INFECTION- ASSOCIATED GELOMERULONEPHRITIS (GN)

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INTRODUCTION

For over a century , acute ‘post- streptococcal glomerulonephritis’ (APSGN) was the prototypical form of bacterial infection-associated glomerulonephritis, typically occurring after resolution of infection and a distinct infection- free latent period.

Nature 2020 (Epidemiology, pathogenesis, treatment and outcomes of infectionassociated glomerulonephritis)

Continues Introduction

The incidence of APSGN has sharply declined in the Western world, whereas the number of Staphylococcus infection- associated glomerulonephritis (SAGN) cases increased owing to a surge in drug- resistant Staphylococcus aureus infections, both in the hospital and community settings.

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Continues Introduction

Glomerulonephritides constitute a major cause of kidney injury and frequently require a kidney biopsy for etiological diagnosis. Among glomerulonephritides associated with immune complexes, lupus nephritis,

IgA nephropathy (IgAN), infection- associated glomerulonephritis (GN) and membranous GN are the most commonly encountered forms; cryoglobulinaemic GN is relatively less common

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Continues Introduction

Infection is one of the most important triggers for the development of acute GN - bacterial, viral and parasitic infections

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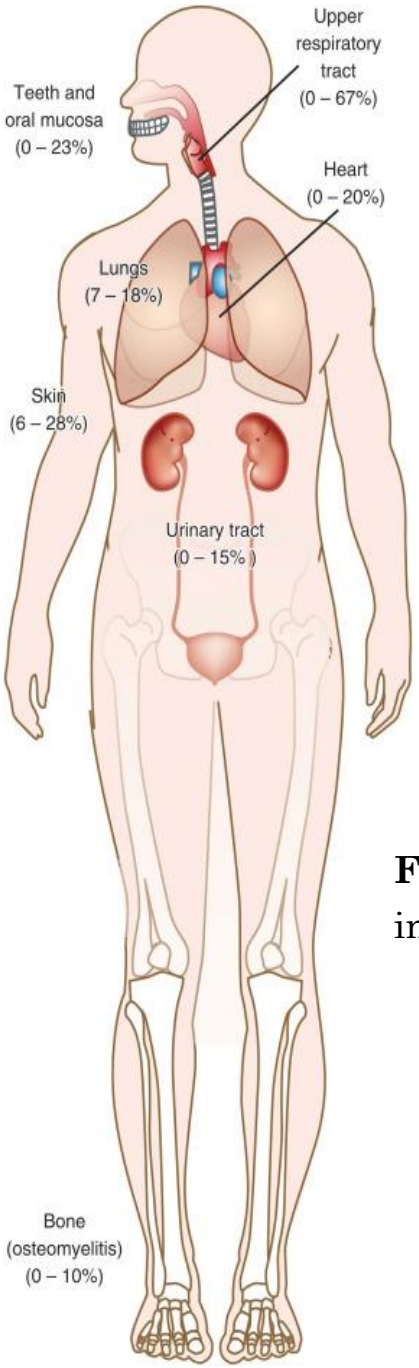

Fig. 1 Sites of infection in adult infection-related glomerulonephritis.

Incidence of APSGN started to gradually decline in most developed countries This decline was largely attributed to improved living standards and socioeconomic.

Staphylococcus infection- associated GN (SAGN) is now far more prevalent than APSGN, at least in developed countries.

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Factors implicated in the upsurge of SAGN cases include:

- lifestyle changes
- elderly patients with comorbidities such as diabetes mellitus
- obesity
- catheters
- and central lines
- intravenous drug use

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Acute post- streptococcal GN

GAS are known to cause a wide spectrum of illnesses, including superficial infections

(such as pharyngitis and skin infections), invasive

infections (such as cellulitis, necrotizing fasciitis and pneumonia)

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Continue

Sequelae of a GAS infection (that is, APSGN and acute rheumatic fever) are usually triggered by upper respiratory tract infections (such as pharyngitis and tonsillitis) in colder climates and by skin infections or superimposed bacterial infection of scabetic lesions in warmer climates.

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Nephritogenic *S. pyogenes strains 12,* 4 and 1 are associated with APSGN triggered by throat infections, whereas APSGN secondary to skin infections is linked to *S. pyogenes M types 49, 42, 2, 57 and* 60.

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- Less than 2% show clinically obvious signs of acute GN.
- predominantly seen aged 3–15 years.
- The risk of nephritis in epidemics ranged

from 5%: throat infections 25% :pyoderma caused by strains of type 49 streptococci.

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The incidence of APSGN remains high

in heavily populated tropical regions of the world and Aboriginal Australians.

It should also be emphasized that in the vast majority of cases, kidney disease is subclinical, which is thought to be 4 to 19 times more common than symptomatic disease.

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کدام جمله صحیح است؟

الف: شیوع PSGN در دختر بچه های ۳ تا ۱۵ سال بیشتر است.
ب: کرایوگلوبولینمی از علل شایع گلومرولونفریت می باشد.
ج: شیوع ASGN رو به افزایش است
د: بیشتر از نیمی از مبتلایان به عفونت پوستی (پیودرما) دچار PSGN میشوند.

