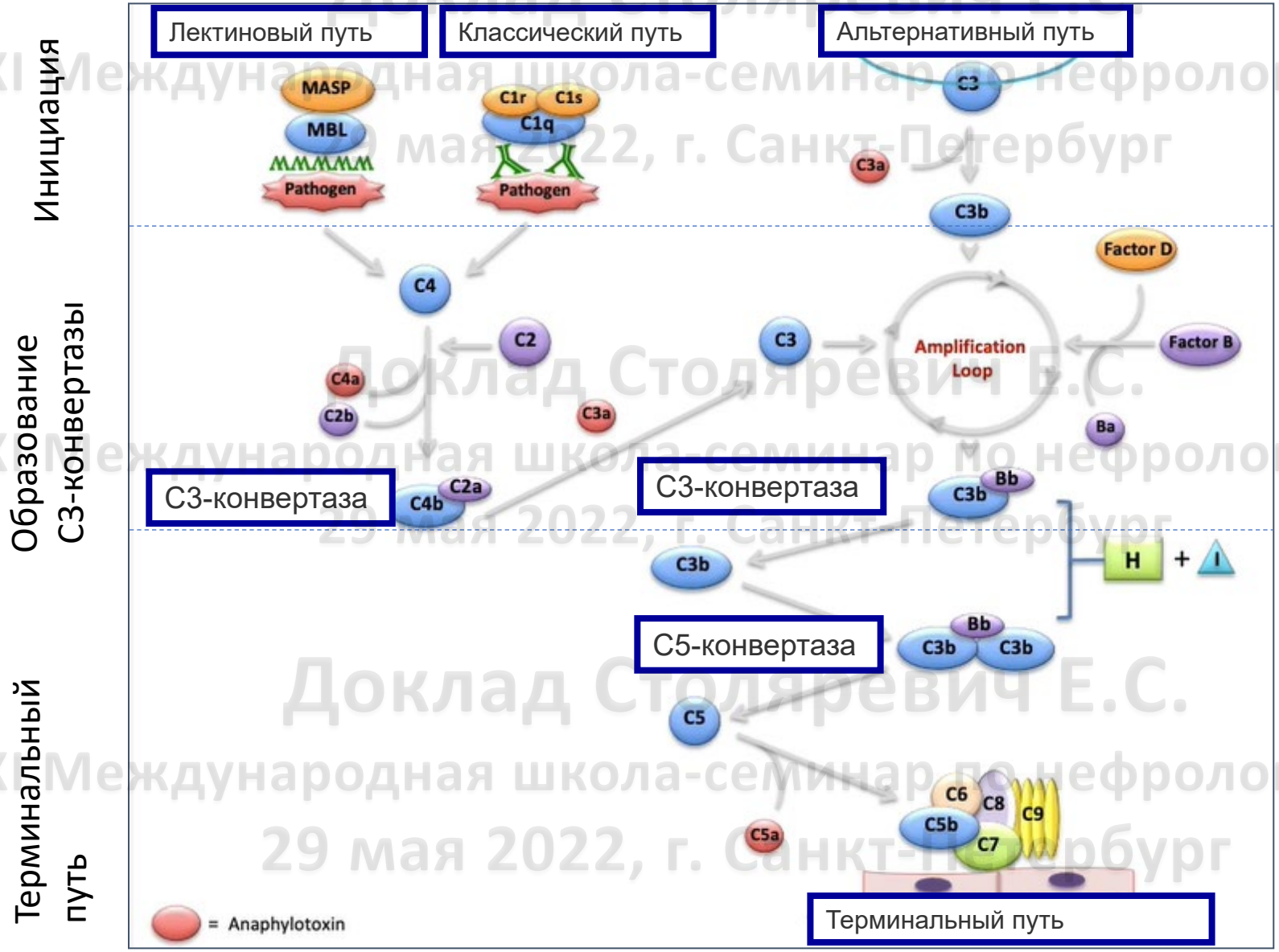
# Морфология и патогенез С3-гломерулопатии

Столяревич Е.С

«XVII Общероссийская научно-практическая конференция РДО»

