IE-associated GN

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INFECTIVE ENDOCARDITIS

- IE is an infection of the endocardial surface of the heart, and it can be an infection of one or more heart valves or of the intracardiac devices
- Incidence of 3–10 cases per 10,000
- 20% mortality rate
- Complications; cardiac, metastatic, neurologic, renal, musculoskeletal, and pulmonary complications

KIDNEY DISEASE IN INFECTIVE ENDOCARDITIS

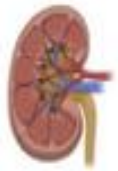
several forms of kidney disease:

- Bacterial infection-related immune complex-mediated glomerulonephritis (GN)
- Renal infarction from septic emboli
- Renal cortical necrosis
- Drug-induced acute interstitial nephritis
- Acute kidney injury (due to acute tubular necrosis) can develop as a result of treating the infection. most common clinical presentation (79 percent)
- IE-associated RPGN is rare and the differential diagnosis from idiopathic vasculitis can be challenging due to overlaps in clinical manifestations, ANCA positivity and typical presentations of IE positive blood cultures and valvular vegetation on echocardiography strongly support the diagnosis of IE

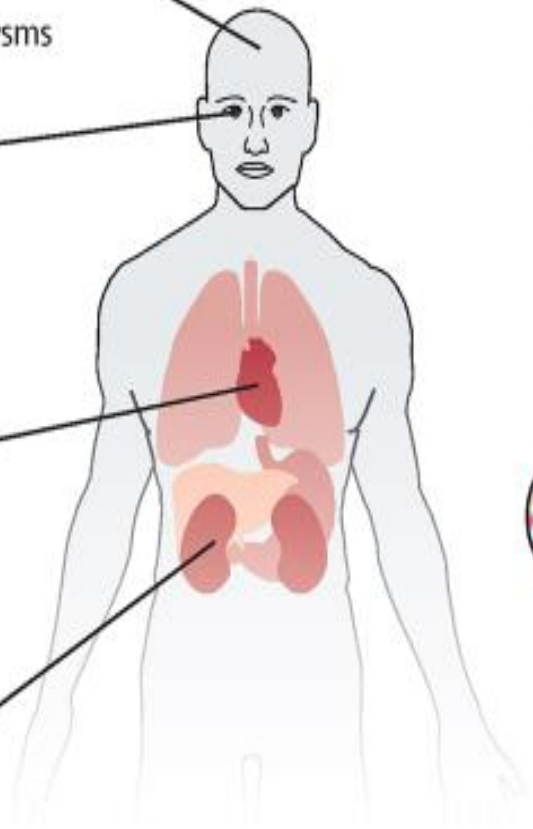
Cerebrum
- Ischaemic stroke
- Abscess
- Intracranial haemorrhage
- Intracerebral abscess
- Meningitis
- Infective intracranial aneurysms

Eye
- Roth spots

Heart
- Congestive heart failure
- Valvular dysfunctions
- Arrhythmias
- Myocardial abscesses
- Myocardial infarction



Kidney
- Acute kidney injury
- Glomerulonephritis
- Infarction



Musculoskeletal complications
- Myalgias
- Arthralgias
- Osteomyelitis

Skin
- Janway lesions
- Osler nodes

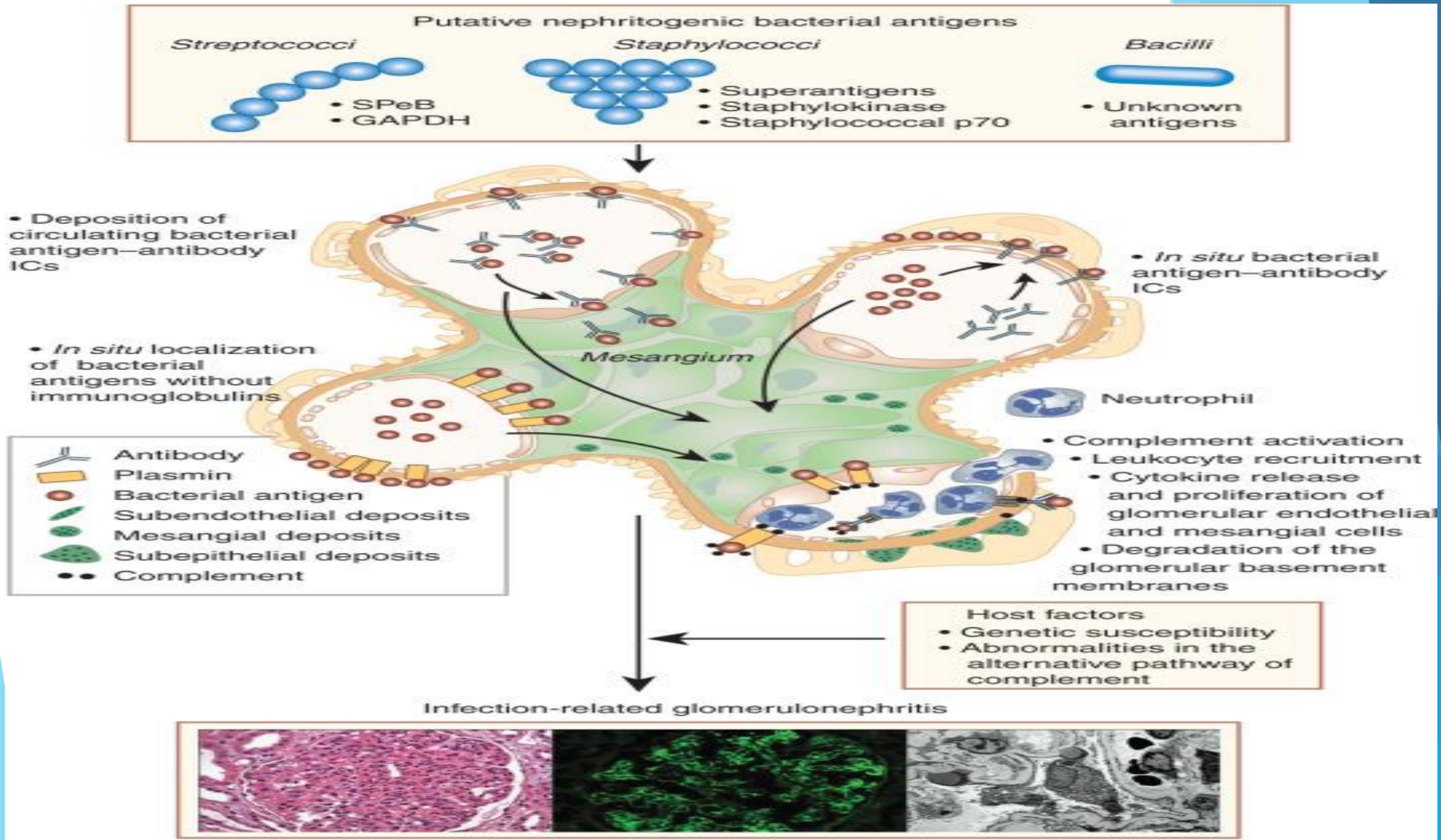
Embolic complications
- Spleen
- Lung
- Kidney
- Liver
- Splinter haemorrhages

