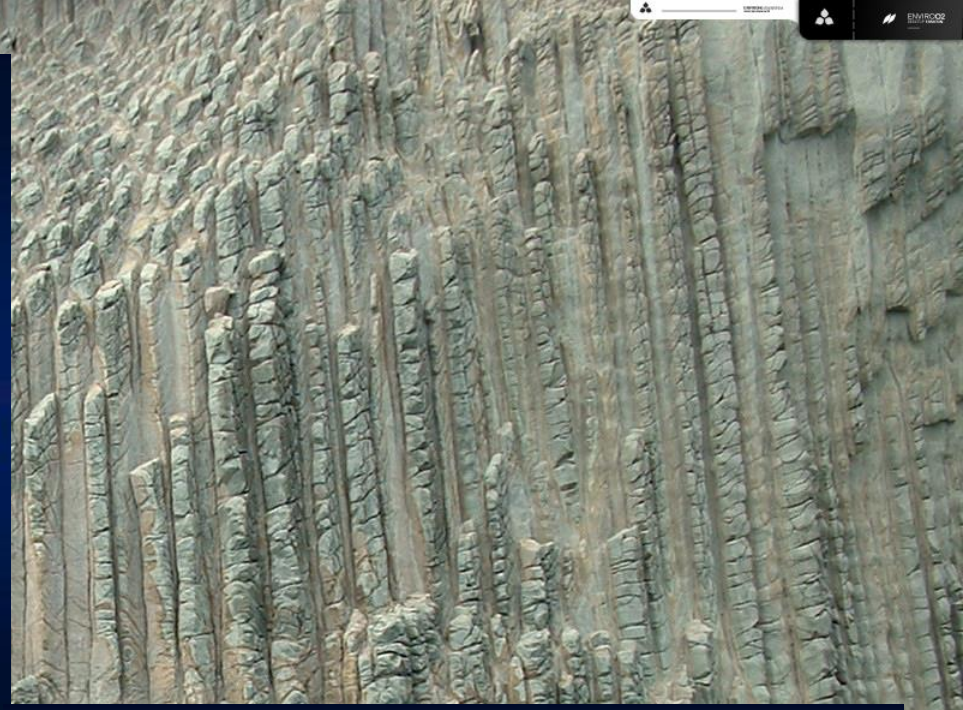
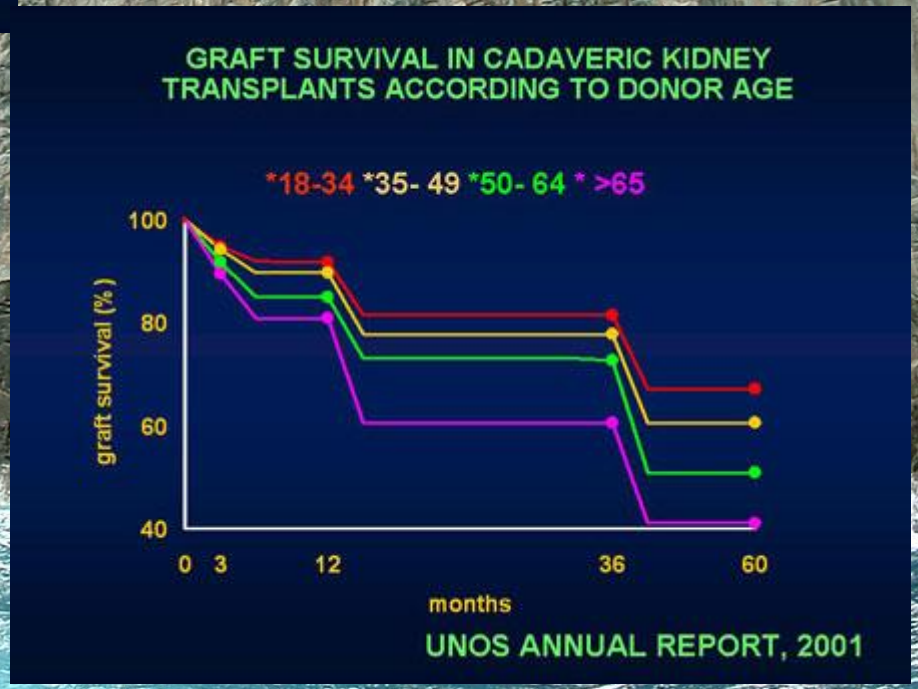
Factors influencing long- term outcome

Pre - Tx		Post - Tx
DONOR	**RECIPIENT**	
• age	• age	• specific diseases
• source	• preformed Ab	• calcineurin-inhibitors
• HLA match	• immune reactivity	• factors progression
	• waiting time	• tx glomerulopathy
	• viral status	• chronic rejection





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Patients with biopsy-proven recurrence of IgA after transplantation

Recurrence	37/106 (35%)
Signs or symptoms of IgA GN in non biopsied patients	3/49 (6%)
Time at clinical diagnosis (mo)	46.9 ± 44.3
Time at biopsy diagnosis (mo)	61.7 ± 50.6

Predictors of FSGS recurrence

Aggressive initial course (ESRD <3yrs)

Age (less than 15 yrs)

Mesangial proliferation at biopsy

Recurrence in a previous transplant

Senggutuvan P Pediat Nephrol 4,21,1990

Tejani A JASN 2,S258,1992

Artero M Am J Med 92,375,1992

Kim M Kidney Int 45,1440, 1994

Baum M Kidney Int 59,329,2001

Circulating factor(s)

30-50 KD plasma protein bound to IgG which may be removed by plasma-exchange or by immunoadsorption by Protein A

(Savin VJ 1996, Dantal J 1998)

Risk of recurrence and permeability factor

(Dall'Amico R. et al AJKD 34,1048,1999)

	Recurrence after Tx
PF positive	11/13
PF negative	4/12
OR	10.99 (C.I. 1.6-75)