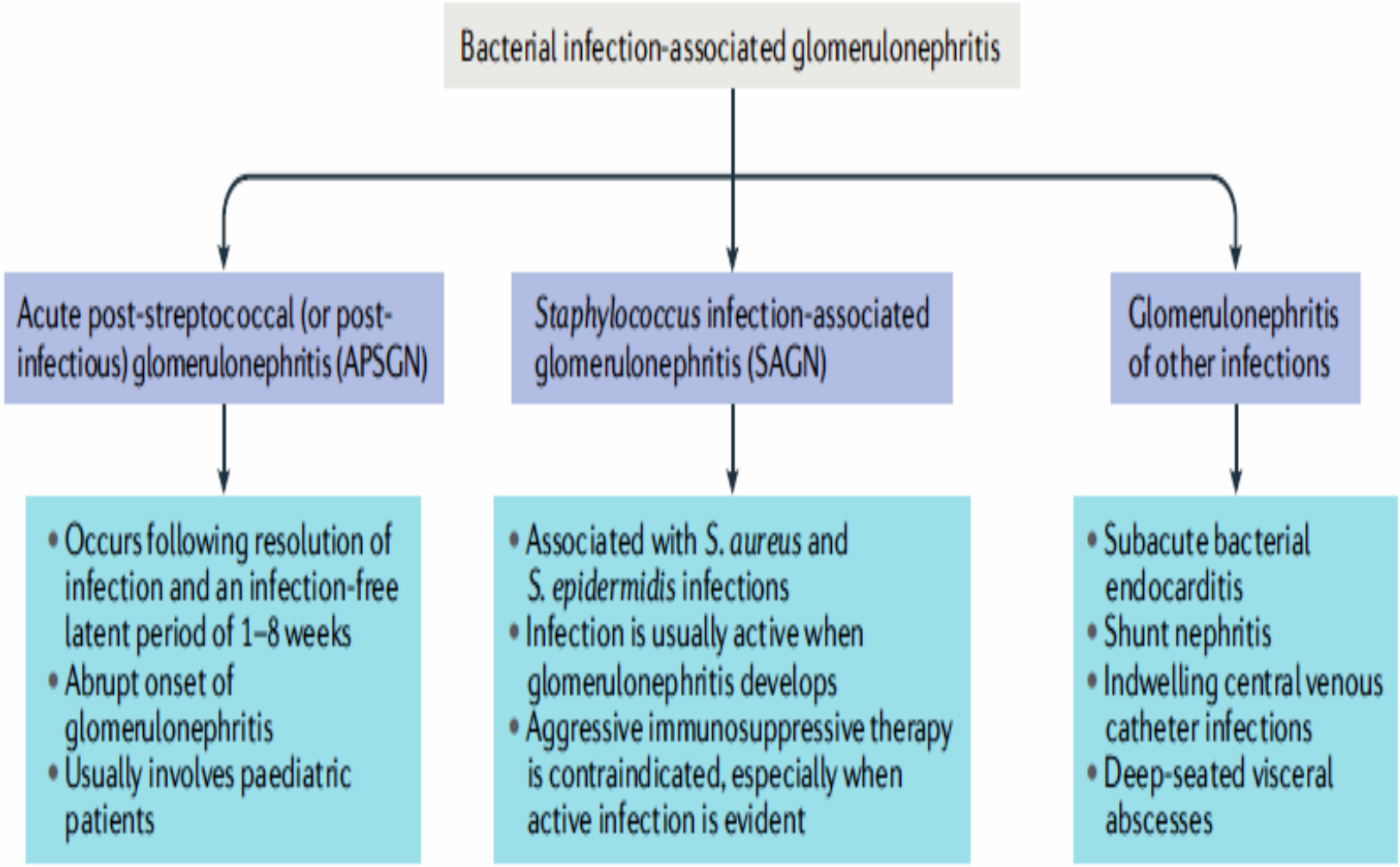

Fig. 2 classification of bacterial infection- associated glomerulonephritis

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APSGN IN ELDERLY PATIENTS

In the adult population, it is more frequently reported among elderly individuals (aged over 60 years). changes in the immune system secondary to:

- Ageing co- morbidities
- Diabetes Mellitus
- Hypertension
- atherosclerotic heart disease,

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Diagnosis of infection- associated GN in elderly patients can be difficult because the concomitant co- morbidities might mask the underlying infection.

CLINICAL AND LABORATORY FINDINGS

The majority of APSGN cases are subclinical, but patients with clinical disease typically present with acute nephritic syndrome:

- facial oedema
- hypertensive urgency
- Hypertensive encephalopathy or left ventricular dysfunction
- acute kidney injury
- Nephrotic syndrome and RPGN are rare

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Serum levels of complement proteins (C3) are always low (ASO) serum titres increase