Санкт-Петербург
27 мая 2022

# Активация системы комплемента

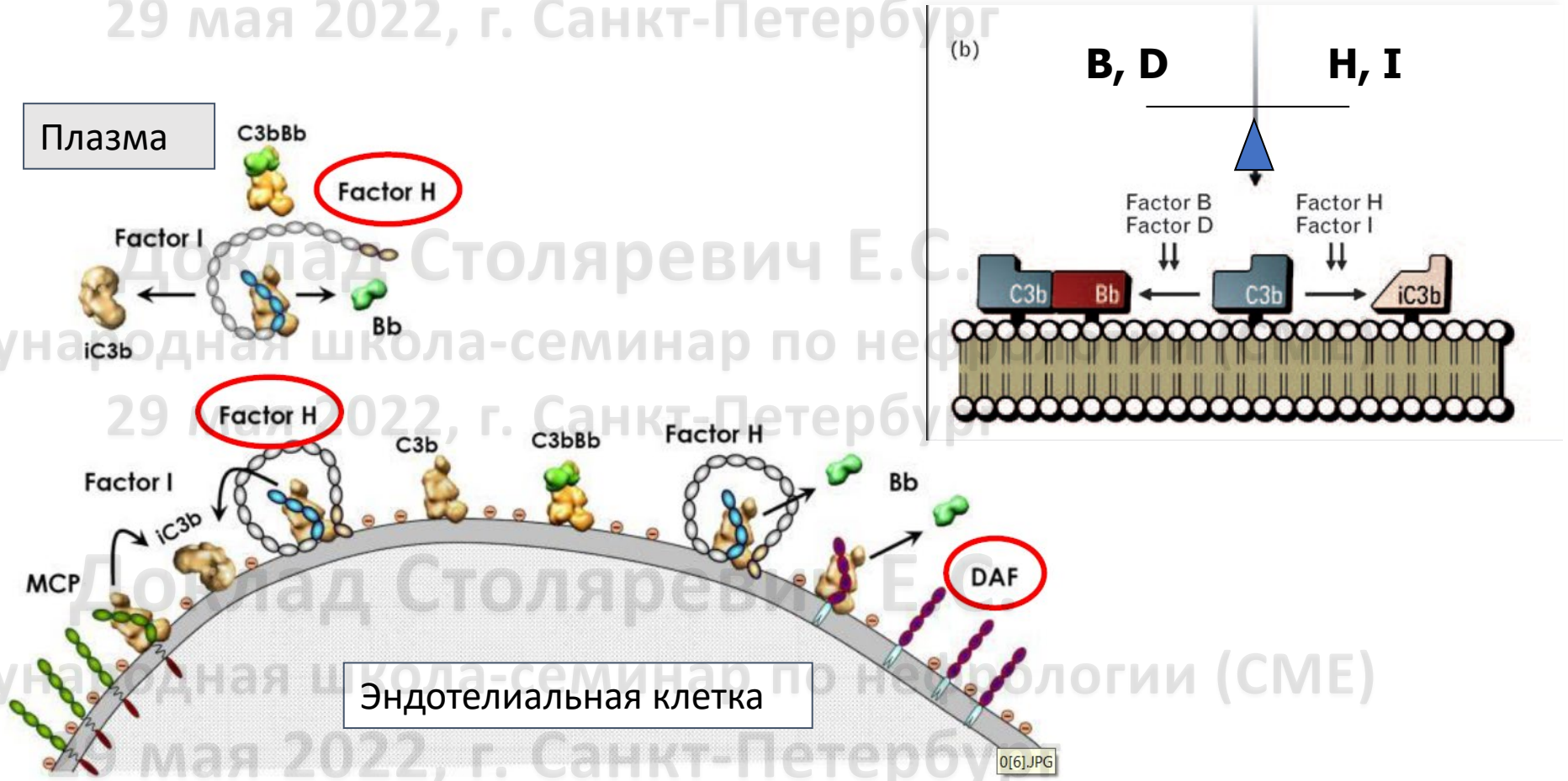





Из лекции С Nester

# Активация системы комплемента в циркуляции либо на клеточной поверхности



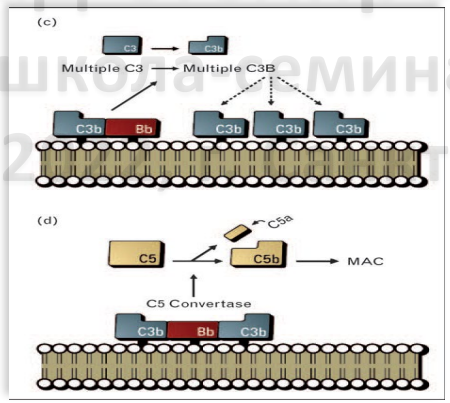



Adapted from Rodríguez de Córdoba S et al., Biochem Biophys Acta, 2011

**H , I**

**B, D, P**






плазма

**Клеточная поверхность**

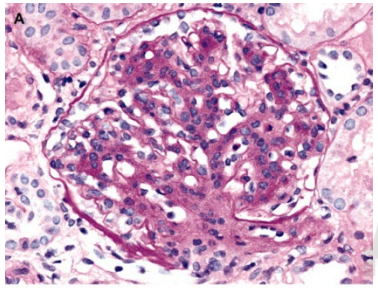
Накопление C3

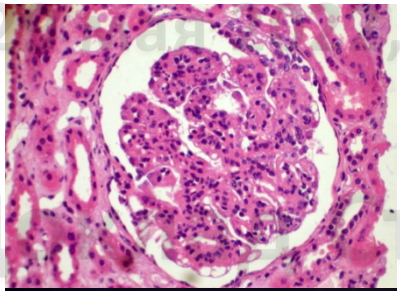