Plasmapheresis for recurrent FSGS

Adults

PD= Pheresis dependent

	Patients	Remission
Artero 1994	9	6
Dantal 1996	10	8 (8 PD)
Andresdottir 1999	7	3 (2 PD)
Osubo 1999	11	7
Matalon 2001	13	4 (3 PD)
Moriconi 2001	3	2
Ponticelli 2002	3	3 (1 PD)
Total	56	33 (59%)

The different patterns of response to plasmapheresis

Complete and stable remission

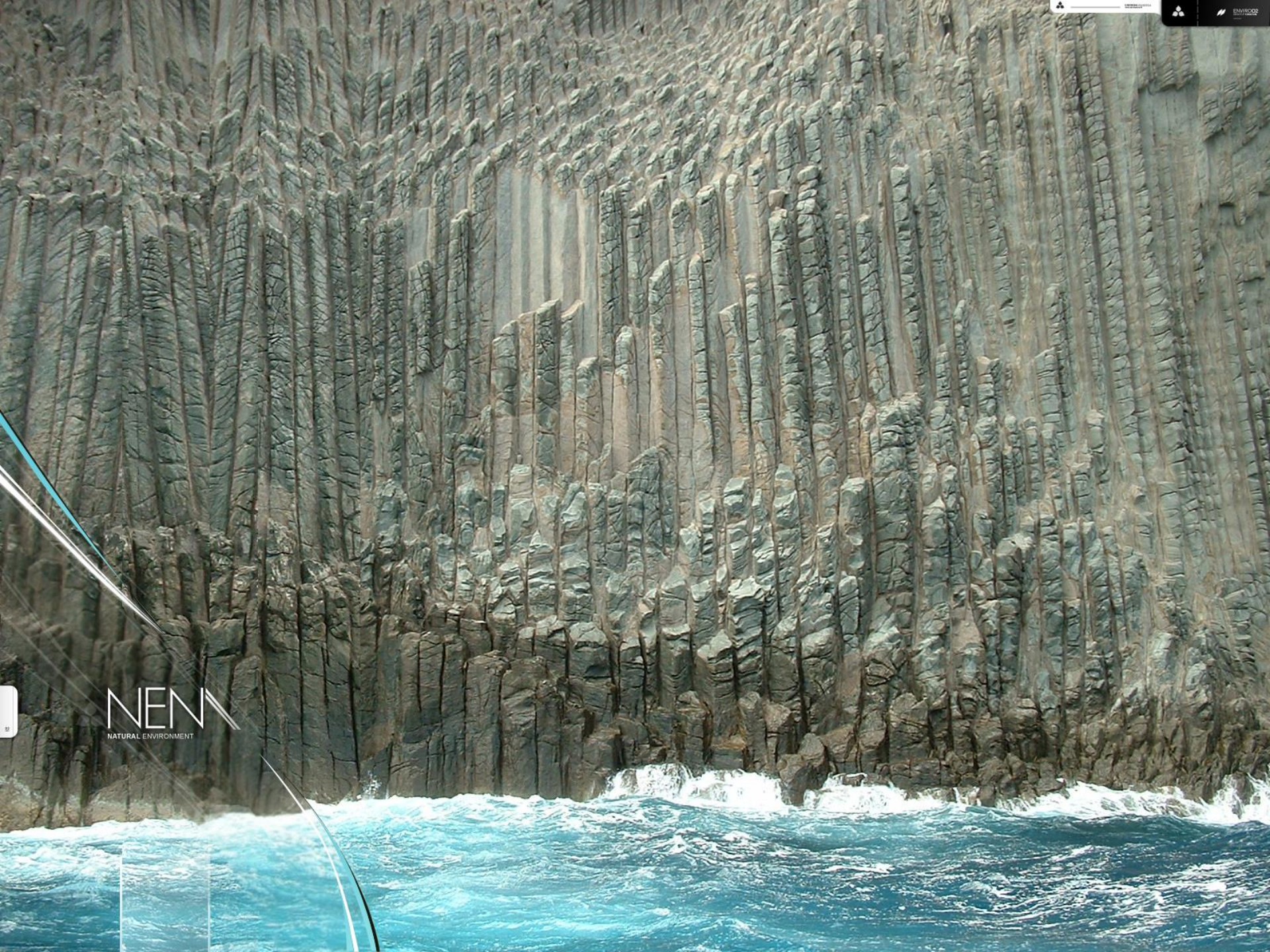
Remission (complete or partial) with relapses