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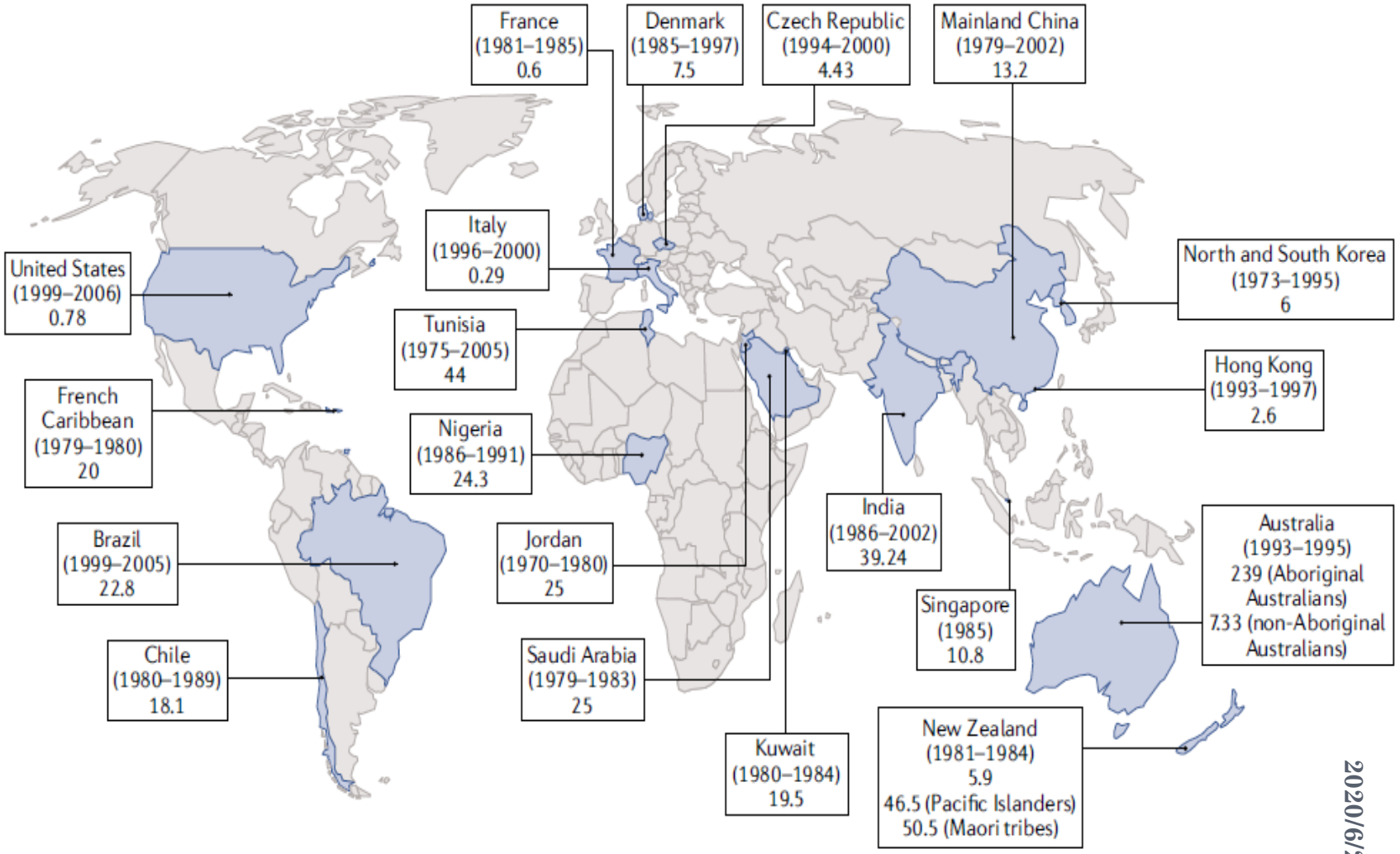

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Fig. 3 Global APSGN incidence

PATHOLOGY

APSGN is characterized by diffuse glomerular endocapillary hypercellularity, frequently with numerous polymorphonuclear leukocytes, also known as “exudative glomerulonephritis

- garland pattern: refers to coarse granular ‘lumpy-bumpy’ staining along the glomerular capillarywalls.
- starry sky: finely granular pattern with few interspersed large deposits
- mesangial staining