Повреждение собственных клеток

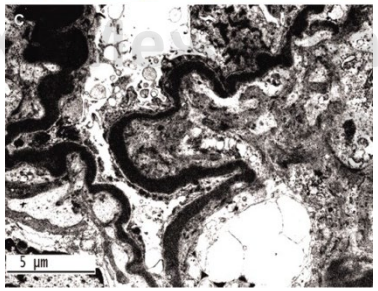
DDD

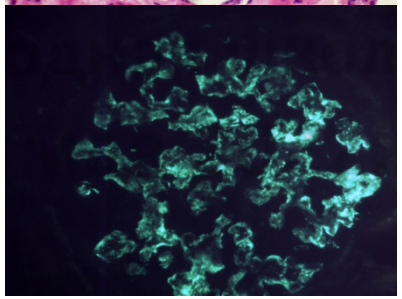
C3 - GP

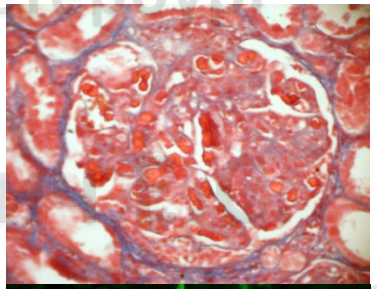
aГУС

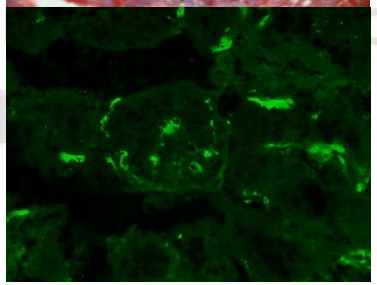


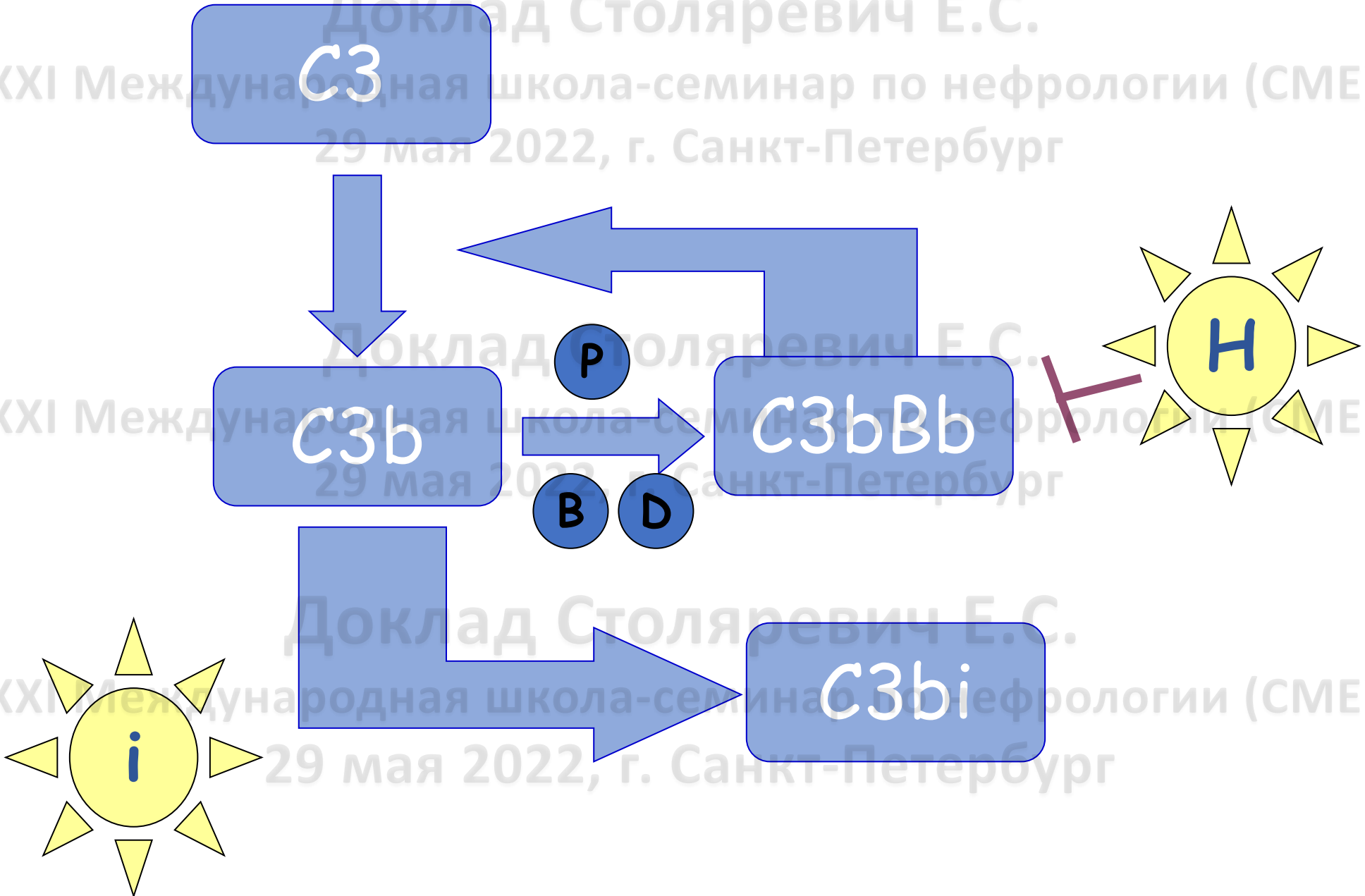



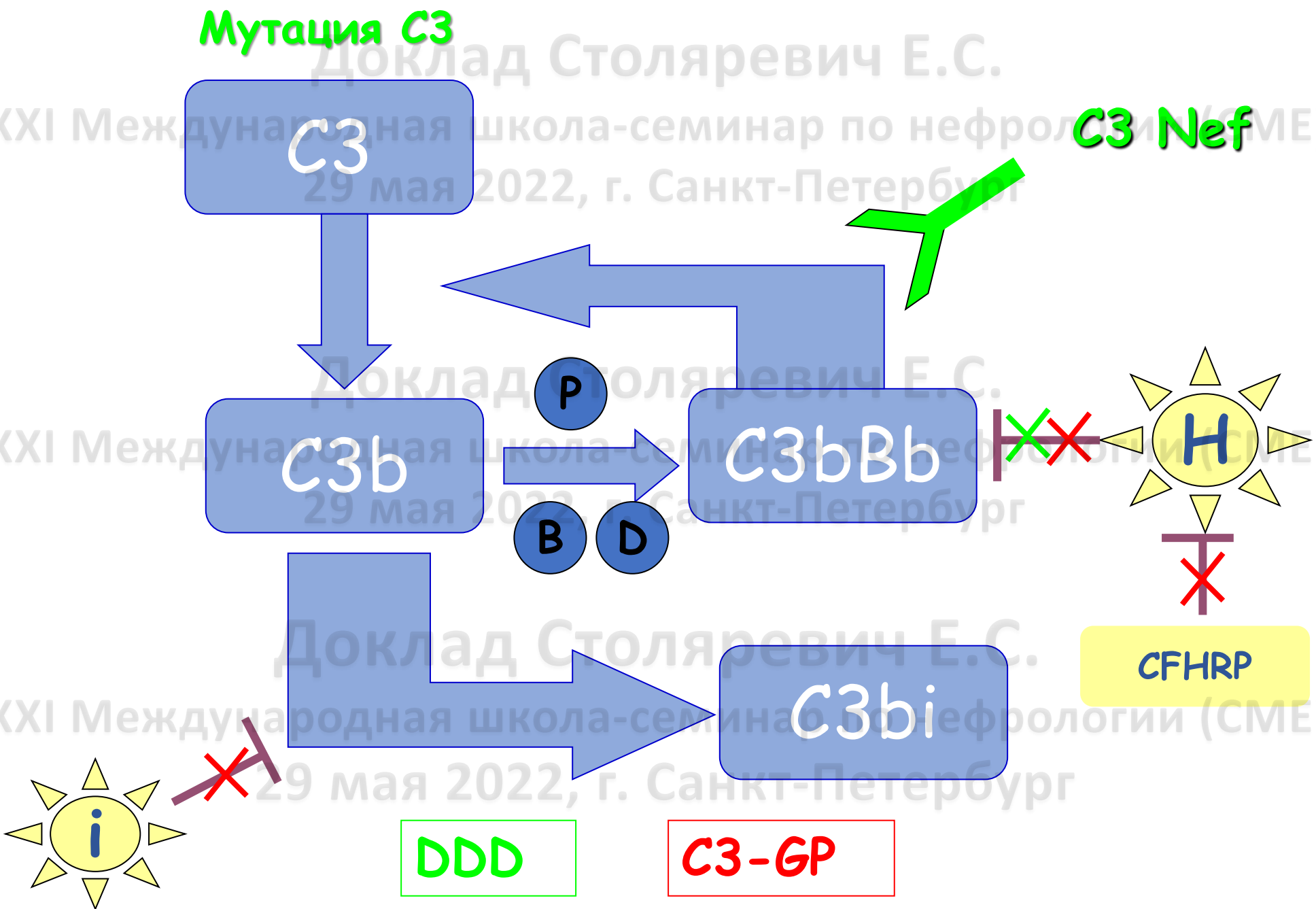




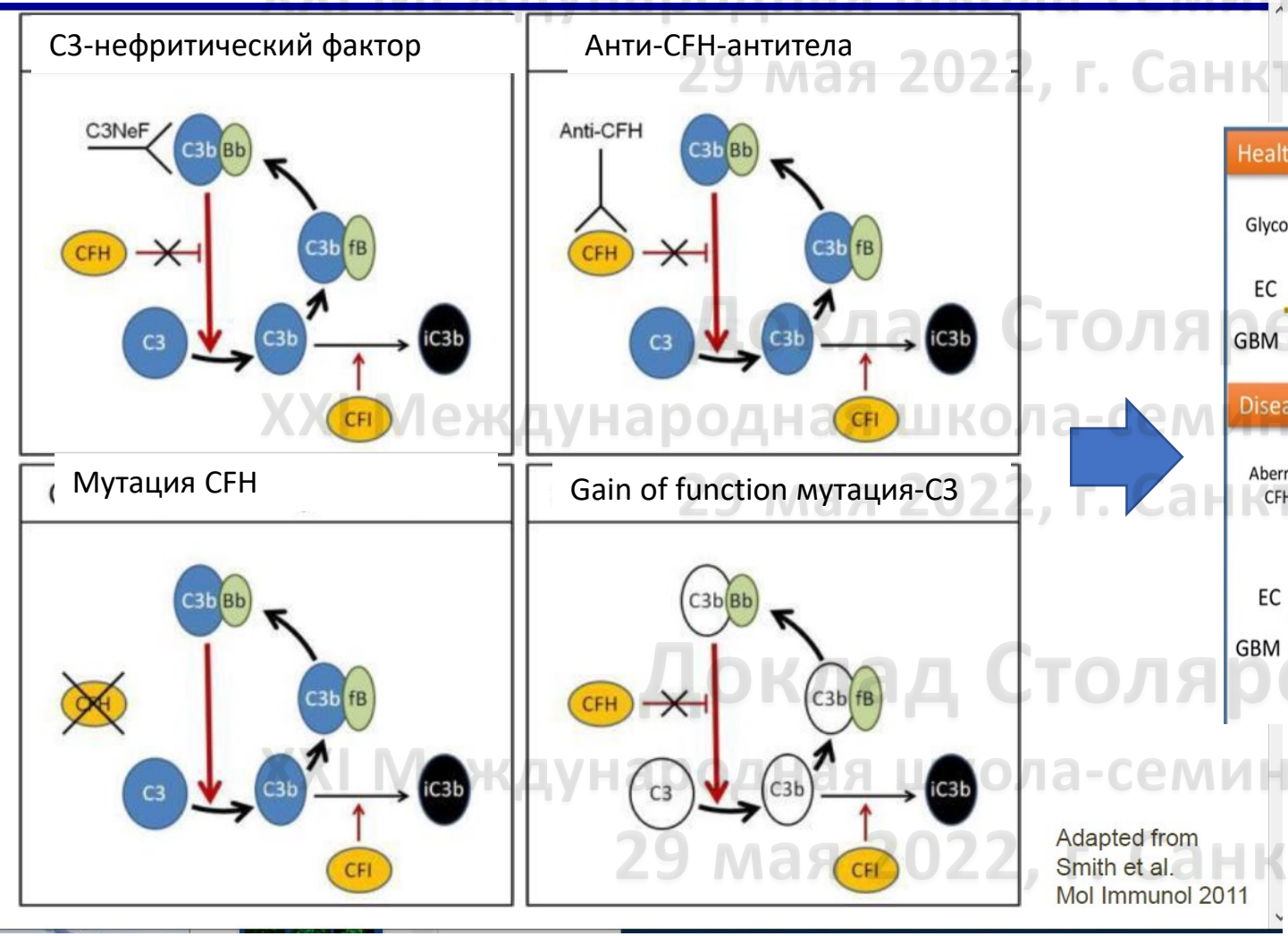


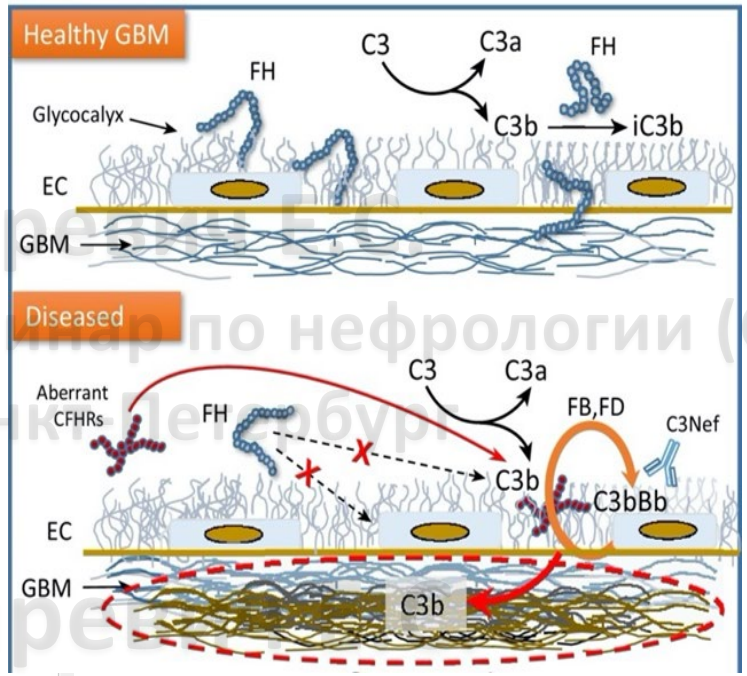


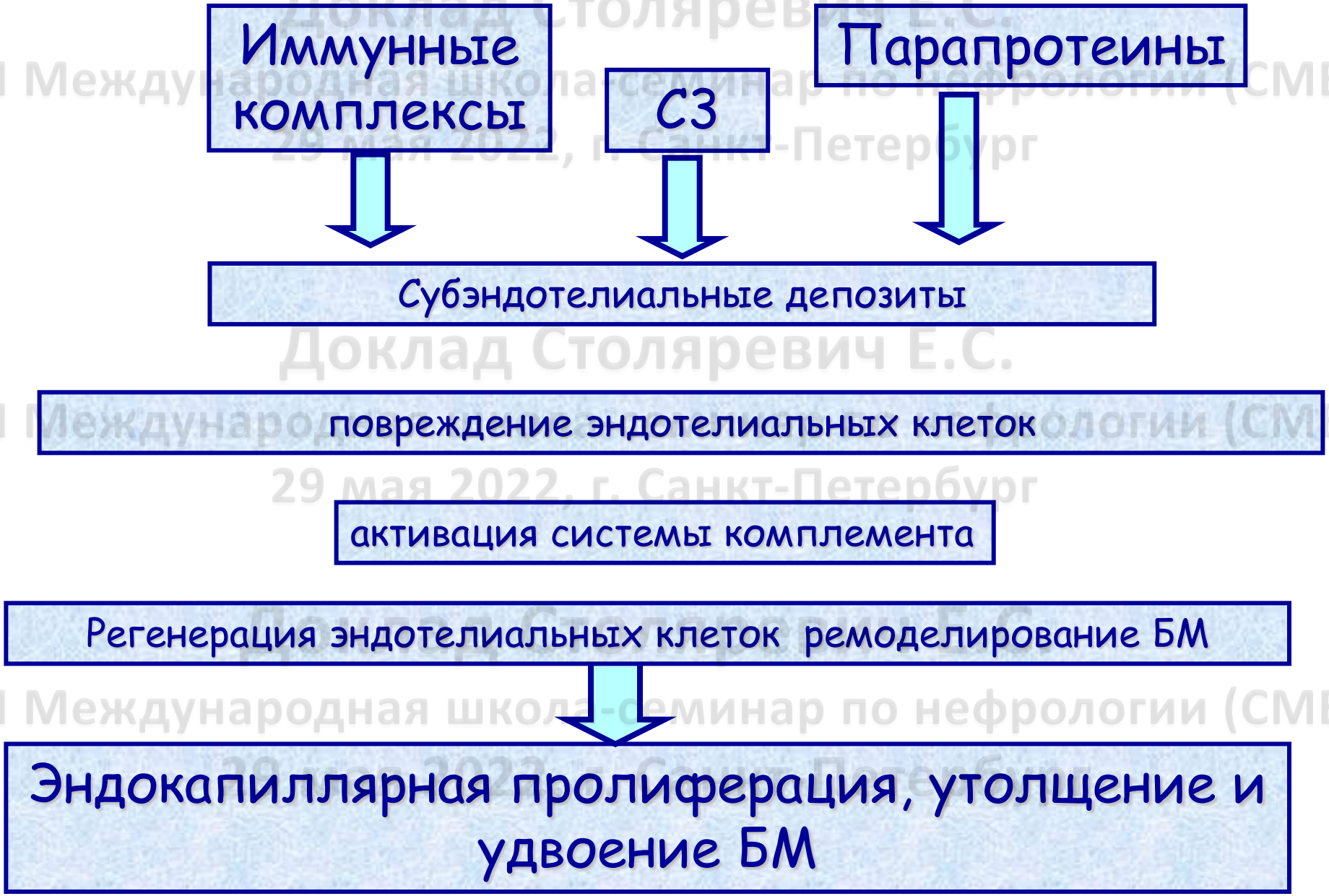