Partial remission PP dependent

No response

Suggestions to prevent/treat FSGS recurrence

- Pre-Tx prophylactic PP can halve the risk (Ohta 2001)
- Start PP as soon as proteinuria appears
- Post-PP cyclophosphamide may be of benefit
- High-dose ACE-i may be of benefit
- Re-start PP in case of relapse after remission
- Continue PP in PP-dependent patients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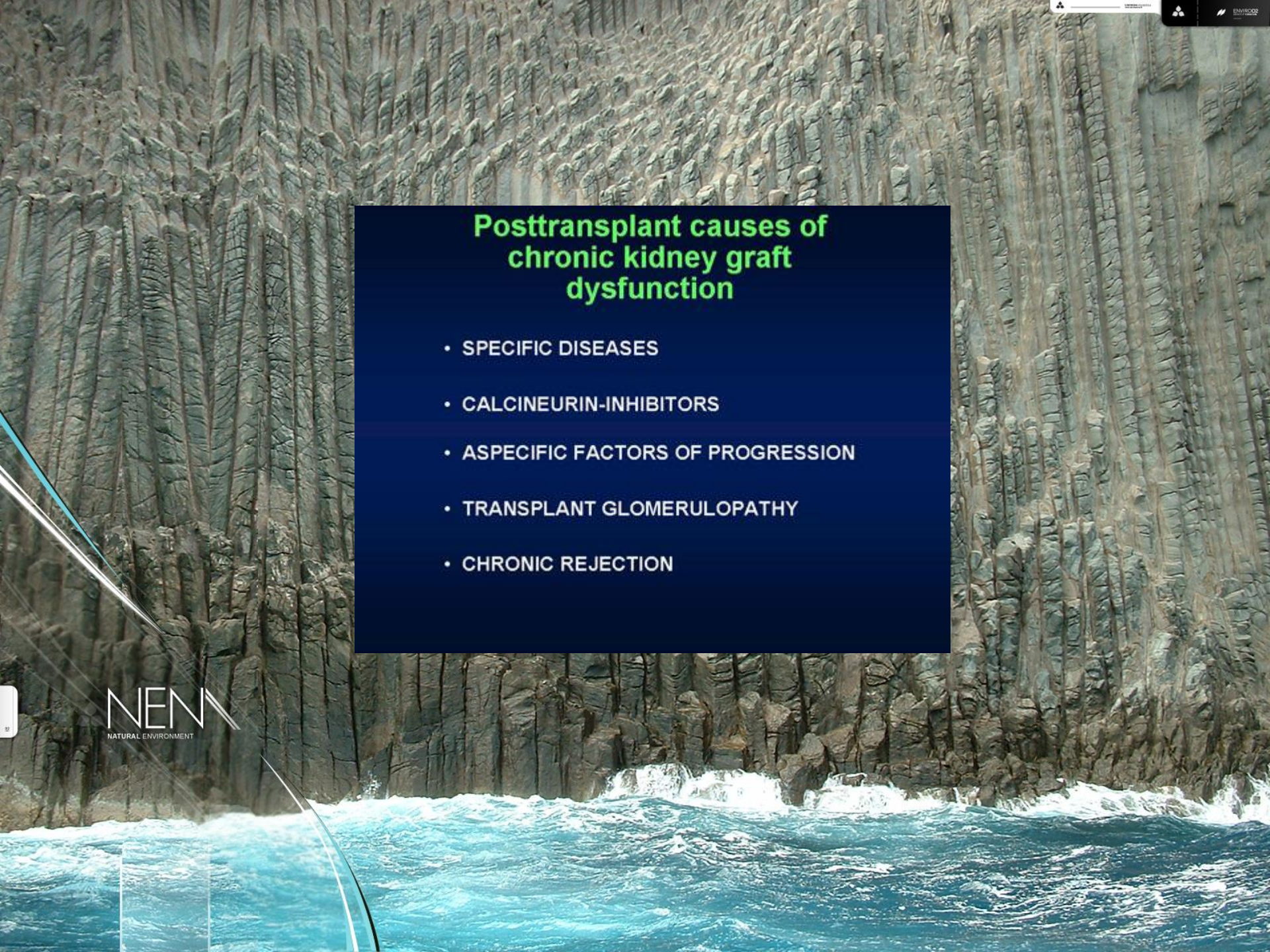
Posttransplant causes of chronic kidney graft dysfunction
• SPECIFIC DISEASES
• CALCINEURIN-INHIBITORS
• ASPECIFIC FACTORS OF PROGRESSION