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NCBI 2019

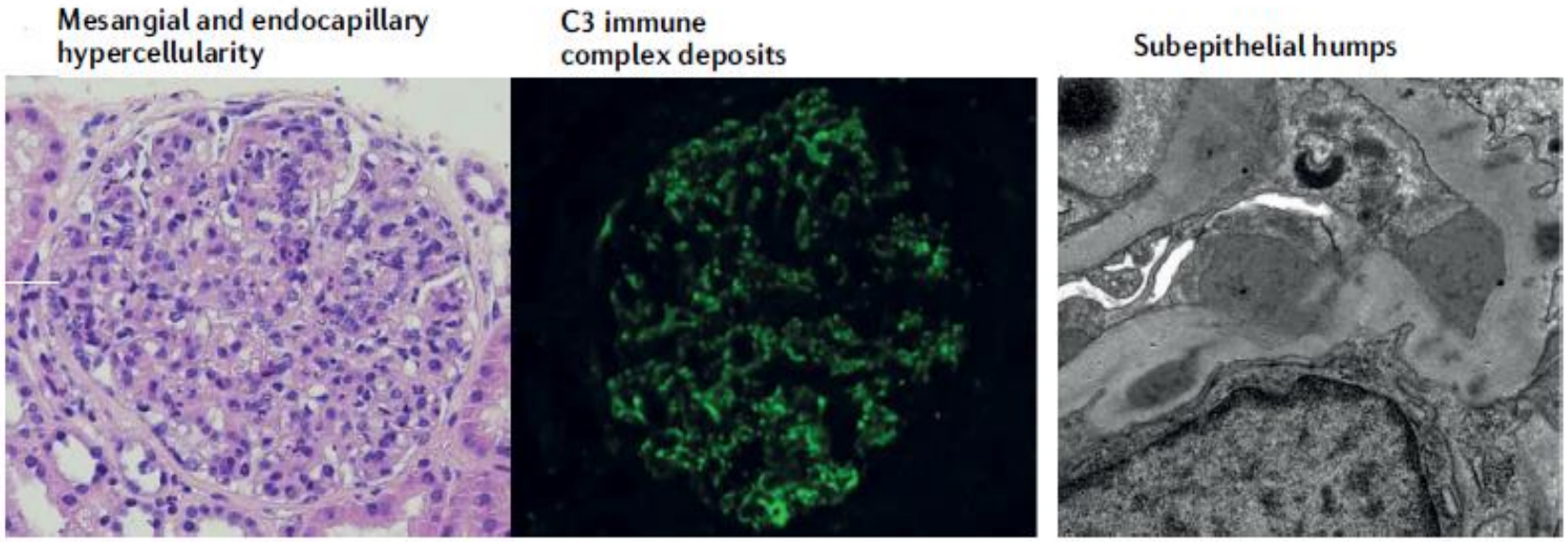

Fig. 4 Glomerular pathology and histological features in APSGN

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Treatment

The treatment of APSGN focuses on the clinical symptoms of acute nephritis and is usually temporary, as clinical manifestations typically begin to improve 1–2 weeks after disease onset and renal function usually returns to baseline levels within 4 weeks.

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Continue

- Restriction of daily sodium consumption

to 2,000–2,500 mg

- fluid intake to 2,000 ml withdiuretic therapy
- Anti- hypertensive agents, including vasodilators such as calcium channel blockers
- ACE inhibitors may further worsen renal function and cause hyperkalaemia
- Antibiotics

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- during the acute infection, antibiotics are recommended to reduce the probability of developing APSGN.
- Prophylactic antibiotics
- use of immunosuppression

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همه موارد زیر صحیح است به جز ؟

الف: در درمان PSGN محدود کردن آب و نمک لازم است

ب: جهت کنترل فشار خون ACEI اکیدا توصیه می شود.

ج: بیوپسی کلیه اغلب در PSGN لازم نمی باشد.

د: آنتی بیوتیک پروفیلاکسی اغلب توصیه نمی شود.

Outcome

The prognosis of APSGN, even in patients with acute crescentic GN and renal failure, is generally excellent.

Renal outcome and overall prognosis are generally worse in adults with APSGN than in children

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STAPHYLOCOCCUS INFECTION- ASSOCIATED GN

- Staphylococci were implicated in chronic infections: endocarditis or ventriculo- atrial shunt infections

- Most cases were secondary to MRSA

- incidence peaked between the fifth and seventh decades of life.

- Both *S. aureus and S. epidermidis infections can lead* to SAGN

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CLINICAL AND LABORATORY FINDINGS

- Patients with SAGN usually present with AKI, microscopic haematuria and nephrotic- range proteinuria.
- Fever is not always present and disease symptoms may be non- specific
- Blood cultures might also be negative
- Positive anti- neutrophil cytoplasmic antibody (ANCA) serology

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PATHOLOGY

- An active proliferative immune complex GN with or without focal crescents.

- IgA and C3 staining by immunofluorescence

is also characteristic.

- Focal segmental glomerular sclerosis (FSGS), or

segmental glomerular scarring lesion are rare in SAGN

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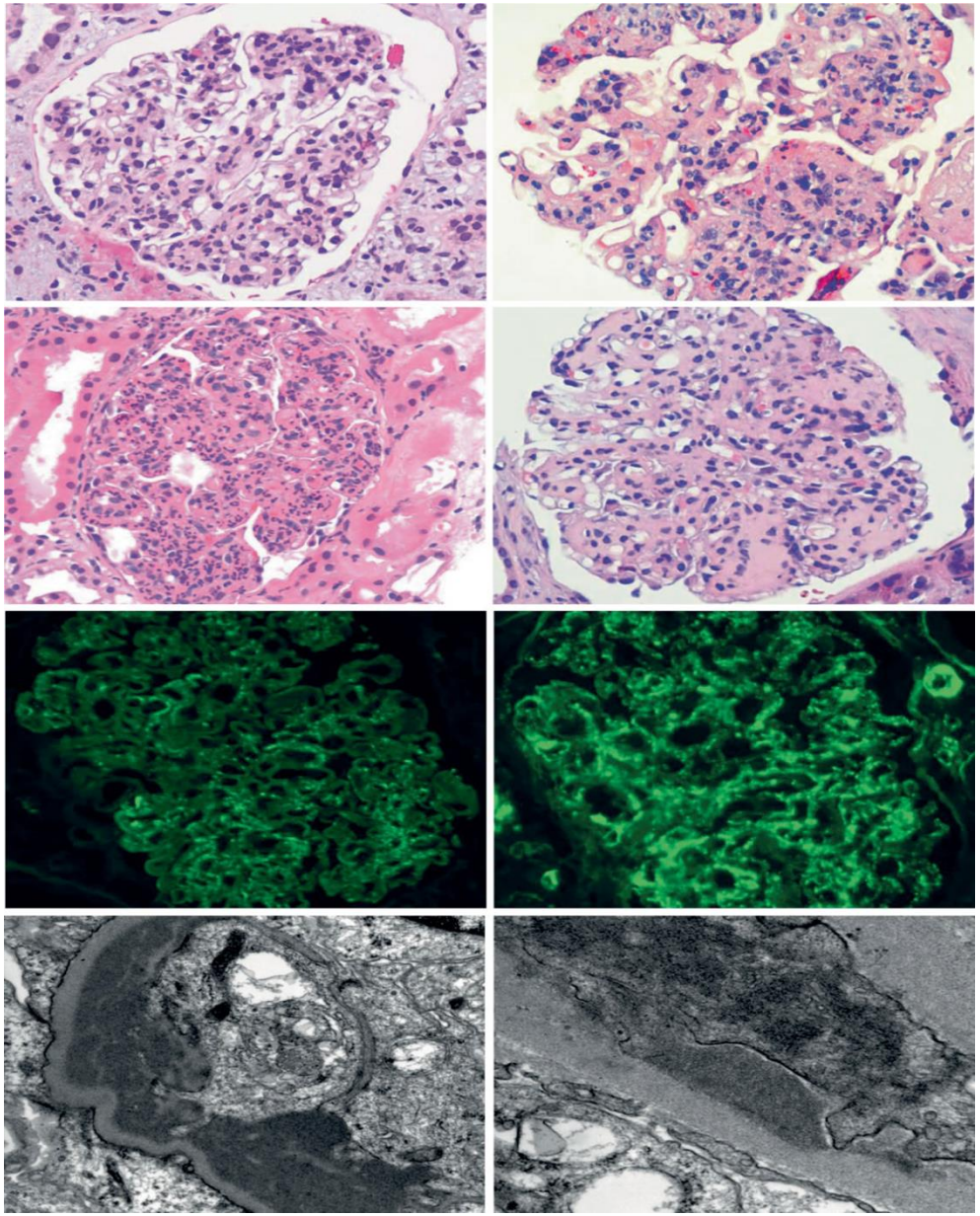