# Причины С3-гломерулопатии

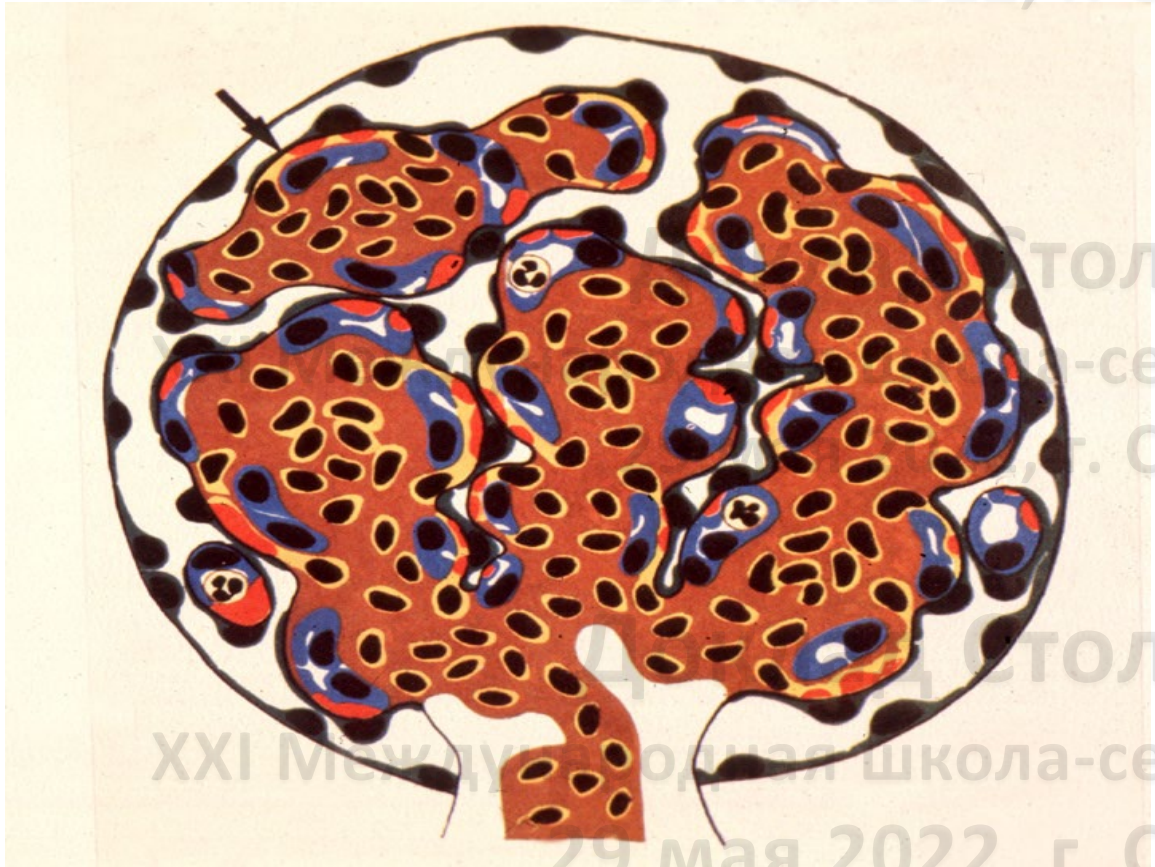


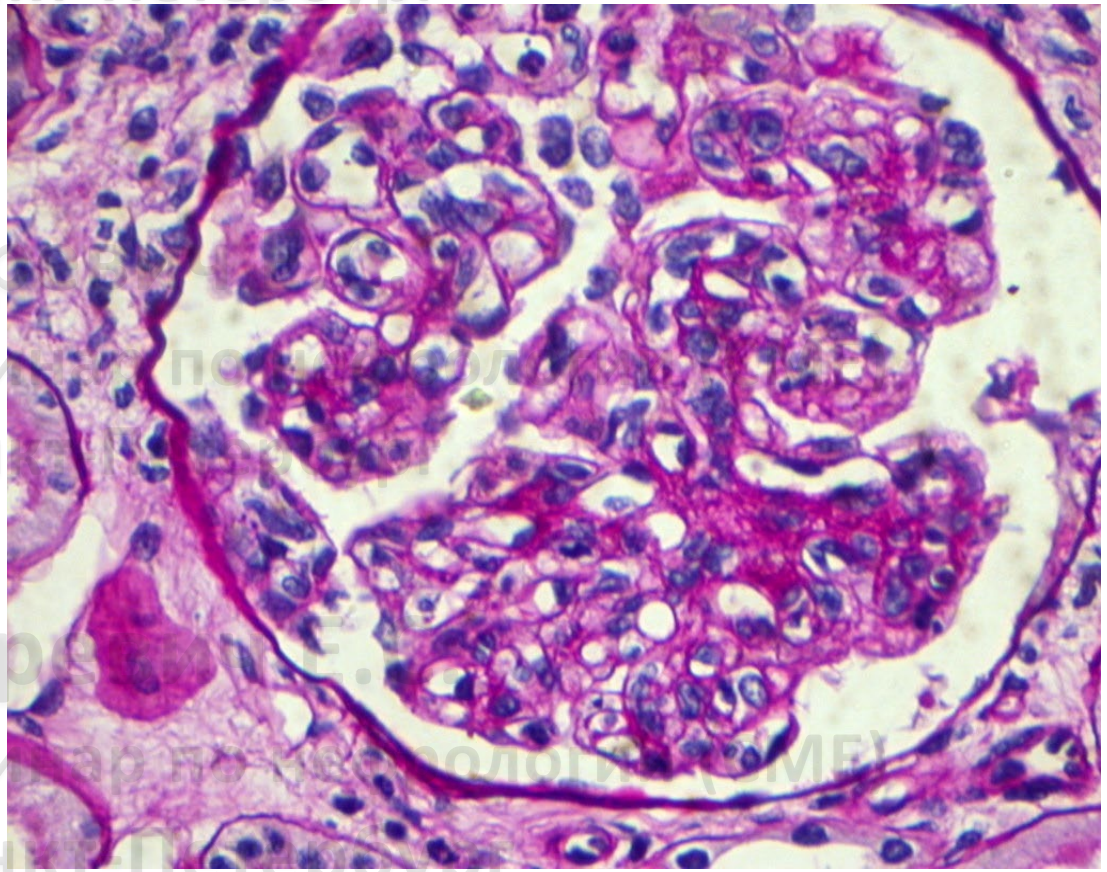


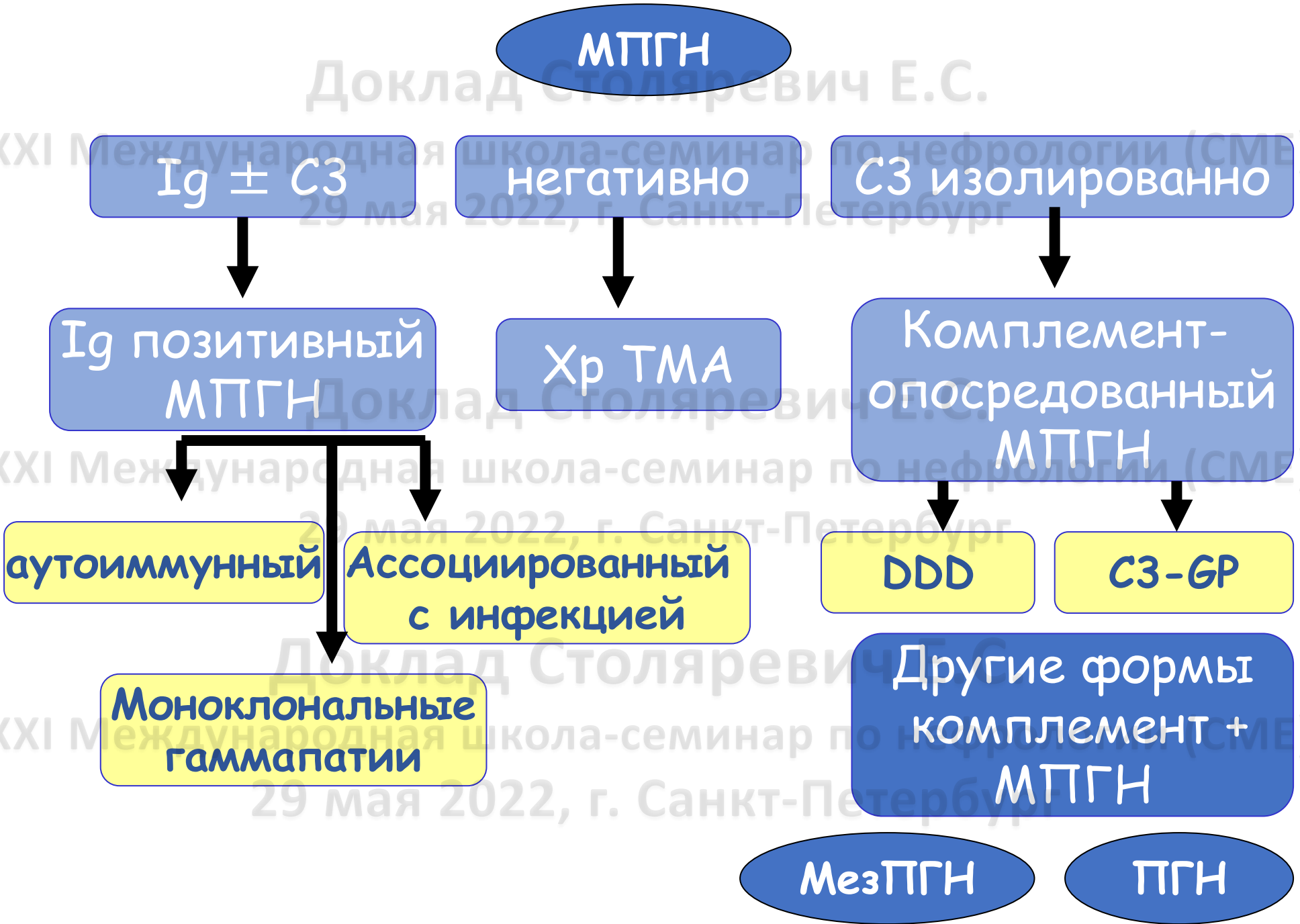





# Мембранопролиферативный ГН



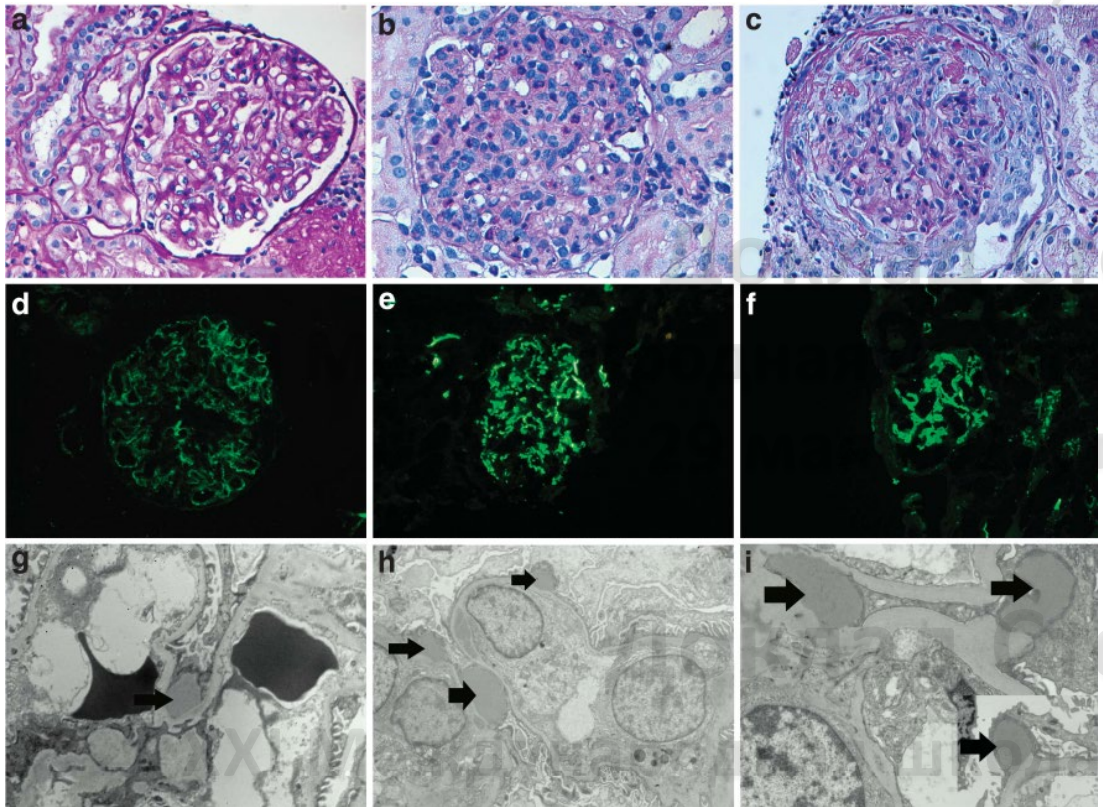




# С3- гломерулопатия: морфологические профили



МезПГН ПГН ЭКГН




| | МПГН | ПГН | МезПГН | ЭКГН | Склероз |
|---|---|---|---|---|---|
| С3-ГН | 60-70% | 5-15% | 15-20% | 5-10%. | 5-10% |
| DDD | 35-50% | 10-20% | 25-35% | 5-10% | 10-15% |