Other symptoms
- Fever
- Hepatosplenomegaly
- Metastatic infection

Mechanisms account for clinical manifestations

- Valvular destruction
- Paravalvular extension of infection and heart failure
- Microvascular and large vessel embolization
- Metastatic infection of target organs
- Immunologic phenomena

- The deposited NAPlr binds with plasmin and maintains its activity by protecting it from physiological inhibitors, and is considered to cause glomerular damage directly by degrading extracellular matrix proteins and indirectly by activating pro-matrix metalloproteases.
- Additionally, glomerular plasmin activity can exert proinflammatory functions by activating and accumulating inflammatory cells


Putative nephritogenic bacterial antigens
Streptococci
• SPeB
• GAPDH
Staphylococci
• Superantigens
• Staphylokinase
• Staphylococcal p70
Bacilli
• Unknown antigens
• Deposition of circulating bacterial antigen–antibody ICs
• In situ bacterial antigen–antibody ICs
• In situ localization of bacterial antigens without immunoglobulins
Mesangium
Neutrophil
• Complement activation
• Leukocyte recruitment
• Cytokine release and proliferation of glomerular endothelial and mesangial cells
• Degradation of the glomerular basement membranes
Antibody
Plasmin
Bacterial antigen
Subendothelial deposits
Mesangial deposits
Subepithelial deposits
Complement
Host factors
• Genetic susceptibility
• Abnormalities in the alternative pathway of complement
Infection-related glomerulonephritis

Endocarditis-Associated GN

- The most common organism in IE-associated GN is S. aureus(56 percent of cases)
- Streptococcus species are the next most common.
- Less common organisms include Bartonella henselae , Coxiella burnetiid , Cardiobacterium hominis, and Gemella .
- One-half of affected patients do not have a known risk factor
- Common comorbidities : cardiac valve disease (30 percent), intravenous drug use (29 percent), hepatitis C (20 percent), and diabetes (18 percent).

Clinical manifestations

- Fever
- cardiac murmurs
- hepatosplenomegaly
- Some patients may show features of a systemic vasculitis, including purpuric skin lesions
- Hypertension
- Edema