Fig. 5 Histological features in SAGN

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IMMUNOFLUORESCENCE MICROSCOPY

- SAGN is characterized by the presence of IgA and C3, typically in the mesangium.

- It should be emphasized that strong

IgA staining is not present in every case of SAGN

- Cryoglobulinlike are rarely seen

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Criteria for the diagnosis of SAGN

No single clinical or pathological feature is pathognomonic for *Staphylococcus* infection- associated glomerulonephritis (SAGN) or other bacterial infection- associated

GN. Clinical features, biopsy findings, culture results and urinalysis findings should all be taken into consideration at the time of diagnosis. Also, not every patient with SAGN might fulfil all diagnostic criteria74.

Definitive diagnostic criteria

- Culture- proven staphylococcal infection (ongoing or in the recent past).
- Acute onset proliferative GN with IgA and complement protein C3 containing glomerular immune complex deposits, acute kidney injury, nephroticrange proteinuria and (usually microscopic) haematuria. The degree of glomerular hypercellularity and the extent of glomerular crescents can be highly variable.

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CONTINUE …

Additional criteria

Although not definitive, these features might suggest the possibility of infectionassociated GN. In the presence of these features, an underlying staphylococcal infection should be carefully investigated. This is especially true in cases of GN and AKI, with recent onset severe proteinuria and microscopic haematuria in combination with any of the following:

- Presence of potential risk factors for infection — diabetes mellitus, intravenous drug use, recent surgical or invasive procedure, prosthetic devices such as pacemakers, heart valves or orthopaedic devices, poor dentition and/or tooth abscesses, multiple trauma with open wounds, non- healing ulcers or post- amputation wounds in diabetic patients, indwelling central or peripheral intravenous catheters or ventriculo-peritoneal shunt.
- Low serum C3 levels
- Leukocytoclastic vasculitic rash (LCV) — IgA staining often seen in the biopsy of affected skin.
- Positive anti- neutrophil cytoplasmic antibody (ANCA) serology (titre might only be mildly positive), atypical ANCA or dual specificity for ANCA antibodies — proteinase 3 and myeloperoxidase. Lupus serologies, rheumatoid factor and cryoglobulin test are

usually negative, but patients with endocarditis may show one or more of these serologies as well.

- Predominantly C3 immunofluorescence detected in the mesangial and capillary walls of the glomerulus (with or without IgA staining) along with electron- dense immune deposits on ultrastructural examination.
- Subepithelial humps identified by electron microscopy.

Treatment

- ✓ Eliminating the underlying infection
- ✓ Cultures of microbial.
- ✓ Common diagnostic studies include transthoracic echocardiogram or, trans- oesophageal echocardiogram, (CT) scan, (MRI) and X- ray also known as panorex
- ✓ Supportive care of patients with SAGN
- ✓ Calcium channel blocker

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- ✓ Suggesting that immunosuppression might not be an effective treatment for SAGN

- ✓ In cases in which inflammation persists after the bacterial insult has been eliminated a course of corticosteroids could be considered to limit further damage to the kidneys.