• TRANSPLANT GLOMERULOPATHY
• CHRONIC REJECTION
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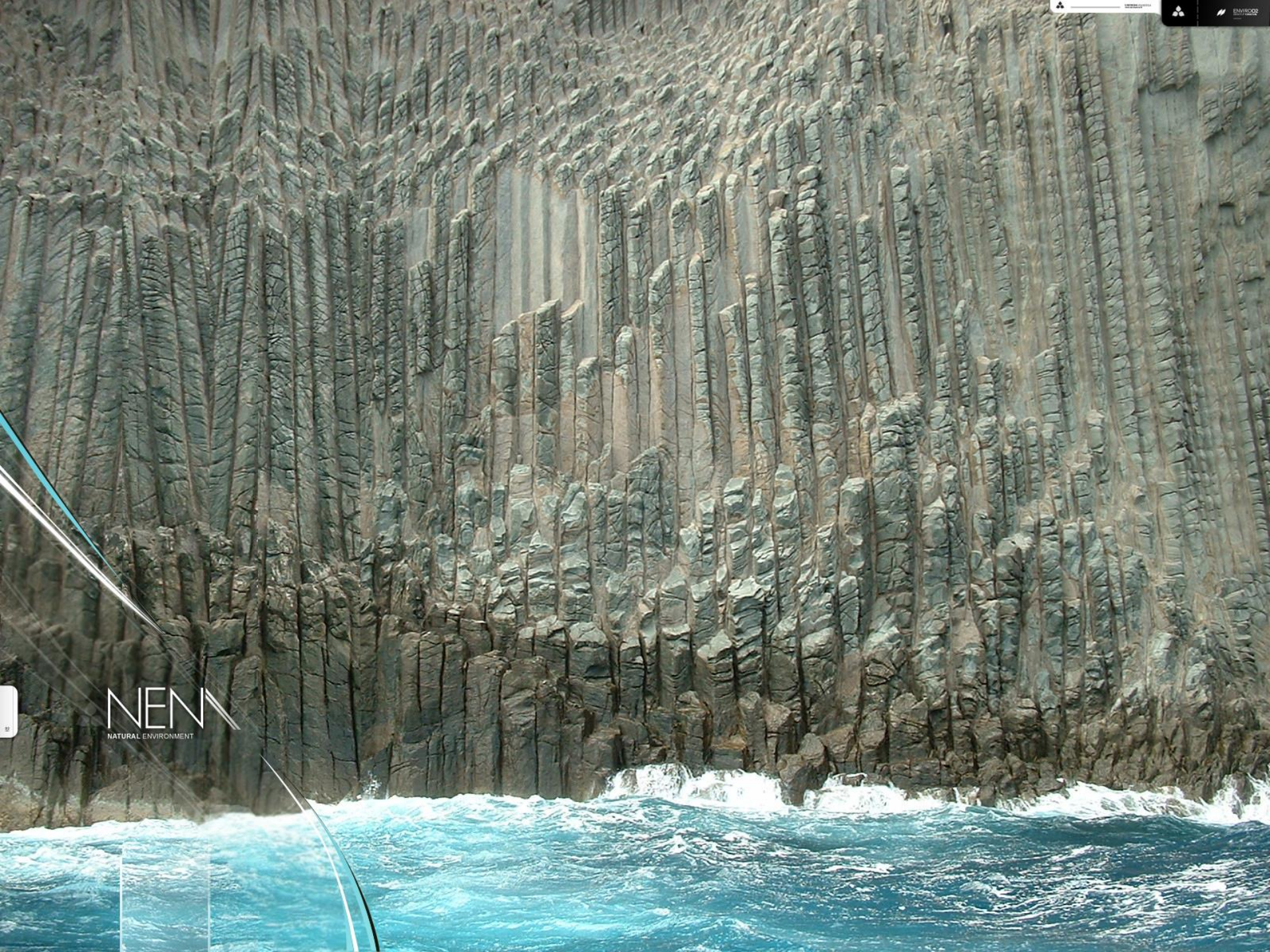
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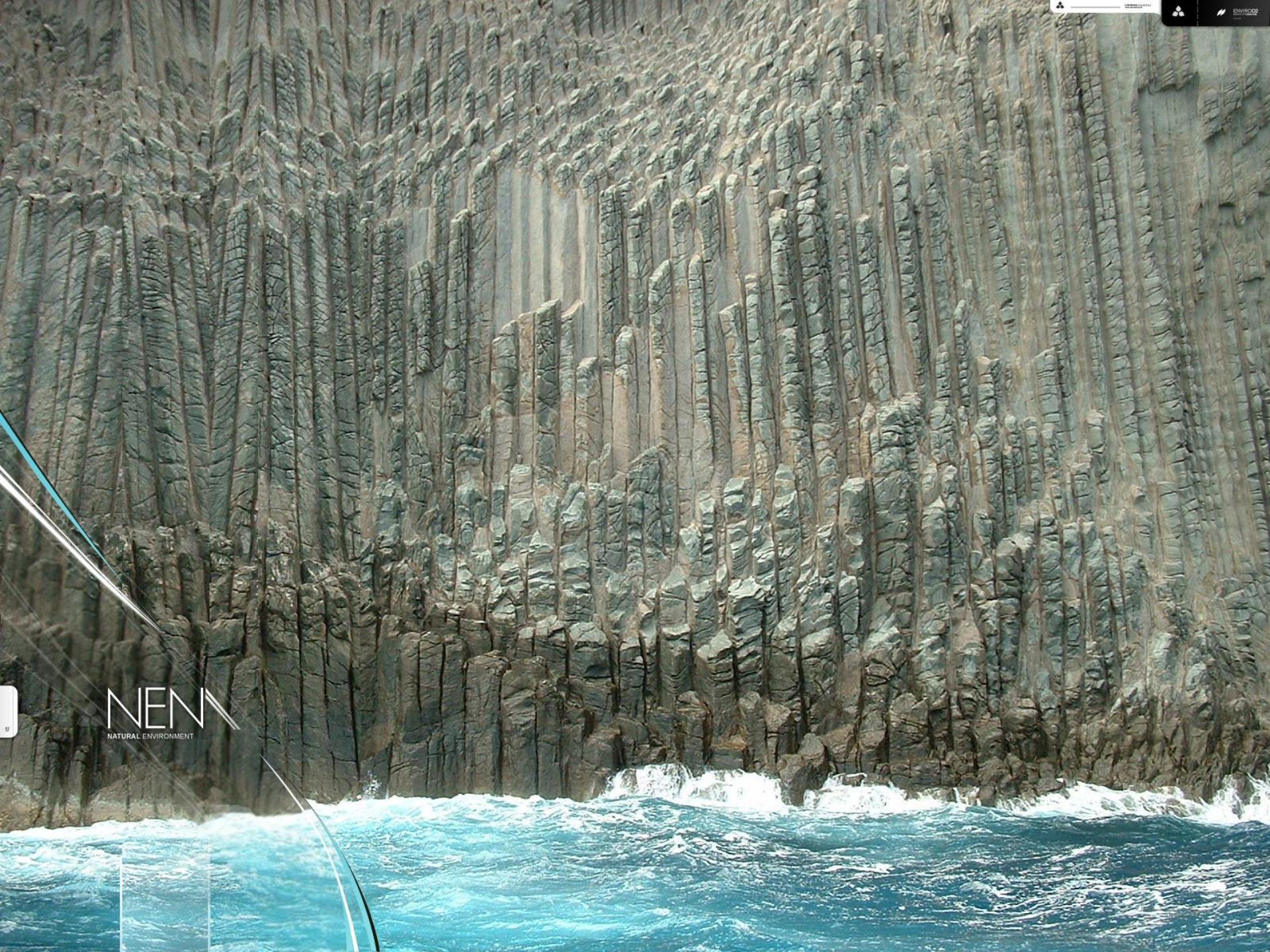