LAB DATA

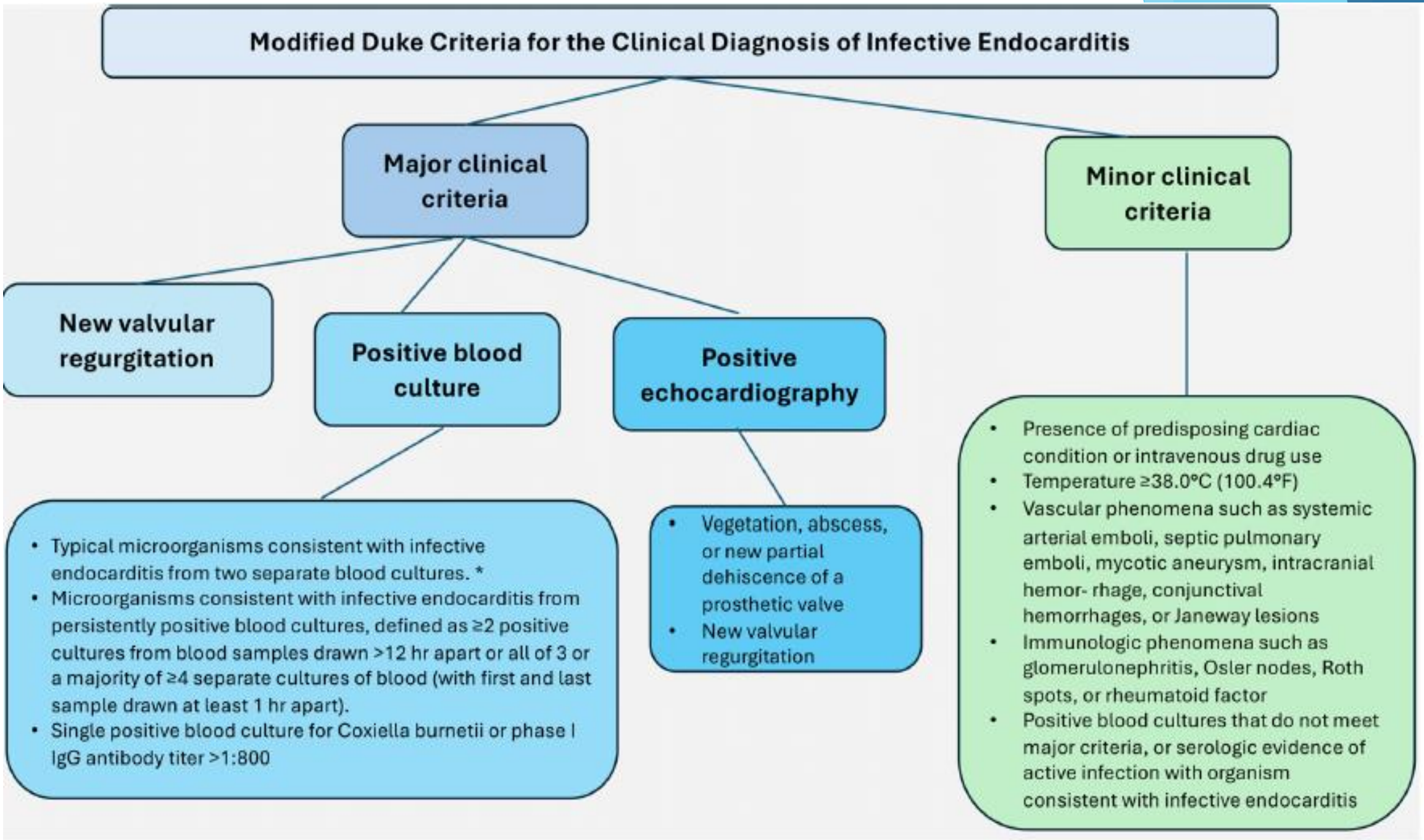
- Positive ANCA testing has been reported in some cases of IE
- 67 percent were positive for proteinase 3 (PR3)-ANCA)
- 53 percent of patients had reduced C3 complement
- 19 percent had reductions in C4 complement
- Some patients also have a positive rheumatoid factor
- Rare patients are positive for anti-GBM autoantibodies

kidney biopsy findings

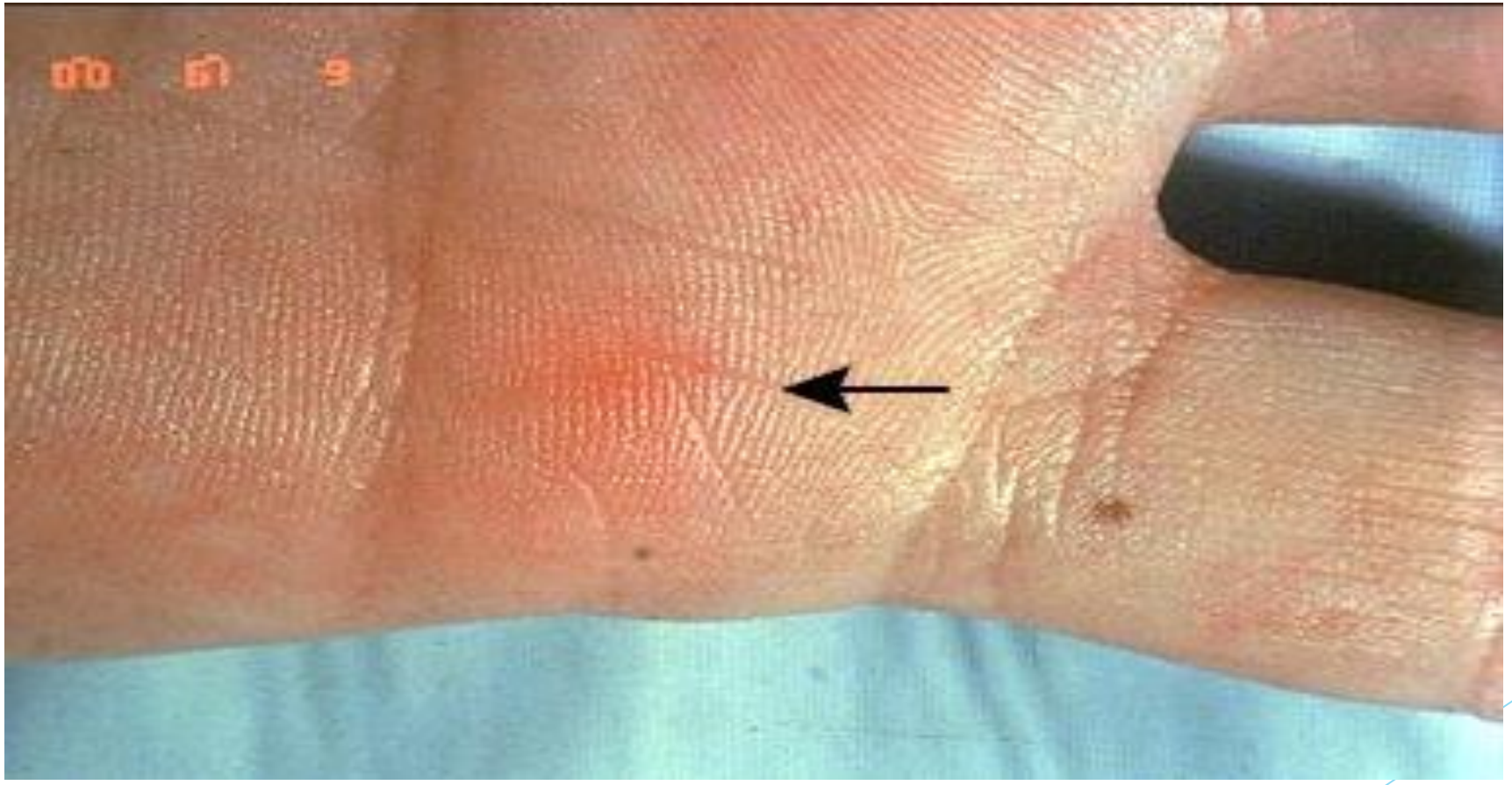
- Light microscopy : crescentic GN most common
- Diffuse proliferative GN
- majority of patients showed tubular injury
- interstitial inflammation
- Immunofluorescence microscopy: C3 was present in 94 percent of cases, immunoglobulin staining in less than one-third of biopsies, and immunoglobulin A (IgA)-dominant (or codominant with IgG) staining was seen in 17 percent.
- Electron microscopy: 90 percent of biopsies showed deposits, most commonly in the mesangial area (84 percent), subendothelial area (45 percent). Only a minority had subepithelial "humps,"