ОНС ±НС ИМС БПГН ПН

Sethi S Fervenza F Kidney Int 2012

Sehi S Kidney International (2009) 75, 952
Bomback A et al. Kidney International (2018) 93, 977–985
Wani Nephron (2020) 144:228
Zair Ped Nephrol (2021) 36:601

## Индексы активности и хронизации

| Component | Definition | Score |
|---|---|---|
| ***(A) Activity score, 0–21*** | | |
| Mesangial hypercellularity | % glomeruli with >3 mesangial cells per mesangial area | 0 = none<br>1 = 1%–25%<br>2 = 26%–50%<br>3 = >50% |
| Endocapillary proliferation | % glomeruli with an increased number of cells within glomerular capillary lumina, causing luminal narrowing | 0 = none<br>1 = 1%–25%<br>2 = 26%–50%<br>3 = >50% |
| Membranoproliferative morphology | % glomeruli with GBM duplication with or without endocapillary proliferation | 0 = none<br>1 = 1%–25%<br>2 = 26%–50%<br>3 = >50% |
| Leukocyte infiltration | % glomeruli with glomerular capillary infiltration by ≥3 neutrophils and/or macrophages | 0 = none<br>1 = 1%–25%<br>2 = 26%–50%<br>3 = >50% |
| Crescent formation | % glomeruli with cellular and/or fibrocellular crescents | 0 = none<br>1 = 1%–10%<br>2 = 11%–25%<br>3 = >25% |
| Fibrinoid necrosis | % glomeruli with presence of ≥2 of fibrin, karyorrhexis, and GBM rupture | 0 = none<br>1 = 1%–10%<br>2 = 11%–25%<br>3 = >25% |
| Interstitial inflammation | % cortical tubulointerstitial area with inflammation in non-fibrotic cortex | 0 = <10%<br>1 = 10%–25%<br>2 = 26%–50%<br>3 = >50% |
| ***(B) Chronicity score, 0–10*** | | |
| Glomerulosclerosis | % glomeruli with global and segmental sclerosis | 0 = <10%<br>1 = 10%–25%<br>2 = 26%–50%<br>3 = >50% |
| Tubular atrophy | % cortical tubulointerstitial area involved with tubular atrophy | 0 = <10%<br>1 = 10%–25%<br>2 = 26%–50%<br>3 = >50% |
| Interstitial fibrosis | % cortical tubulointerstitial area involved with interstitial fibrosis | 0 = <10%<br>1 = 10%–25%<br>2 = 26%–50%<br>3 = >50% |
| Arterio- and arteriolosclerosis | Intimal thickening ≥ thickness of media | 0 = absent<br>1 = present |

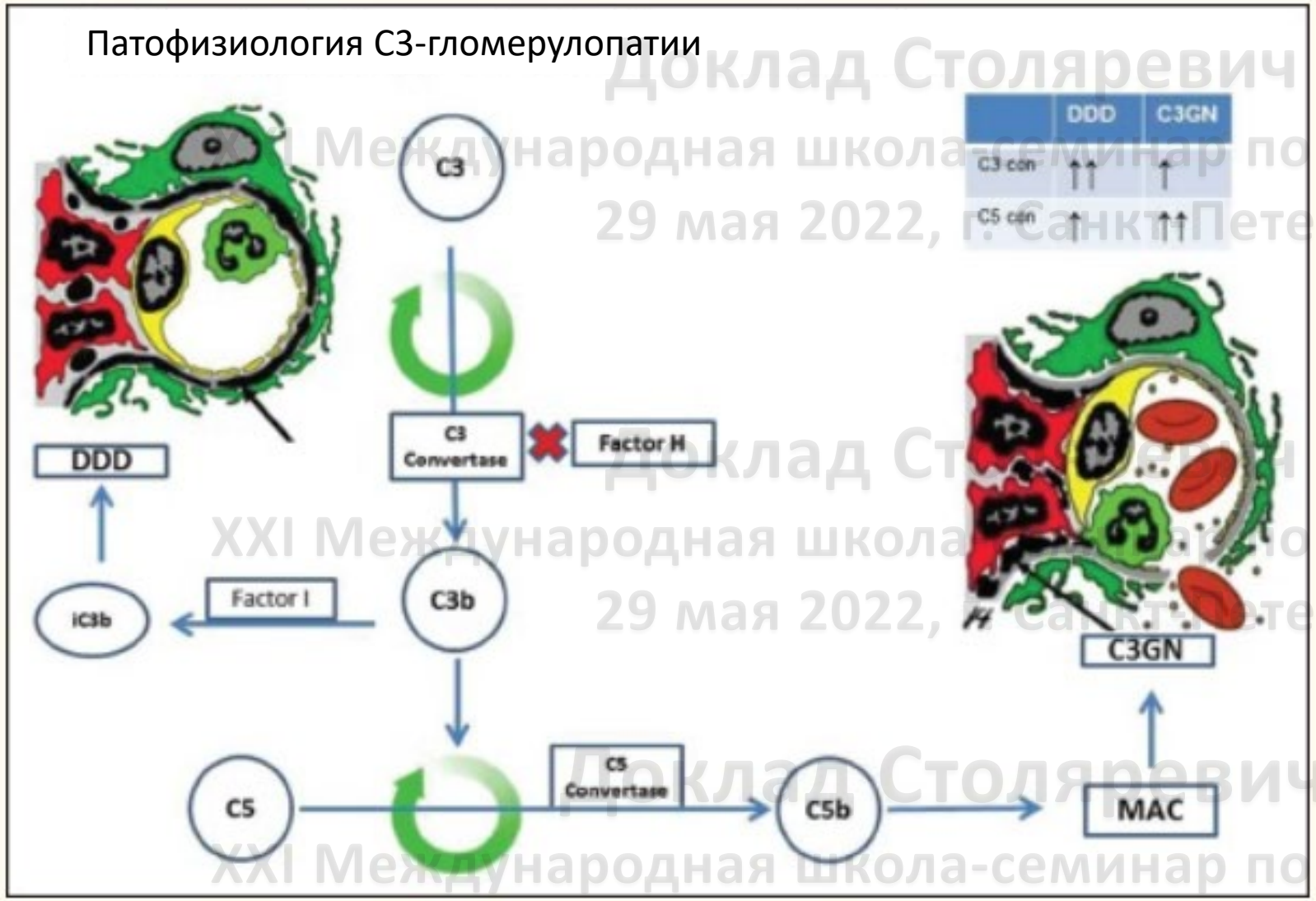
GBM, glomerular basement membrane.

## Факторы прогрессирования С3 ГП

| Predictor | Hazard ratio (95% CI) | *P* value |
|---|---|---|
| **(A) Clinical variables model** | | |
| Female | 1.44 (0.53–3.92) | 0.5 |
| Age | | |
| Less than 18 years | 1.00 (reference) | N/A |
| 18-50 years | 0.91 (0.28–3.03) | 0.9 |
| Over 50 years | 1.19 (0.30–4.81) | 0.8 |
| Race/ethnicity | | |
| White | 1.00 (reference) | N/A |
| Hispanic | 1.29 (0.48–3.47) | 0.6 |
| Asian | 4.01 (0.81–19.77) | 0.09 |
| African-American | 3.24 (0.33–32.00) | 0.3 |
| eGFR via CKD-EPI equation (per 10 ml/min per 1.73 $m^2$) | 0.69 (0.57–0.83) | <0.001 |
| Proteinuria at diagnosis (per 1 g/d) | 1.03 (0.93–1.14) | 0.6 |
| Low C3 and/or C4 | 1.35 (0.54–3.37) | 0.5 |
| Detectable complement abnormality (gene variant and/or antibody) | 0.57 (0.15–2.10) | 0.4 |
| Use of immunosuppression | 0.87 (0.33–2.29) | 0.8 |
| **(B) Histopathology variables model** | | |
| Light microscopy pattern | | |
| MPGN | 1.00 (reference) | N/A |
| Mesangial proliferative GN | 1.16 (0.20–6.68) | 0.9 |
| Diffuse endocapillary proliferative GN | 0.27 (0.02–3.57) | 0.3 |
| Diffuse sclerosing GN | 0.93 (0.08–10.15) | 0.9 |
| Globally sclerotic glomeruli (per 10% increase) | 0.69 (0.44–1.08) | 0.1 |
| Segmentally sclerotic glomeruli (per 10% increase) | 1.28 (0.99–1.66) | 0.06 |
| Exudative features | 1.26 (0.30–5.31) | 0.8 |
| Cellular or fibrocellular crescents, any identified | 3.86 (0.93–15.97) | 0.06 |
| Tubular atrophy/interstitial fibrosis (per 10% increase) | 2.04 (1.33–3.15) | 0.001 |
| C3-only staining on immunofluorescence | 5.09 (1.49–17.35) | 0.009 |
| DDD by electron microscopy (vs. C3GN) | 1.30 (0.31–5.38) | 0.7 |
| **(C) C3G histologic index model** | | |
| Total activity score | 1.18 (1.03–1.34) | 0.02 |
| Total chronicity score | 1.59 (1.26–2.01) | <0.001 |