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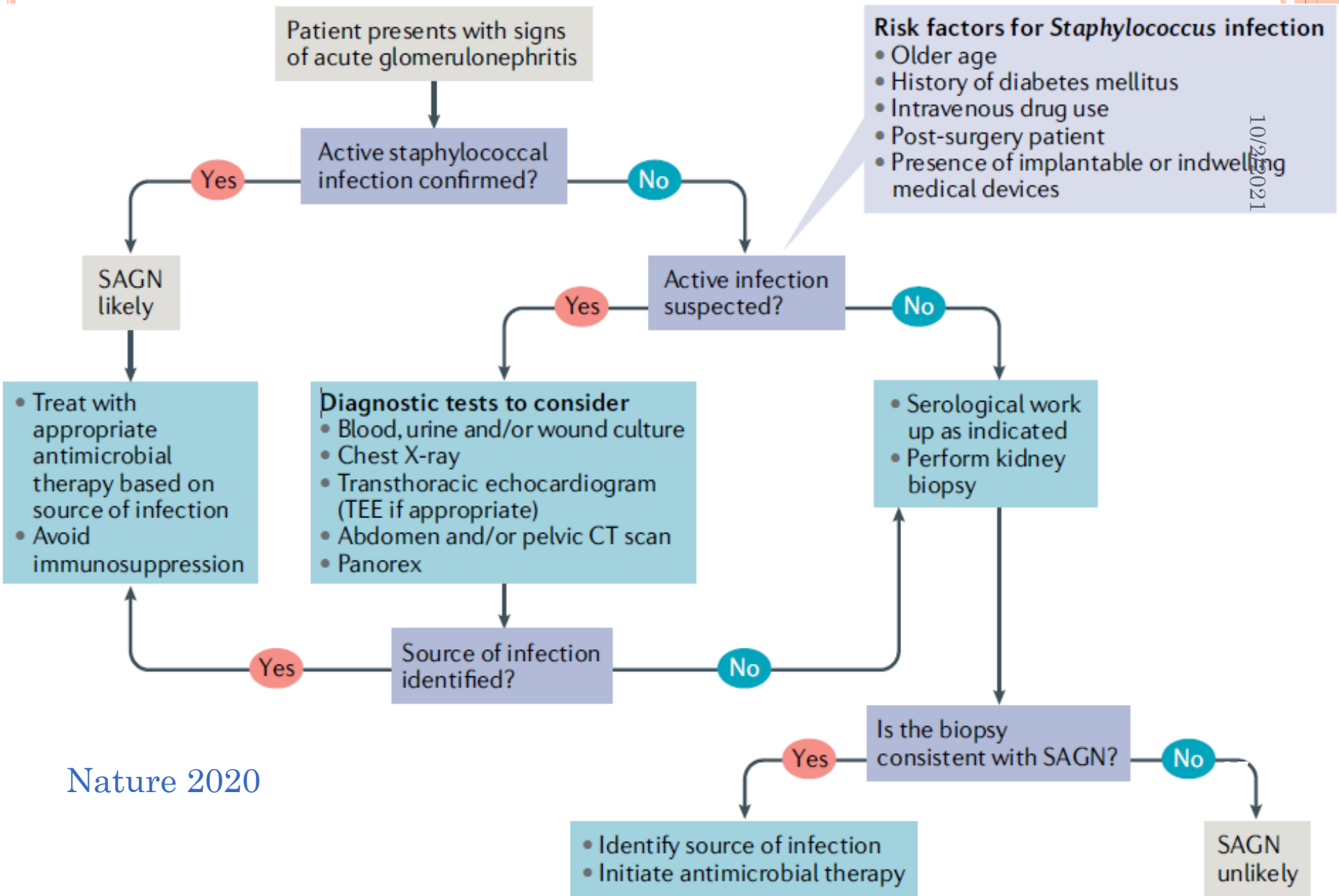
Algorithmic approach to the management of SAGN



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10/22/2021

Endocarditis- associated GN

Endocarditis has historically been divided into subacute bacterial endocarditis and acute bacterial endocarditis.

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Subacute bacterial endocarditis and renal disease

- Subacute bacterial endocarditis usually affects damaged heart valves
- the bacterial organisms involved are often oral cavity with low virulence, such as viridans group streptococci, Streptococcus mutans and the HACEK

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- ✓ Valvular deformities secondary to congenital heart disease or rheumatic fever were common causes.
- ✓ usually involves the left- sided heart valves.
- ✓ Osler nodes, Janeway lesions and splinter haemorrhages are commonly
- ✓ diffuse exudative endocapillary proliferative lesions or (MPGN) lesions