Diagnosis

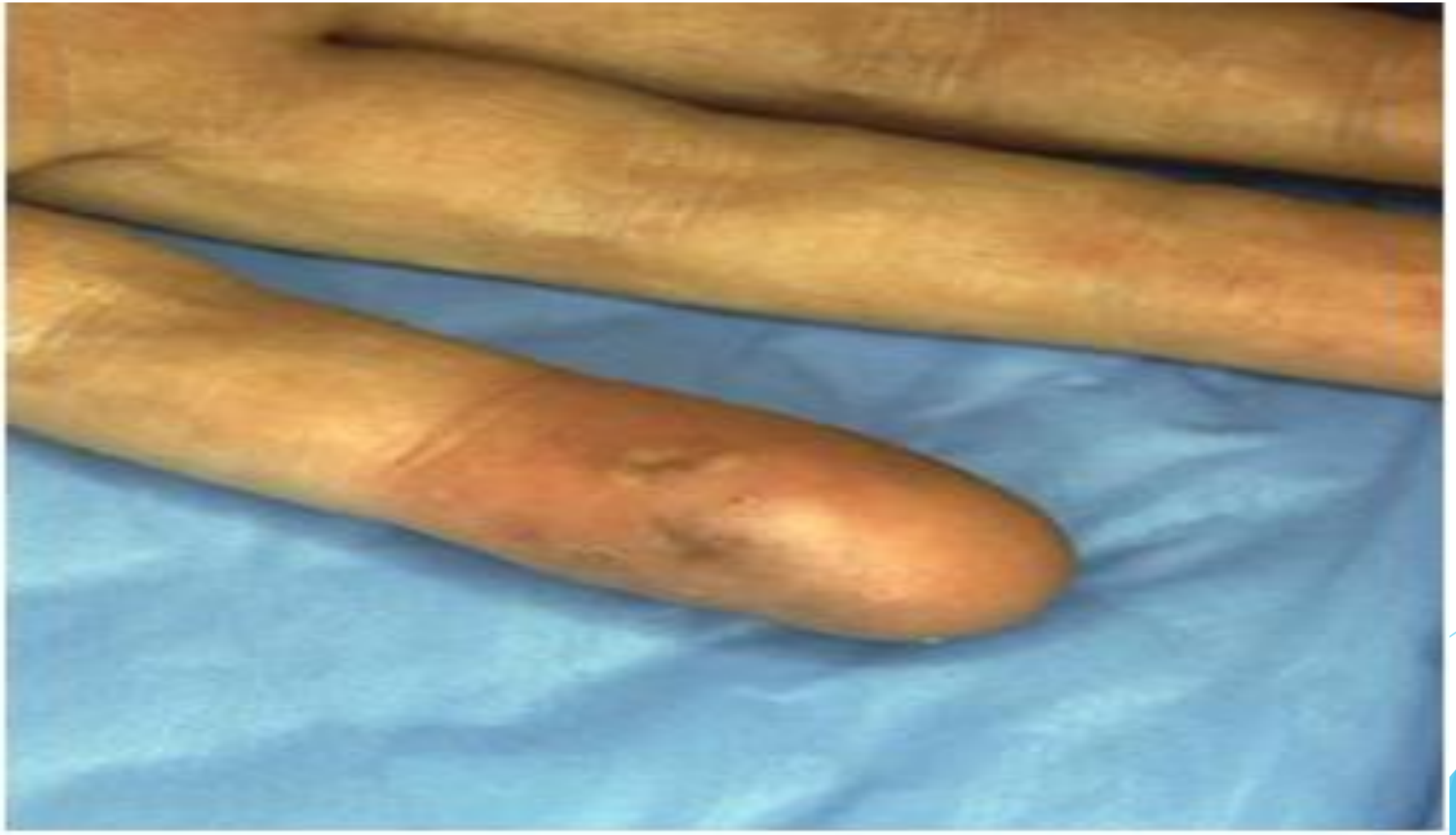
- History
- Cardiac examination
- Positive blood cultures
- In patients with IE and acute kidney injury or an abnormal urinalysis, GN is suspected based upon urinary findings