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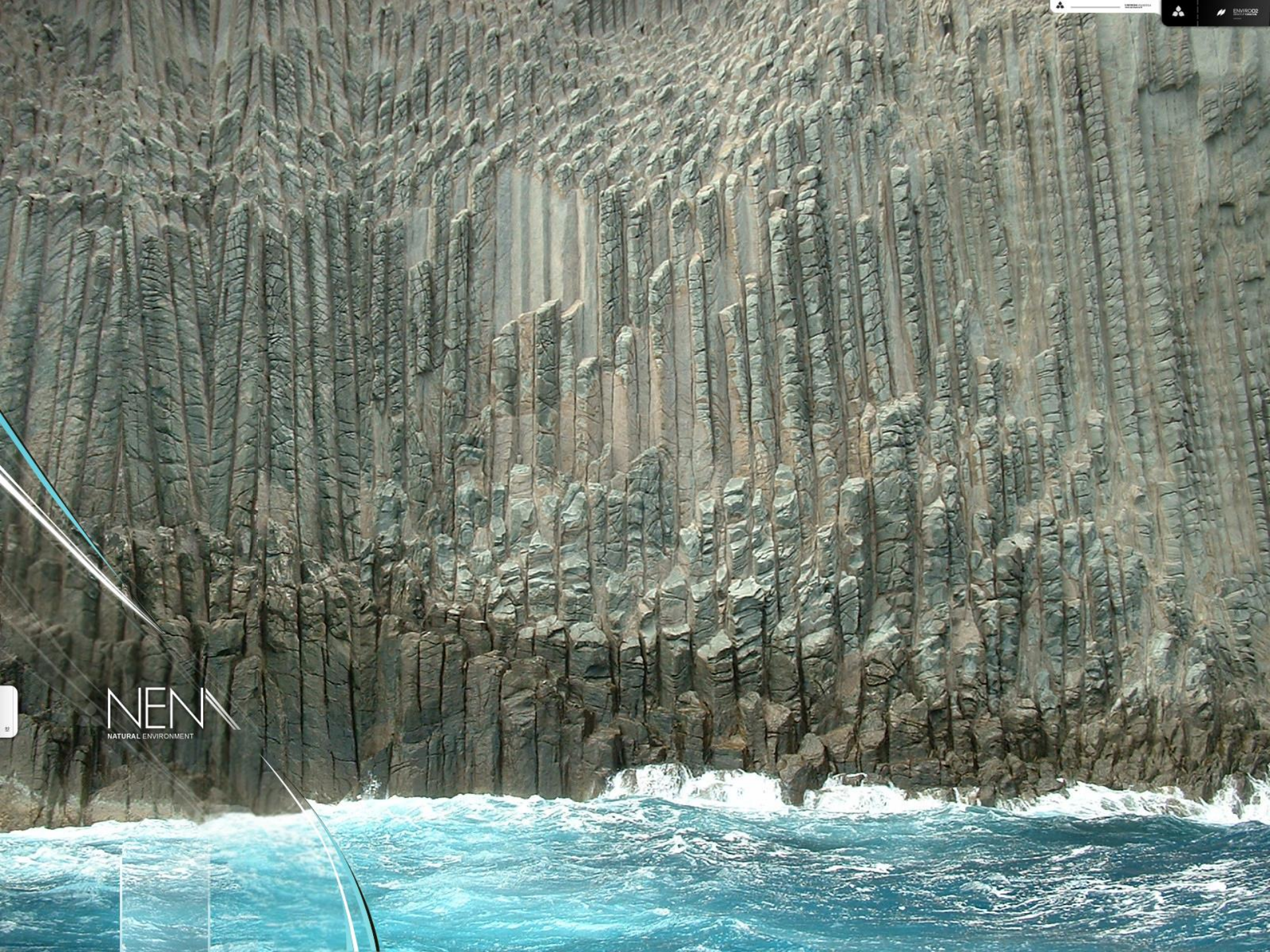
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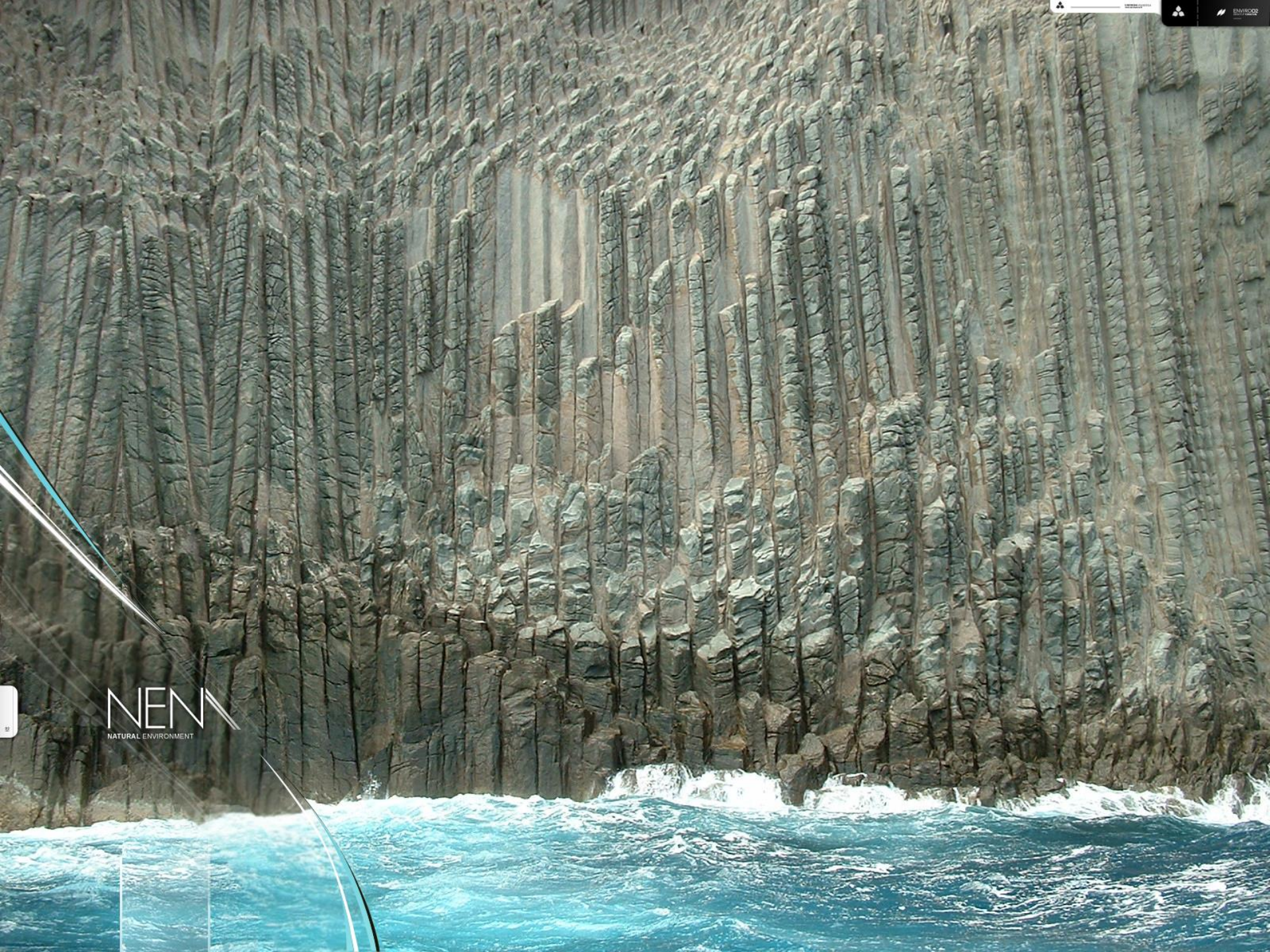
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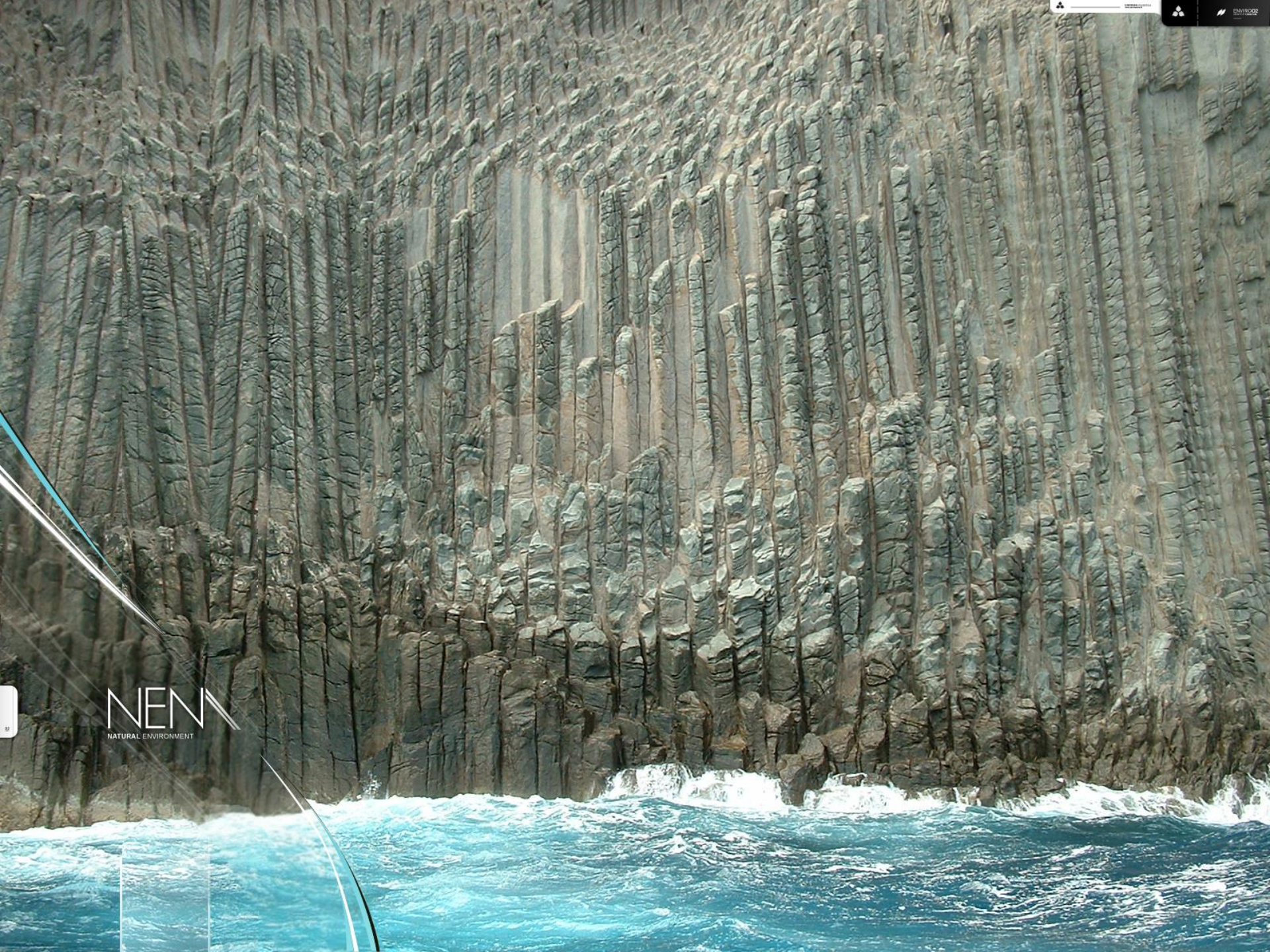
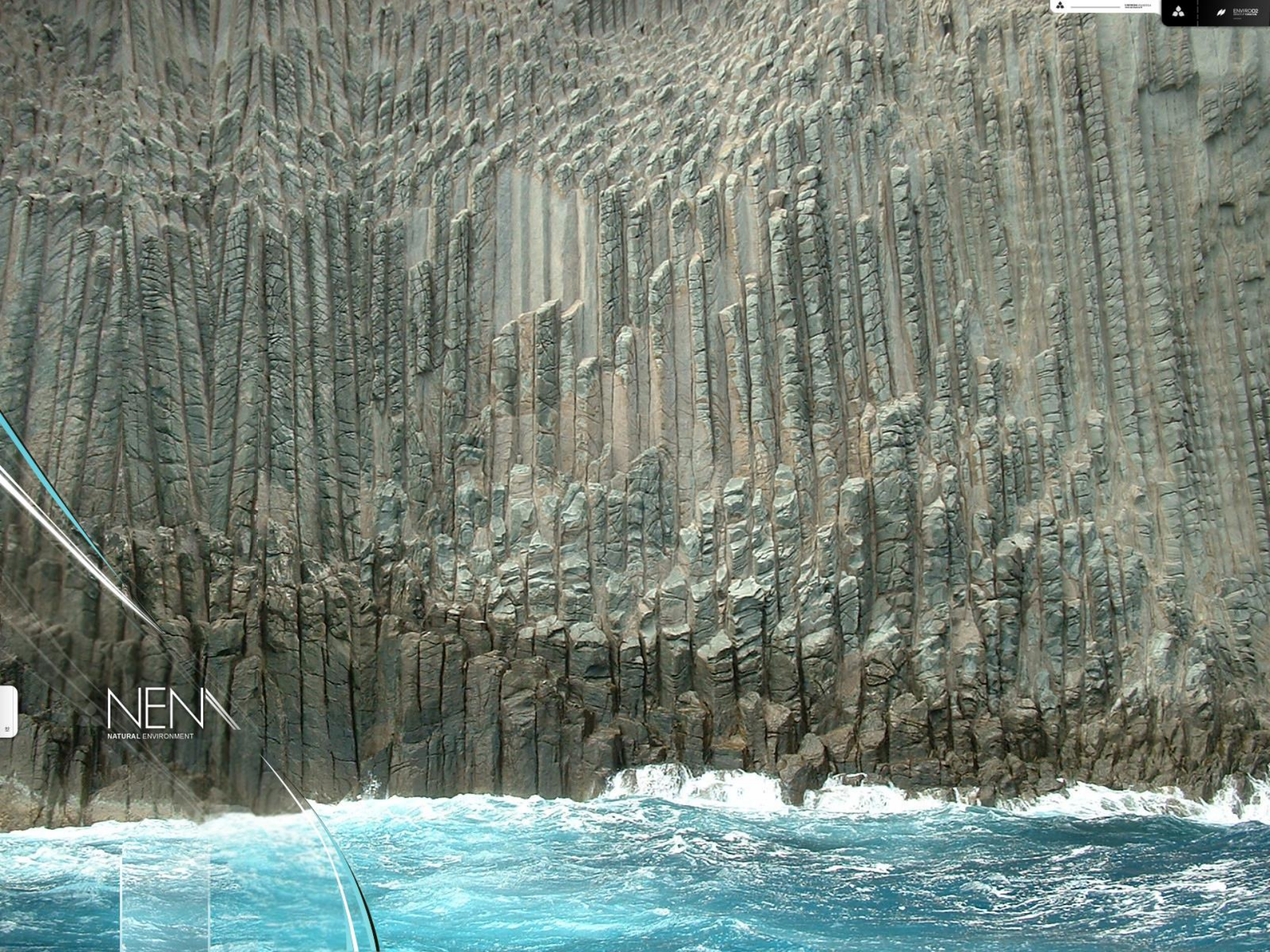