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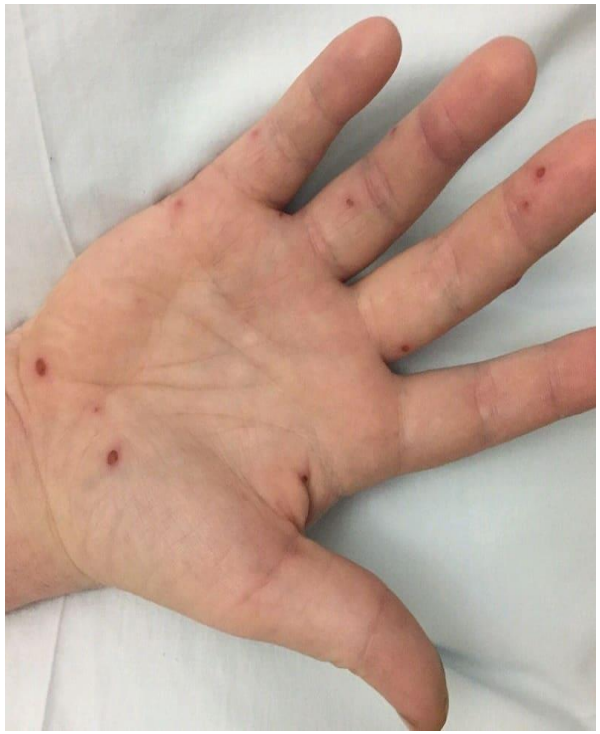
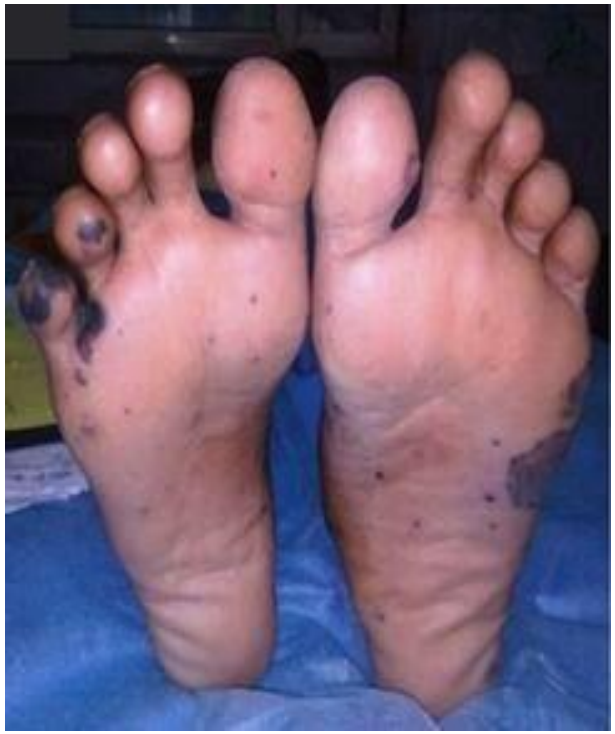
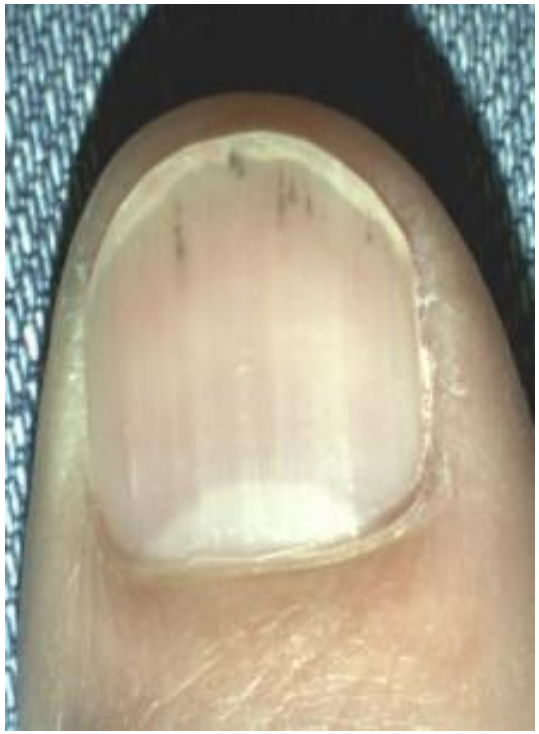
Fig. 6



Osler node



Janeway Lesion



Splinter Hemorrhages

Harrison 2017

Acute bacterial endocarditis and renal disease

- Acute bacterial endocarditis usually involves previously healthy heart valves and the bacterial organism is highly virulent, frequently MRSA.

- The infection typically involves the right- sided heart valves.

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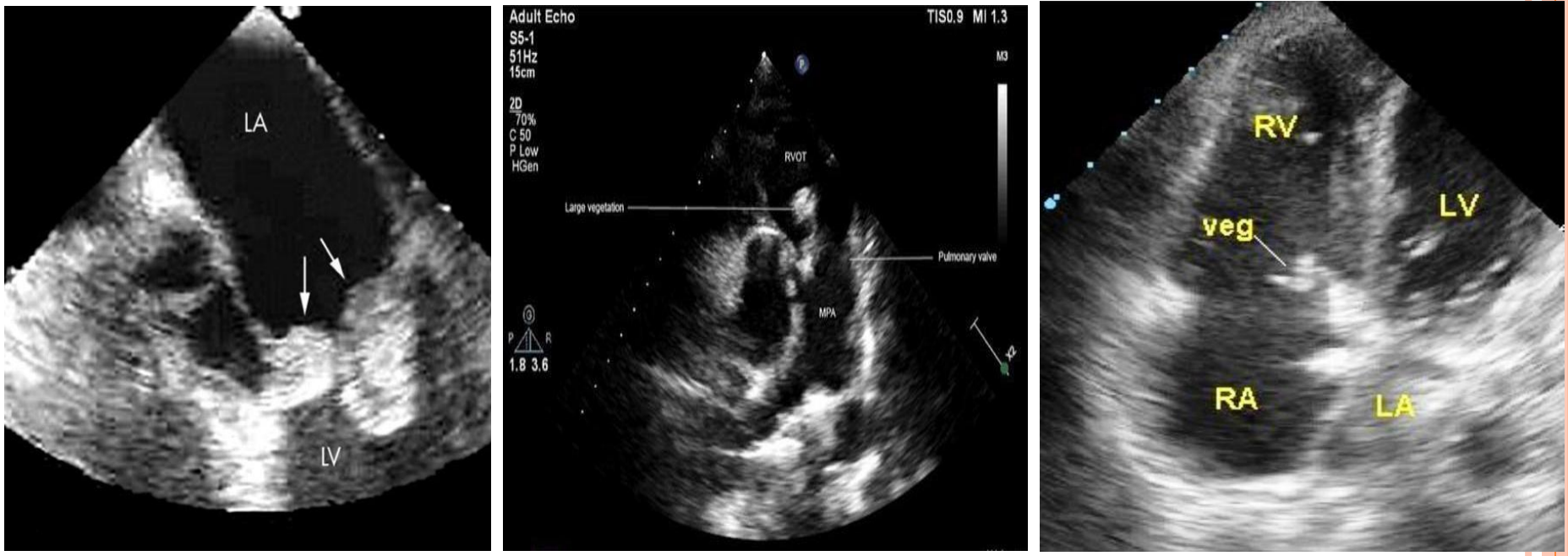