Modified Duke Criteria for the Clinical Diagnosis of Infective Endocarditis
Major clinical criteria
Minor clinical criteria
New valvular regurgitation
Positive blood culture
Positive echocardiography
• Typical microorganisms consistent with infective endocarditis from two separate blood cultures. *
• Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as ≥2 positive cultures from blood samples drawn >12 hr apart or all of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 hr apart).
• Single positive blood culture for Coxiella burnetii or phase I IgG antibody titer >1:800
• Vegetation, abscess, or new partial dehiscence of a prosthetic valve
• New valvular regurgitation
• Presence of predisposing cardiac condition or intravenous drug use
• Temperature ≥38.0°C (100.4°F)
• Vascular phenomena such as systemic arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemor- rhage, conjunctival hemorrhages, or Janeway lesions
• Immunologic phenomena such as glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
• Positive blood cultures that do not meet major criteria, or serologic evidence of active infection with organism consistent with infective endocarditis

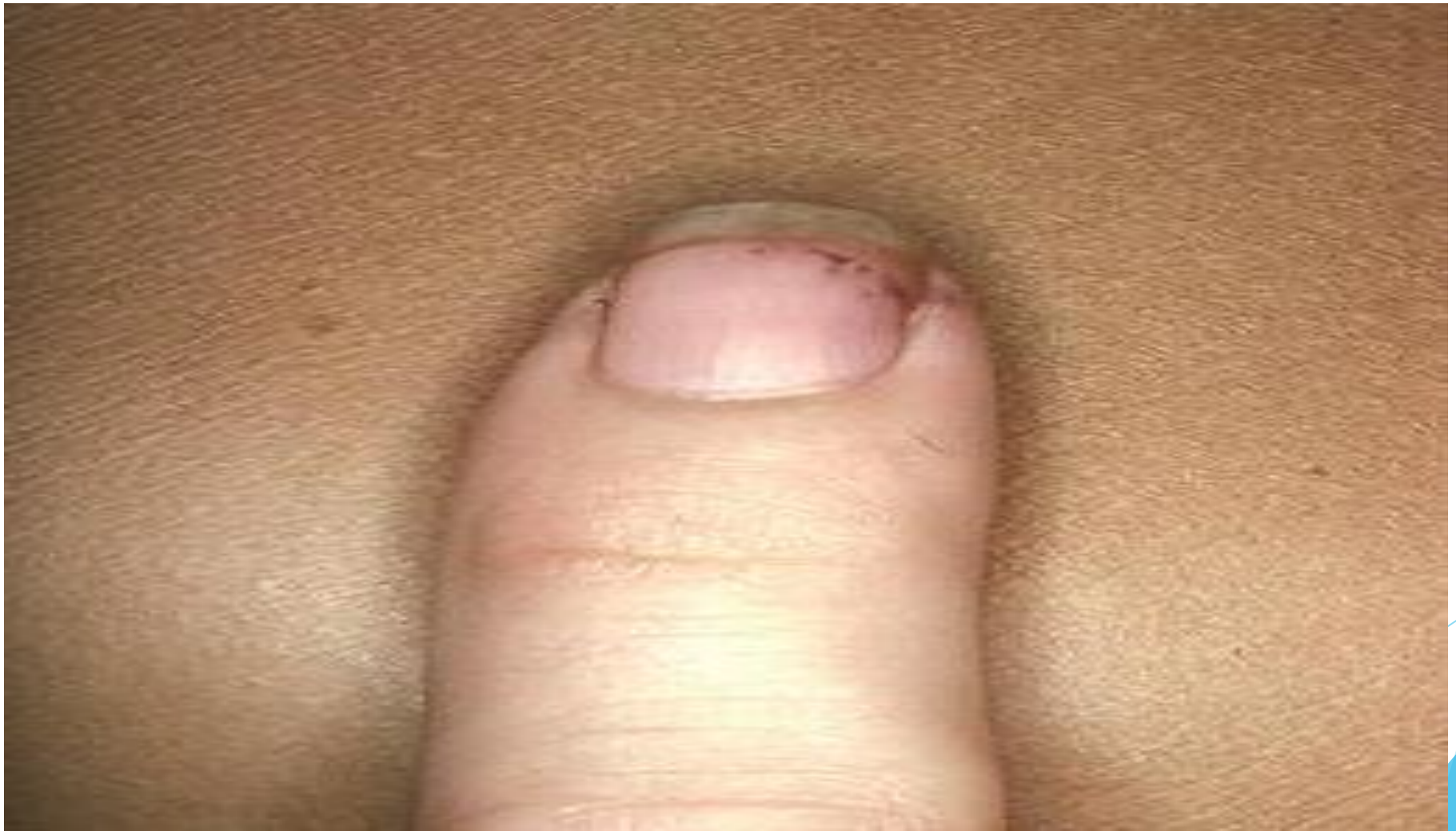
Janeway lesion



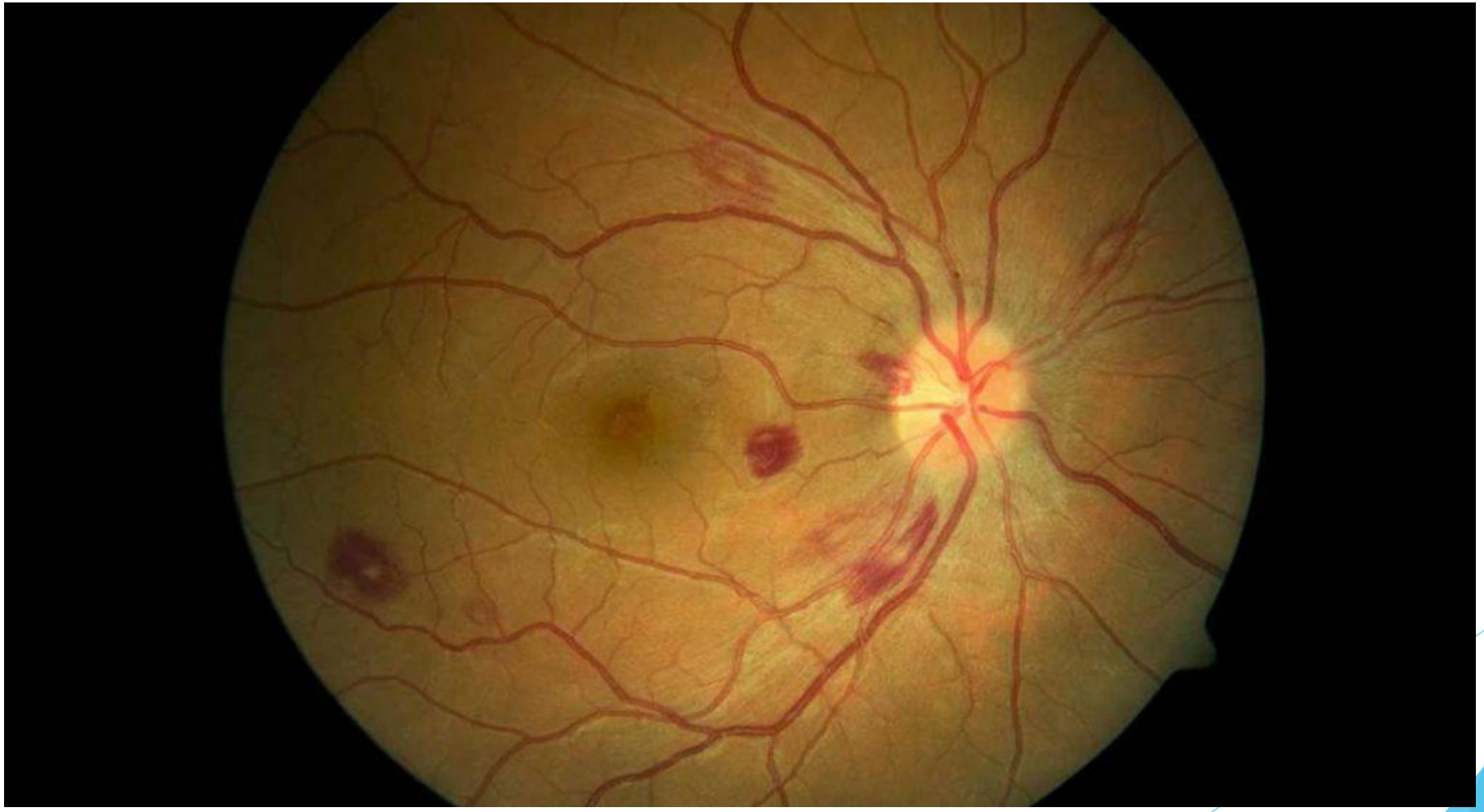
Osler nodes



Splinter hemorrhage



Roth spots



Diagnosis of Culture-Negative Endocarditis⚓

Bartonella henselae, B. quintana	*Tropheryma whipplei*	Staphylococci, strepto-cocci, enterococci, HACEK	*Coxiella burnetii*	Brucella species	Mycoplasma species	Legionella species	Fungi
Exposure to cats (B. henselae), homelessness (B. quin- tana), body lice (B. quintana), human immuno- deficiency virus infection; most common cause of culture-negative endocarditis in the United States	Chronic systemic illness, arthralgias, weight loss, gastro intestinal symptoms, central nervous system involvement	Previous use of antibiotics	Contact with farm animals (cattle, goats, or sheep), abattoir exposure, laboratory exposure; common cause of culture-negative IE in southern Europe and Middle East	Consumption of unpasteurized dairy products, exposure to tissue or fluids from infected animals (cattle, goats, sheep, or dogs)	Acute infection, prosthetic valve	Immuno compromised host, prosthetic valve	Injection drug use, immunosuppression, prosthetic valve