AS Bomback et al. Kidney International (2018) 93, 977–985

Патофизиология С3-гломерулопатии




| | DDD | C3GN |
|---|---|---|
| Mean age(years) | 14 | 24 |
| Gender | M=F | M=F |
| ESRD | 50% in 10 yrs | 10% in 2.5 yrs |
| Transplant Outcome | Poor, 5yr raft loss >50% | Poor, 60% Recurrence |
| Associated disorders | Acquired partial lipodystrophy, T1iabetes, Macular degeneration | - |
| C3 convertase dysregulation | ↑↑ | ↑ |
| C5 convertase dysregulation | ↑ | ↑↑ |
| C3NF | +++ | + |
| FHAA | ++ | ++ |
| sMAC | ↑ | ↑↑↑ |

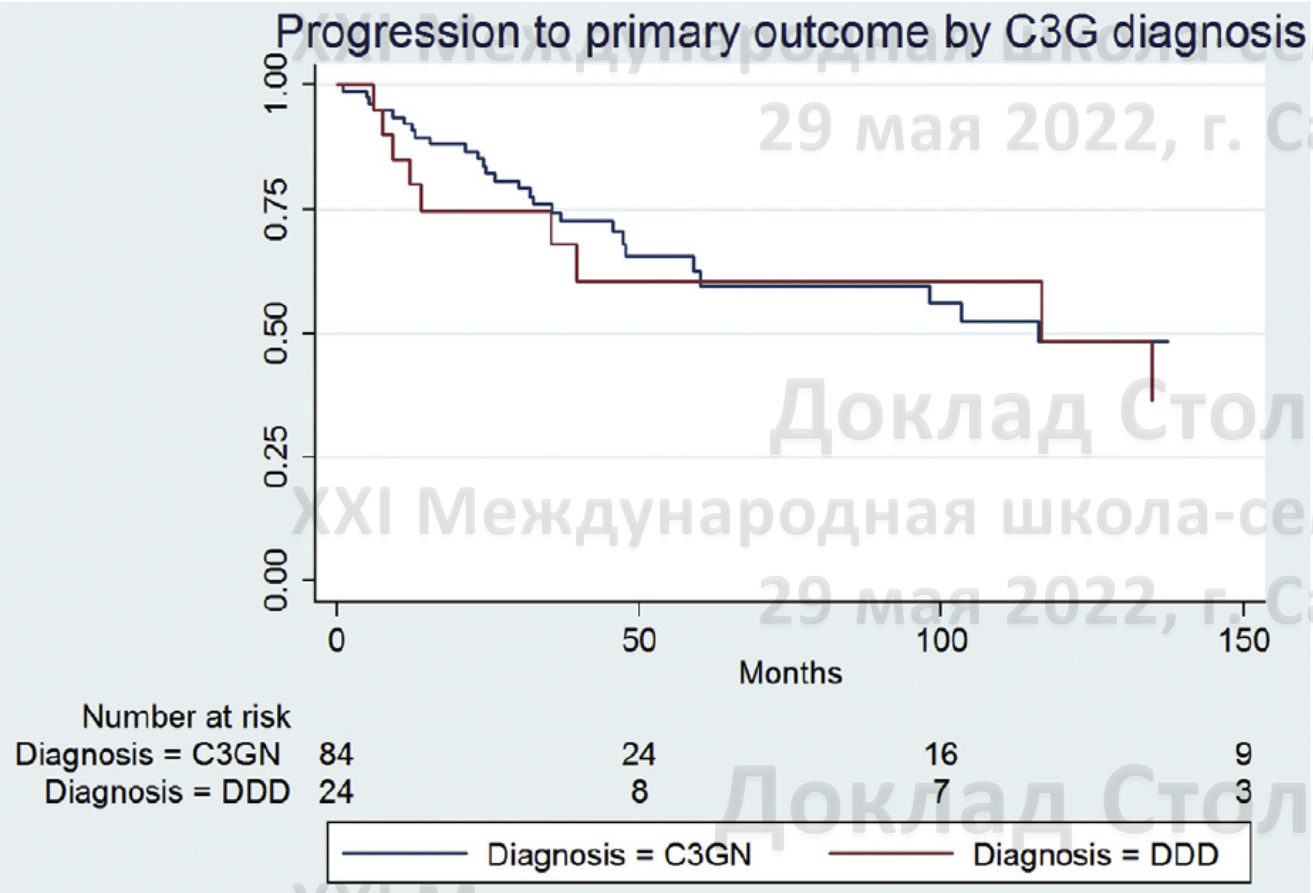
DDD: Dense deposit disease, ESRD: End stage renal disease, C3 NeF: Complement component 3 nephritic factor, FHAA: Factor H associated antibody, sMAC: Soluble membrane attack complex

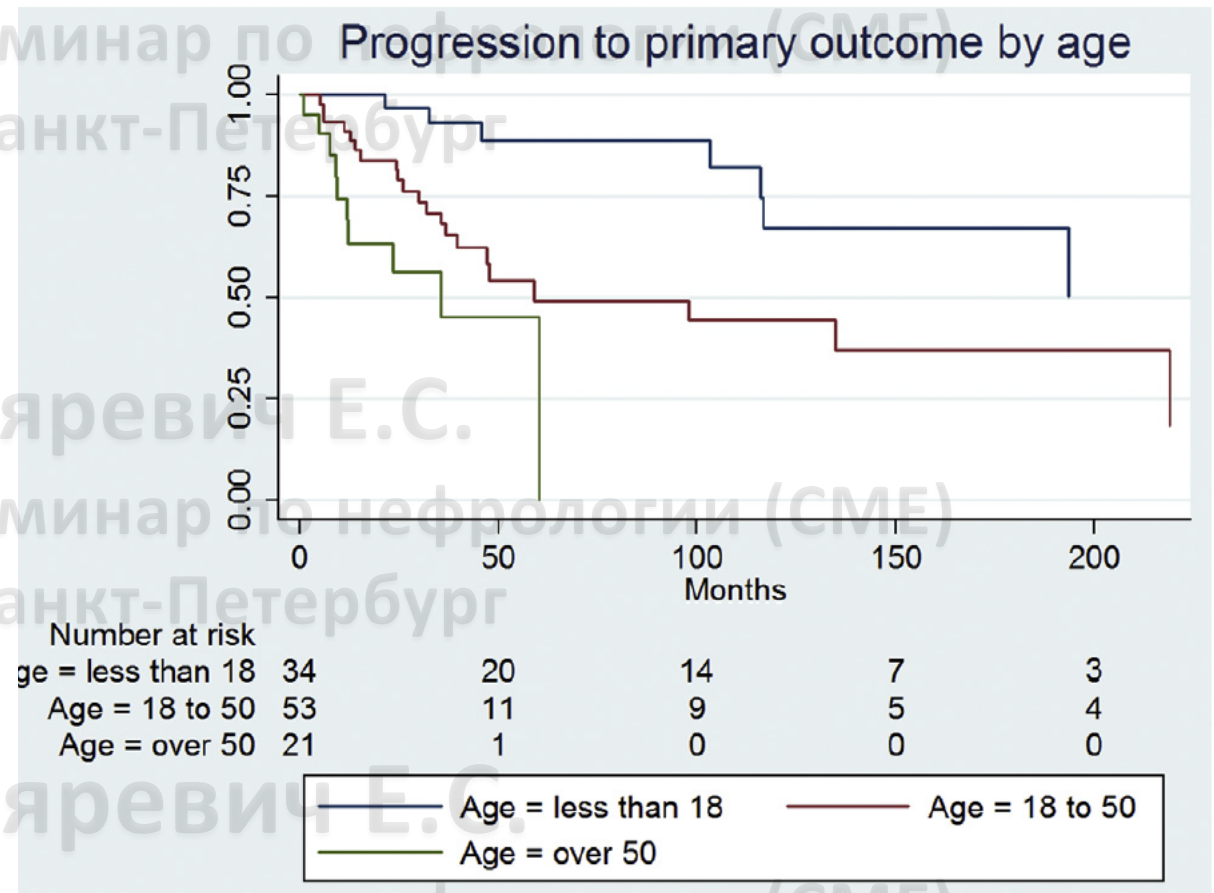


Thomas, S et al. “Current concepts in C3 glomerulopathy.” *Indian journal of nephrology* vol. 24,6 (2014): 339-48.

# Факторы прогрессирования С3-ГП

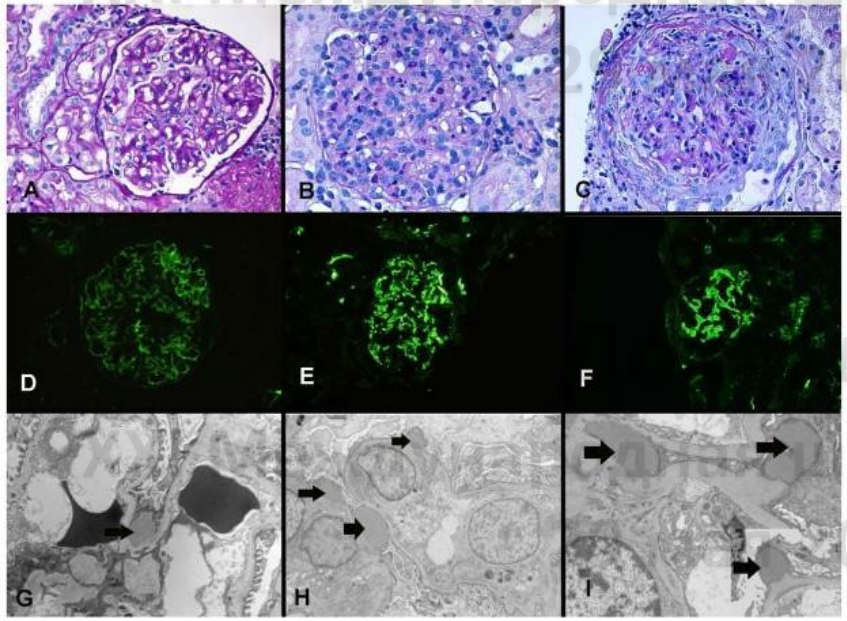


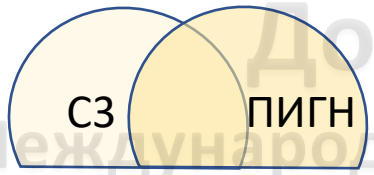



AS Bomback et al. Kidney International (2018) 93, 977–985

# С3-гломерулопатия, ассоциированная с ПИГН



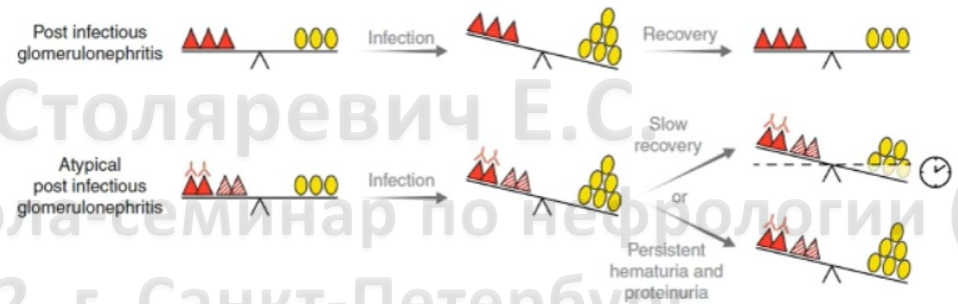




**Table 4 | Kidney biopsy features of postinfectious glomerulonephritis, 'atypical' postinfectious glomerulonephritis, and C3 glomerulonephritis**