Fig. 7 infective endocarditis

CLINICAL AND LABORATORY FINDINGS

- ✓ The most common clinical presentation of infective endocarditis- associated GN is AKI
- ✓ acute nephritic syndrome (that is, haematuria, hypertension and renal failure).
- ✓ low serum levels of complement proteins (mainly C3).
- ✓ Some patients with endocarditis also have positive autoimmune serologies, mainly ANCA

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PATHOLOGY

The glomerular pattern of injury in endocarditis associated GN is variable and similar to that of SAGN. focal crescents and necrotizing lesions are more frequently.

A membranoproliferative pattern is common in endocarditis owing to persistent long- standing glomerular injury.

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TREATMENT AND OUTCOME

Treatment of endocarditis associated GN is the same as that described for SAGN. it is crucial to differentiate endocarditis- associated GN with positive ANCA serology from true ANCA-associated GN, because the latter requires aggressive immunosuppressive therapy.

1. Antibiotics to eliminate the infection
2. Supportive treatment of the acute nephritis

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Differential diagnosis of infection- associated GN

Disease	Light microscopy	Direct immunofluorescence	Electron microscopy
SAGN	Endocapillary hypercellularity common, with exudative pattern in some cases · Focal crescents are frequent, but necrotizing vasculitis is not seen · FSGS pattern not seen	· C3 stronger than IgA · Sometimes weak to negative IgA , but C3 usually present · Some cases are pauci-immune	· Mesangial deposits most common. Few small subendothelial deposits · 31% of the cases show subepithelial humps · Humps not required for diagnosis
Primary IgA nephropathy	· Mesangial hypercellularity most common · Endocapillary hypercellularity less frequent · Crescents are uncommon, and FSGS lesions are frequently seen	IgA usually stronger than C3	· Mesangial deposits most common · Absence of subepithelial humps · Capillary wall deposits uncommon
ANCA vasculitis	· Crescents are defining lesions · Co- existence of fibrous, fibrocellular and active crescents · No endocapillary hypercellularity · Necrotizing arterial lesions may be present (not seen in SAGN)	· Negative or weak scant granular IgG and/or C3. Pauci- immune pattern · Co- incidental IgA in rare cases	Few to absent immune complex deposits

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Disease	Light microscopy	Direct immunofluorescence	Electron microscopy
APSGN	· Diffuse endocapillary hypercellularity common · Exudative pattern often seen · Crescents are uncommon	· Strong C3 with lumpy- bumpy coarse granular pattern · IgG may be present in early stages · IgA absent	· Subepithelial humps almost always present; usually large and numerous · Few mesangial deposits are seen
C3 GN (excluding dense- deposit disease)	Mesangial and endocapillary hypercellularity · Membranoproliferative pattern frequent · Crescents are uncommon but may be focal and segmental	· Strong C3 and weak to absent IgG. IgA absent · Staining can be global or segmental mesangial and capillary wall · Lumpy- bumpy C3 deposits may be seen	· Mesangial, and capillary wall deposits · Humps may be seen, but are not required for diagnosis
Cryoglobulinaemic GN	MPGN common · Intracapillary inflammatory cells are monocytes, not PMNs · Segmental hyaline thrombi often seen	Wide spectrum depending on the type of cryoglobulins, usually mixed IgG and IgM · IgA staining extremely rare	· Microtubular substructure frequently seen · Deposits can be few and small

PATHOGENESIS OF INFECTION- ASSOCIATED GN

All forms of infection- associated GN are thought to result from immune- mediated glomerular injury triggered by systemic infection

- Deposition of immune complexes
- Target antigens : streptococcal M protein
- Urinary plasmin activity is higher in patients with APSGN than in healthy individuals
- Staphylococcal enterotoxins Serum levels of IL-1ß, IL-2, IL-6, IL-8 and TNF were also higher in patients with SAGN

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AJKD 2015

GN BY OTHER INFECTIONS

Grampositive anaerobes: Propionibacterium acnes,

Gram- negative :Neisseria gonorrhoeae,

Pseudomonas.

Brucella

Coxiella burnetii

Yersinia

Legionella

Bartonella

Mycoplasma

Treponema

Parasitic infections: schistosomiasis, malaria, leishmaniasis

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SHUNT NEPHRITIS

Shunt nephritis became a rare GN after ventriculo-atrial shunts were replaced by ventriculo-peritoneal shunts for the treatment of hydrocephalus.

MPGN pattern is frequently seen.

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CONCLUSIONS

Incidence of APSGN is declining worldwide, although it remains high in tropical.

APSGN is still the most common cause of acute GN in children worldwide.

SAGN is 3–4 times more common than APSGN and is increasingly encountered in the elderly population.

Future research should investigate non- invasive imaging techniques for the detection and localization of *S. aureus infections*


Thank You