TESTING

Sierological Testing

- *Bartonella henselae, B. quintana*
- Brucella species
- *Coxiella burnetii*
- Fungi
- *Legionella species#*
- *Mycoplasma species##*

Specific RT-PCR Assay§

- *Bartonella henselae, B. quintana*
- *Coxiella burnetii,*
- *Tropheryma whipplei**
- *Legionella species*
- Staphylococci, strepto- cocci, enterococci, HACEK

Ribosomal RNA PCR Assay§†

- *Bartonella henselae, B. quintana*
- Brucella species
- *Coxiella burnetii,*
- *Tropheryma whipplei*
- Fungi
- *Legionella species*
- *Mycoplasma species,*
- Staphylococci, strepto- cocci, enterococci, HACEK

Table 1. Comparison of clinical characteristics of ASPGN and IEAGN[8, 9, 16, 23, 28]

	APSGN	IEAGN
Age	Mainly pediatric age	Mainly adults, particularly the elderly
Host background		diabetes mellitus[9] Immunocompromised Indwelling devices Valvular disease[8]
Causative bacterium	Group A Streptococcus	MRSA viridans Streptococcus HACEK group
Latent period	1 to 2 weeks after adenoiditis 3 to 6 weeks after skin infection	No infection-free latent period
Clinical presentation	Edema and hypertension Proteinuria and hematuria Normal to mild renal dysfunction	Acute renal failure Anemia and thrombopenia Purpura
Laboratory findings	Low C3 level Elevated ASO titer	Low C3 in 50% of patients[16] Positive ANCA in some patients
Treatment and outcome	Usually complete recovery without immunosuppressive therapy or antibiotics	Antibiotic therapy Steroids may be considered for protracted glomerulonephritis[23] Poor prognosis in some cases

Factors affecting the progression of infection-related glomerulonephritis to chronic kidney disease

1. Persistent infection
2. Genetic background of the host’s complement system
3. Tubulointerstitial changes
4. Pre-existing renal histological damage due to comorbidities
5. older age
6. Diabetes mellitus
7. Heart failure

other kidney diseases that can occur in the setting of endocarditis:

- Drug-induced interstitial nephritis, usually with a penicillin, cephalosporin, or quinolone : hematuria (occasionally, with red cell casts), mild proteinuria, and kidney function impairment. Pyuria and white cell casts can be seen in both disorders but are typically the major finding in acute interstitial nephritis.

The distinction can usually be made from the timing of the renal manifestations. Glomerular involvement is typically near or at its peak of severity just before the institution of appropriate antimicrobial therapy. By contrast, acute interstitial nephritis is a later event, generally requiring 10 or more days of drug treatment

other kidney diseases that can occur in the setting of endocarditis

- Aminoglycoside-induced acute tubular necrosis also occurs late (after at least five to seven days of therapy) and is associated with different urinary findings from either the GN or interstitial nephritis. The urinalysis can vary from a bland sediment to one showing multiple muddy brown granular casts, renal epithelial cells, and epithelial cell casts
- Renal emboli, which can occur as late as several months after bacteriologic cure, should be suspected if there is acute, often unilateral flank pain or evidence of other peripheral emboli. The diagnosis can be confirmed by the finding of focal perfusion defects on a radionuclide scan.

other kidney diseases that can occur in the setting of endocarditis

- Libman-Sacks endocarditis associated with systemic lupus erythematosus (SLE) and lupus nephritis may present with a clinical picture resembling that of infection-related GN. Serologic abnormalities typically associated with SLE (anti-DNA antibodies) and kidney biopsy showing a "full house" staining pattern are suggestive of SLE

Treatment and outcome

- Antimicrobial therapy to promptly eradicate the infection
- In the series of patients reported, 21 percent of patients died; of the surviving patients, 10 percent progressed to end-stage kidney disease, 37 percent had persistent kidney function impairment, and only 32 percent had complete kidney recovery
- There is no conclusive evidence that immunosuppressive therapy improves the outcome of IE-associated glomerulonephritis
- Immunosuppressive therapy may be beneficial in carefully selected patients whose kidney function does not improve with antibiotics alone.

Microorganism and Regimen for Treatment of Native-Valve Infective Endocarditis.

Methicillin-susceptible *Staphylococcus aureus*

Nafcillin or Oxacillin
12 g/day intravenously in 6 divided doses for 6 wk

Cefazolin
6 g/day intravenously in 3 divided doses for 6 wk

Comments
Vancomycin or daptomycin is an option for aureus patients who cannot receive beta-lactam antibiotics without adverse effects or with immediate hypersensitivity to beta-lactam antibiotics

Methicillin-resistant *S. aureus*

Vancomycin
30–60 mg/kg/day intravenously in 2–4 divided doses for 6 wk

Daptomycin
10 mg/kg/day intravenously once daily for 6 wk

Comments
For Vancomycin the target 24-hr area under the concentration curve is 400–600 μg× hr/ml

HACEK*

Ceftriaxone
2 g intravenously once daily for 4 wk

Ciprofloxacin
800 mg/day intravenously or 1500 mg orally in 2 divided doses for 4 wk