| | Postinfectious glomerulonephritis (PIGN) | 'Atypical' postinfectious glomerulonephritis (aPIGN) | C3 glomerulonephritis (C3GN) |
|---|---|---|---|
| LM | Diffuse proliferative, less commonly mesangial proliferative, or crescentic | Diffuse proliferative, less commonly mesangial proliferative, or crescentic | Membranoproliferative and less commonly mesangial proliferative |
| IF | Bright mesangial and capillary wall C3, usually with Igs (garland pattern) | Bright mesangial and capillary wall C3, usually without Igs. If present IgG (trace to 1+) | Bright mesangial and capillary wall C3, usually without Igs |
| EM | Numerous subepithelial humps, few mesangial, and subendothelial deposits | Numerous subepithelial humps, many mesangial and subendothelial deposits, and ± intramembranous deposits | Many mesangial and subendothelial deposits, ± few intramembranous, and subepithelial humps |

Abbreviations: EM, electron microscopy; IF, immunofluorescence; Ig, immunoglobulin; LM, light microscopy.

Sethi S Fervenza F Kidney Int 2013

http://www.kidney-international.org meeting report



OPEN

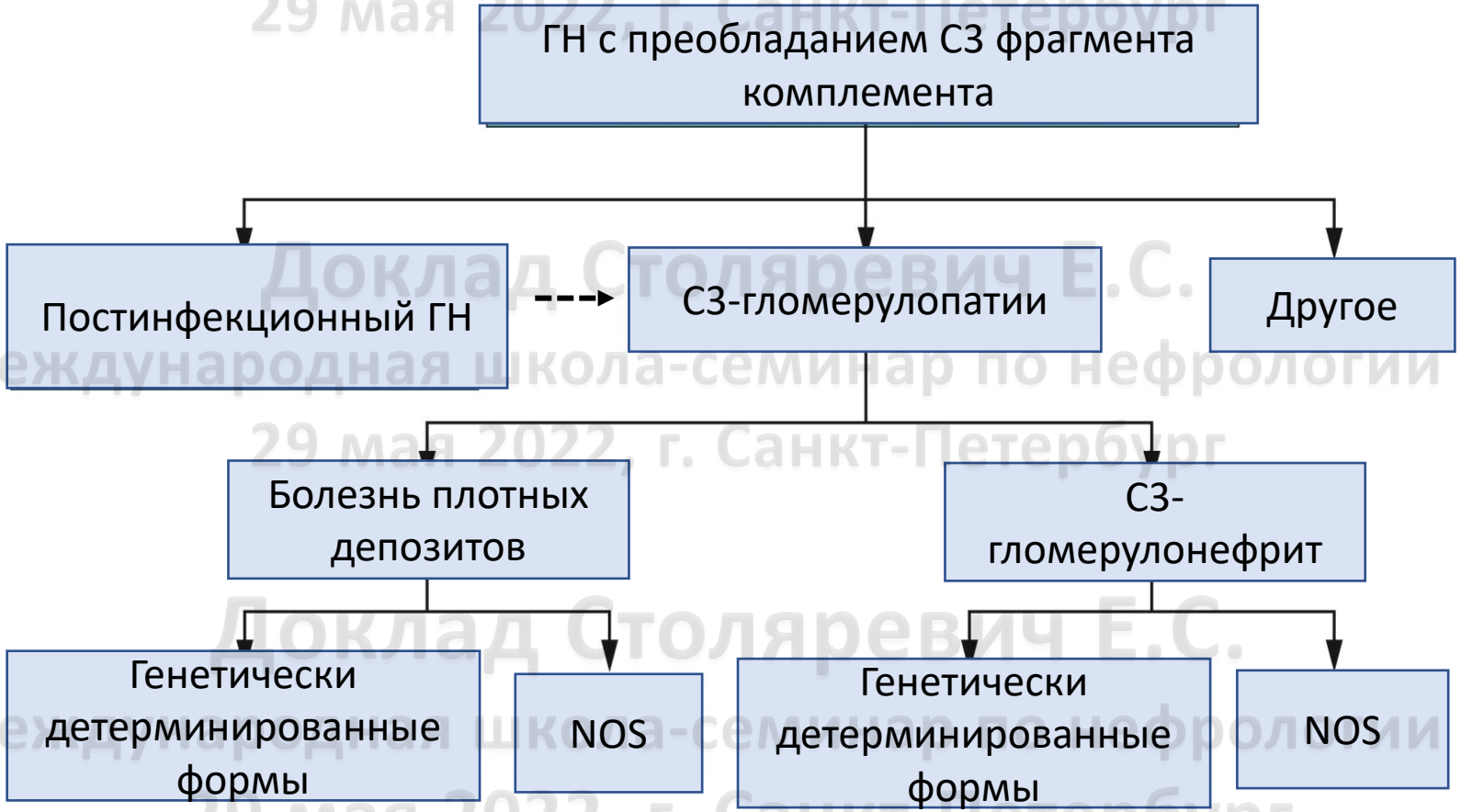
# C3 glomerulopathy: consensus report

Matthew C. Pickering[1], Vivette D. D'Agati[2], Carla M. Nester[3,4], Richard J. Smith[3,4], Mark Haas[5], Gerald B. Appel[6], Charles E. Alpers[7], Ingeborg M. Bajema[8], Camille Bedrosian[9], Michael Braun[10], Mittie Doyle[9], Fadi Fakhouri[11], Fernando C. Fervenza[12], Agnes B. Fogo[13], Véronique Frémeaux-Bacchi[14], Daniel P. Gale[15], Elena Goicoechea de Jorge[1], Gene Griffin[9], Claire L. Harris[16], V. Michael Holers[17], Sally Johnson[18], Peter J. Lavin[19], Nicholas Medjeral-Thomas[1], B. Paul Morgan[16], Cynthia C. Nast[5], Laure-Hélène Noel[20], D. Keith Peters[21], Santiago Rodríguez de Córdoba[22], Aude Servais[23], Sanjeev Sethi[24], Wen-Chao Song[25], Paul Tamburini[9], Joshua M. Thurman[17], Michael Zavros[26] and H. Terence Cook[1]

*[1]Centre for Complement and Inflammation Research, Imperial College London, London, UK; [2]Division of Renal Pathology, Department of Pathology, Columbia University Medical Center and the New York Presbyterian Hospital, New York, New York, USA; [3]Division of Nephrology, Departments of Internal Medicine and Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA; [4]Molecular Otolaryngology and Renal Research Laboratories, Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA; [5]Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA; [6]Division of Nephrology, Department of Medicine, Columbia University Medical Center and the New York Presbyterian Hospital, New York, New York, USA; [7]Department of Pathology, University of Washington, Seattle, Washington, USA; [8]Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands; [9]Alexion Pharmaceuticals, Cheshire, Connecticut, USA; [10]Division of Pediatric Nephrology, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas, USA; [11]Nephrology Department, Institut de Transplantation Urologie et Nephrologie, CHU de Nantes, Nantes, France; [12]Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA; [13]Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [14]Service d'Immunologie Biologique, Hôpital Georges Pompidou, AP-HP, Paris, France; [15]Division of Medicine*

## Диагностический алгоритм при ГН с доминированием С3 фрагмента комплемента






**C3 glomerulopathy: consenus report**

*Pickering M. et al, Kidney Int 2013*

# C3-Гломерулопатия при моноклональных гаммопатиях



| Автор | Публикация | Вариант ГП | n | МГПЗ (%) |
|---|---|---|---|---|
| Sethi S et al | **2010**<br>Am J Kidney Dis 56 (5) 977-982 | DDD | N=14<br>(>49 лет) | 71% |
| Zand L. et al | **2013**<br>Am J Kidney Dis 62(3) 506-514 | C3 GN | N=32 | 31% (любой возраст)<br>60% (>49 лет) |
| Lloyd I et al | **2016**<br>Clin Kidney J 9(6):794-799 | C3GN (9)/DDD (3) | N=12<br>(>49 лет) | 83% |