NEN
NATURAL ENVIRONMENT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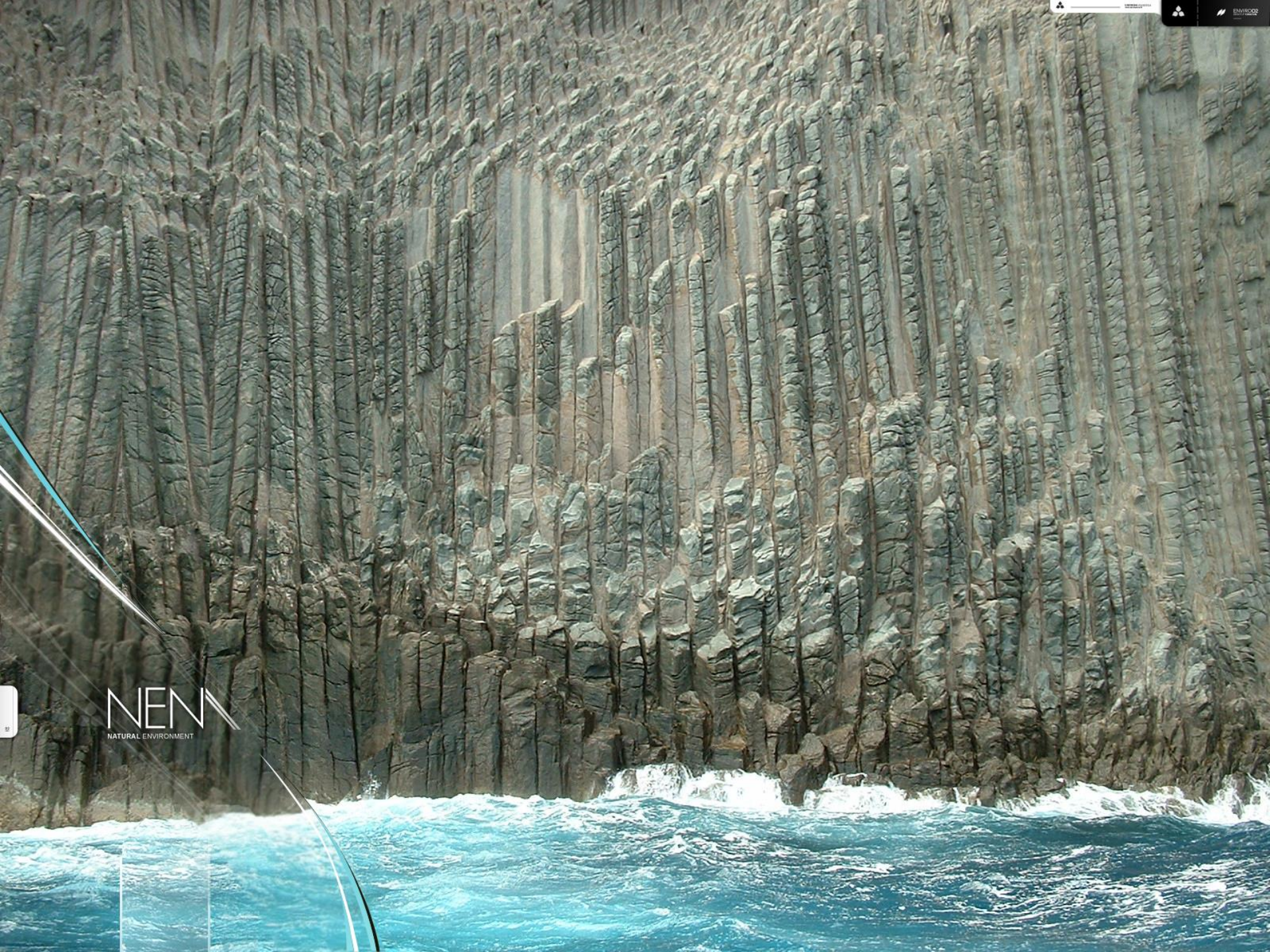
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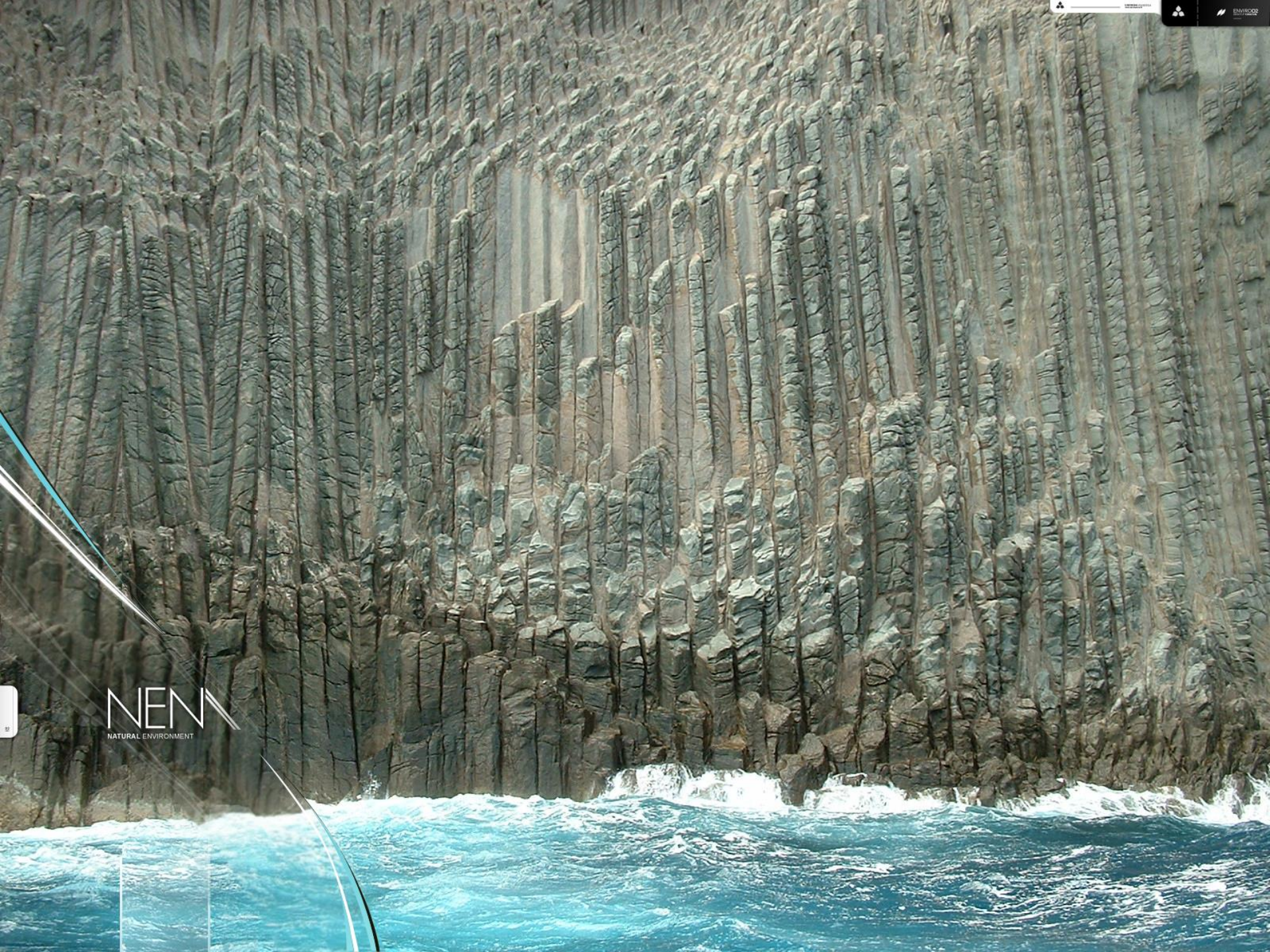
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Questions