Levofloxacin
750 mg intravenously or orally once daily for 4 wk

surgical intervention

- A persistently elevated temperature for a period of five to seven days in the absence of a negative blood culture suggests a state of uncontrolled infection, with the concomitant possibility of local abscess, extensive vegetation, a false aneurysm, fistula formation, and dehiscence of a prosthetic valve
- In instances where the infection is caused by fungi, multidrug-resistant organisms, or Pseudomonas aeruginosa, surgical intervention may be a viable option
- The results of two meta-analyses indicate that early surgery, in comparison to conventional therapy (i.e., medical treatment or late surgery after >20 days), is associated with a reduction of mortality from any cause from 40 to 60%

Indication for Early Cardiac-Valve Surgery

Heart failure

- Refractory pulmonary edema or cardiogenic shock due to aortic-valve or mitral-valve dysfunction, obstruction, fistula, or shunt
- Aortic-valve or mitral-valve regurgitation or dysfunction with poorly compensated hemodynamic function

Prevention of systemic embolization

Aortic-valve or mitral-valve vegetation >10 mm, especially when accompanied by ≥1 embolic events while the patient is receiving appropriate therapy

Uncontrolled infection

- Fungal causative microorganism
- Multidrug-resistant microorganism
- Blood cultures that are persistently positive for an antibiotic-susceptible pathogen in a patient receiving appropriate antimicrobial therapy for 6 or 7 days despite adequate source control of other foci of infection
- Paravalvular complications (e.g., abscess)

KIDNEY DISEASE WITH INFECTED VENTRICULAR SHUNTS

- Ventricular shunts used for the treatment of hydrocephalus
- The mechanism of kidney injury probably involves persistent antigenemia derived from an infectious agent with subsequent immune complex formation
- Common pathogens include Staphylococcus epidermidis, Proprionibacterium acnes, and other organisms such as Staphylococcus aureus.

Shunt nephritis

- Shunt nephritis is an immune-complex- mediated glomerulonephritis (GN) associated with chronically infected ventriculoatrial shunts
- Shunt nephritis with ventriculoperitoneal shunts is rare
- The incidence of shunt infection is 7.1%
- Shunt nephritis was reported to occur in 0.7 to 2 percent
- More than 75% occur in connection with AV shunts.
- If patients progress to ESRD and if peritoneal dialysis is considered, the insertion of a VA shunt appears to be preferable

Complications associated with VA shunt

- Shunt nephritis
- Bacterial endocarditis
- Sepsis
- Recurrent pulmonary embolism
- Cor pulmonale

Clinical manifestations

- Occurs within five years of surgery to place the shunt but can occur decades later
- Systemic symptoms and signs (eg, recurrent fever, malaise, nausea , hepatosplenomegaly, vasculitis skin rash, anemia, arthralgias , and cerebral symptoms).
- Hypertension is common.
- Kidney function impairment may range from normal kidney function to a rapidly progressive glomerulonephritis (GN) .

Laboratory testing

- Hematuria (sometimes, gross hematuria)
- Proteinuria (occasionally, nephrotic range)
- Decreased C3 complement levels
- Positive cryoglobulins
- Antineutrophil cytoplasmic autoantibodies (ANCA)
- Rheumatoid factor
- Antinuclear antibodies are frequent serologic findings
- Cultures of blood and cerebrospinal fluid show mainly S. epidermidis (which might be mistaken for a contaminant in blood cultures)
- Cultures may be negative, especially if antibiotics were prescribed before obtaining the cultures

Kidney biopsy

- light microscopy include endocapillary proliferation, membranoproliferative changes, and endocapillary and extra capillary proliferation with crescents.
- Immunofluorescence microscopy demonstrates granular subendothelial and mesangial deposits containing polyclonal immunoglobulins (immunoglobulin M [IgM] and immunoglobulin G [IgG]) and complement (mainly, C3)
- EM subendothelial (64%) and mesangial (39%) deposits

Evaluation

- Diagnosis of shunt nephritis should be considered in patients with a history of ventriculovascular shunt placement who present with proliferative GN
- In patients presenting with proliferative GN who have positive blood cultures, it is important to exclude the presence of a ventriculo vascular shunt and, if present, obtain cultures of the cerebrospinal fluid.

Treatment and prognosis

- Antibiotic treatment of the underlying infection and shunt removal are essential to kidney recovery
- Delayed removal or lack of removal of the infected shunt, even if appropriate antibiotics are administered, may be associated with progressive kidney function impairment leading to end-stage kidney disease
- A temporary external drainage of CSF should be performed for about 1–2 weeks before a new shunt is reinserted

- By intraventricular instillation of antibiotics the chance for reinfection is reduced.
- Antibiotics (e.g. vancomycin, rifampicin) should be given intravenously for at least 10 days
- Following removal of an infected shunt, a VP rather than a VA shunt should be inserted
- Up to now no recurrence of shunt nephritis in the transplanted kidney was reported
- Recovery of renal function is common following treatment
- The renal outcome of shunt nephritis is good if early diagnosis and treatment is provided including i.v. antibiotics and total removal of the infected shunt

main goals in the treatment of shunt infections

- Clearing up the infection
- Maintaining a functioning device if still needed
- Minimizing mortality and morbidity

Strategies to prevent shunt infections

- Antibiotic prophylaxis during insertion of CSF shunts or in periods of possible bacteriaemia
- Packs soaked in antiseptic agents to isolate wound edges
- Regular glove-changing before handling the shunt
- Alternative biomaterials for VA shunts


THANKS FOR ATTENTION