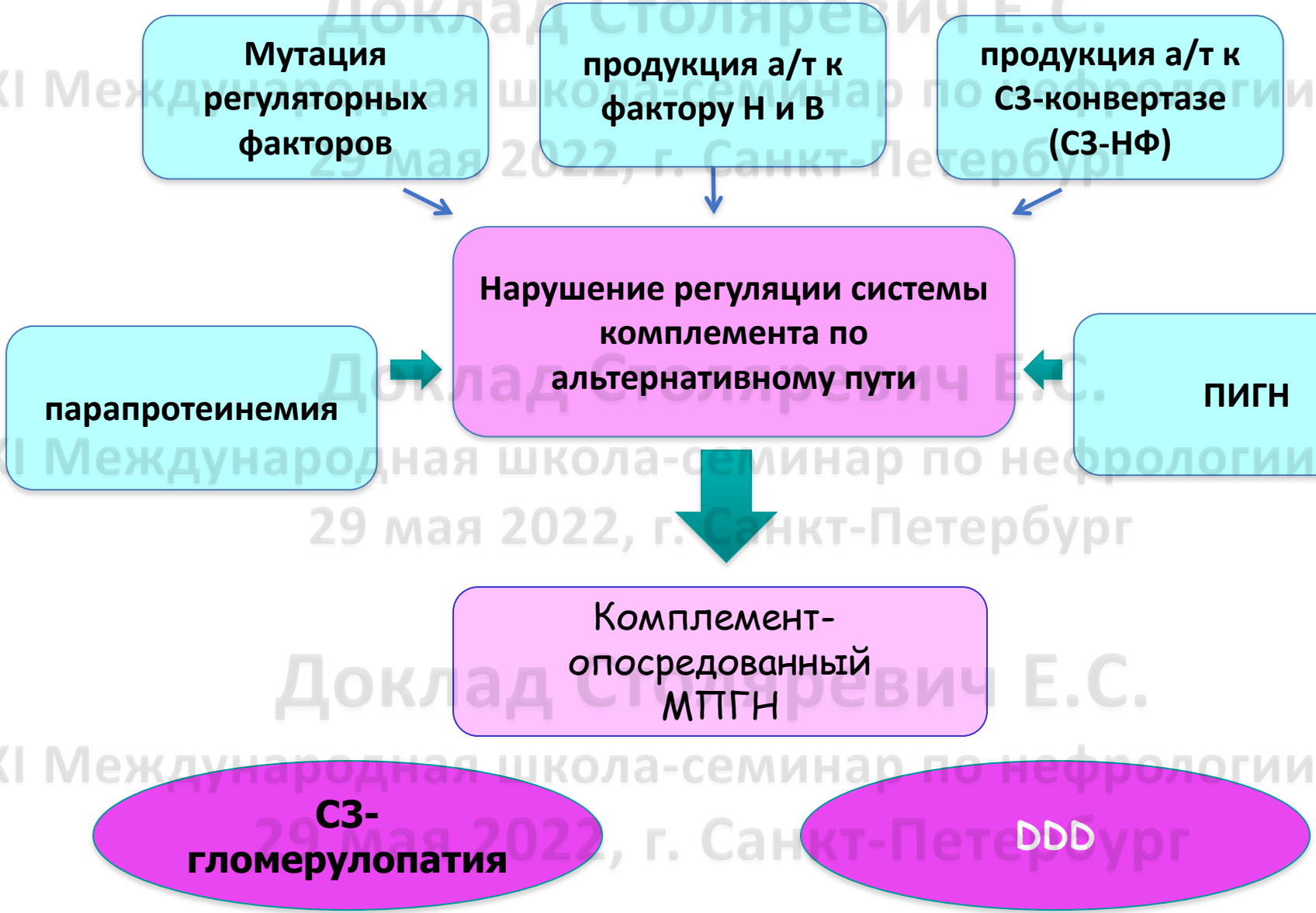
ckj OXFORD
Clinical Kidney Journal, 2016, vol. 9, no. 6, 794–799
doi: 10.1093/ckj/sfw090
Advance Access Publication Date: 23 September 2016
Original Article

ORIGINAL ARTICLE

## C3 glomerulopathy in adults: a distinct patient subset showing frequent association with monoclonal gammopathy and poor renal outcome

Isaac E. Lloyd[1], Alexander Gallan[2], Hunter K. Huston[3], Kalani L. Raphael[3], Dylan V. Miller[1], Monica P. Revelo[1] and Mazdak A. Khalighi[1]

[1]Department of Pathology, University of Utah, 1950 Circle of Hope Drive, Room N3100, Salt Lake City, UT 84112.



OPEN

# Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits

Christopher P. Larsen[1], Nidia C. Messias[1], Patrick D. Walker[1], Mary E. Fidler[2], Lynn D. Cornell[2], Loren H. Hernandez[2], Mariam P. Alexander[2], Sanjeev Sethi[2] and Samih H. Nasr[2]

[1]Nephropath, Little Rock, Arkansas, USA and [2]Division of Anatomic Pathology, Mayo Clinic, Rochester, Minnesota, USA

- 16 cases of MPGN pattern (LM/EM) with negative staining for Igs by routine IF-F and monoclonal Ig deposits (IgGκ in 75%) by IF-P
- 10 were consistent with "C3 GN" based on IF-F
- 14 had **M-Ig** that matched the glomerular paraprotein on IF-P
- 2 had **clonal B-cell population** on bone marrow biopsy
- 13 had **abnormal bone marrow biopsy** with plasma cell neoplasm (9) and B-cell neoplasms (4)

KI REPORTS
KIReports.org
REVIEW

# Paraffin Immunofluorescence: A Valuable Ancillary Technique in Renal Pathology

Check for updates

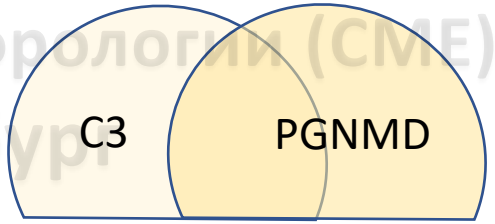
Samih H. Nasr[1], Mary E. Fidler[1] and Samar M. Said[1]

[1]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

Immunofluorescence on frozen tissue is the gold standard immunohistochemical technique for evaluation of immune deposits in the kidney. When frozen tissue is not available or lacks glomeruli, immunofluorescence can be performed on paraffin tissue after antigen retrieval (paraffin immunofluorescence). Excellent results can be obtained by paraffin immunofluorescence in most immune complex–mediated glomerulonephritides and dysproteinemia-associated kidney lesions, and thus this technique has become a valuable salvage technique in renal pathology. Furthermore, new data have emerged suggesting that paraffin immunofluorescence can be used as an unmasking technique, as it is more sensitive than frozen tissue immunofluorescence in some kidney lesions, such as crystalline light chain proximal

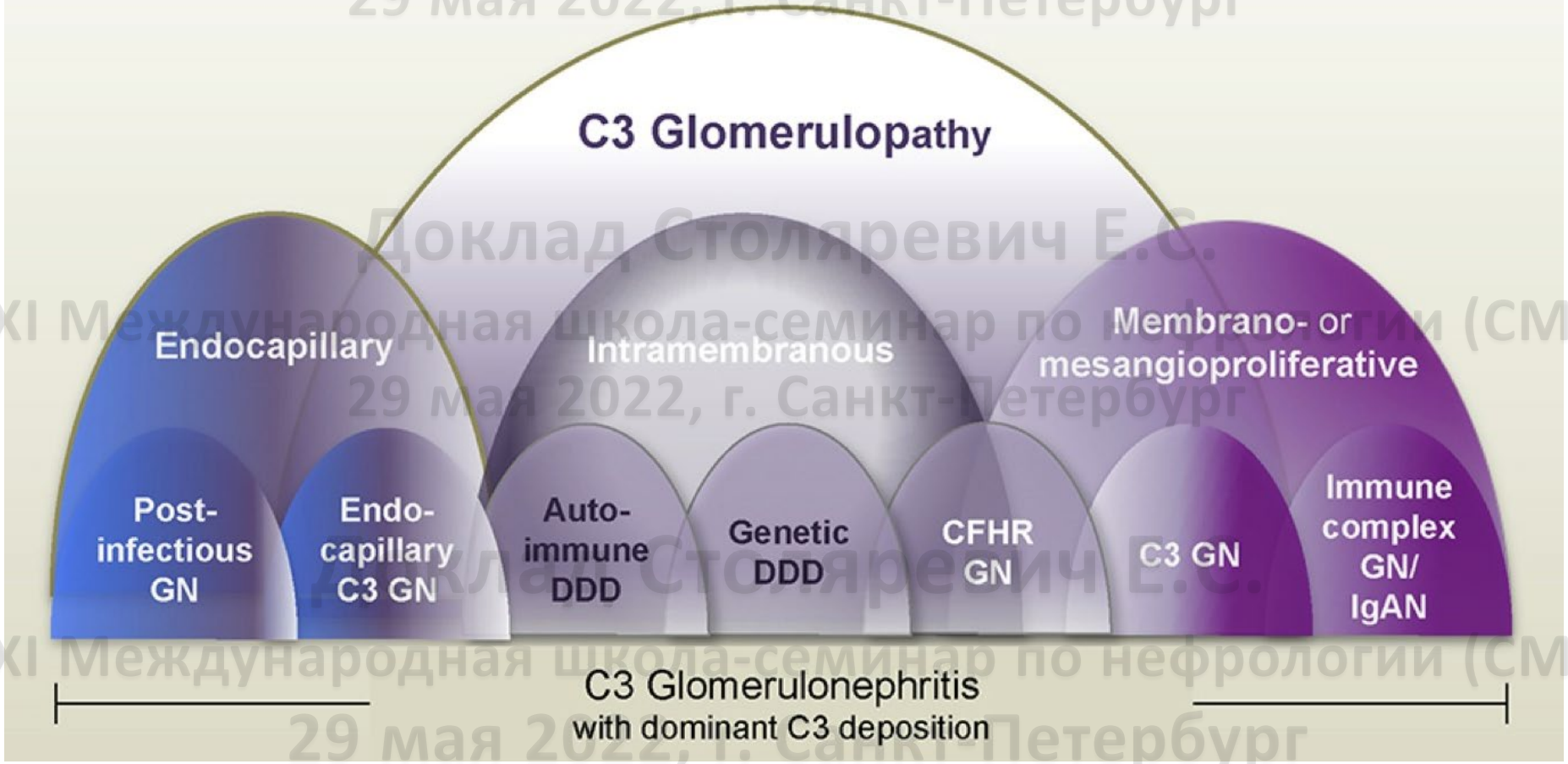
Сравнительная характеристика ИФ метода на замороженных и парафиновых срезах

| Significantly less sensitive | Slightly less sensitive | Comparable | More sensitive | Needed for diagnosis "masked deposits" |
|---|---|---|---|---|
| - C3 GN<br>- Bacterial infection-associated GN<br>- Primary membranous nephropathy<br>- Anti-GBM nephritis | - IgA nephropathy<br>- Lupus nephritis<br>- AL amyloidosis<br>- MIDD<br>- PGNMID | - Myeloma cast nephropathy<br>- Immunotactoid GN<br>- C1q nephropathy | - LCPT<br>- Crystalglobulin-induced nephropathy<br>- Cryoglobulinemic GN<br>- Fibrillary GN | - MGMID<br>- MPGN with masked monoclonal deposits |



# Гетерогенная структура C3-гломерулопатии






*Zipfel P.F. et al., Mol Immunol 2015*