- Is pregnancy advisable in transplant recipients?
- Will pregnancy be complicated?
- Will the baby be healthy?
- Will there be any long-term harm (mother and the baby)?

Kidney Transplantation and Pregnancy

- High-risk pregnancy
- Good prognosis:
  - 1-2 years waiting time
  - Scr<1.5 mg/dl and stable
  - Normal blood pressure (target level?)
  - No proteinuria or minimal proteinuria (level?)
  - No recent acute rejection episode
  - Low-dose prednisone (≤7.5 mg/d)
  - No recent infections especially CMV
  - Normal blood glucose level

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Comorbid Factors That May Influence Pregnancy Outcome

- Etiology of original disease (recurrence?)
- Chronic allograft dysfunction
- Cardiovascular and pulmonary status
- DM or HTN
- Inherited diseases in mother or father
- Infections might affect the fetus: CMV, herpes simplex, toxoplasmosis, HBV, HCV (transmission?)
- Obesity

Potential Risks to Children Born to Transplant Recipients

- Preterm birth (14-83% vs 5-15% in general population)
- Intrauterine growth retardation (IUGR) and low birth weight (19-67% vs 5-13% in general population)
- Congenital abnormalities (no increase with CsA, chromosome aberrations with AZA)
- Adrenocortical insufficiency
- Hyperkalemia, renal dysfunction
- Immunologic abnormalities, malignancies
- Infections (CMV, hepatitis B and C, sepsis)

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