Staphylococcus aureus
Grande manipulador da hemostasia

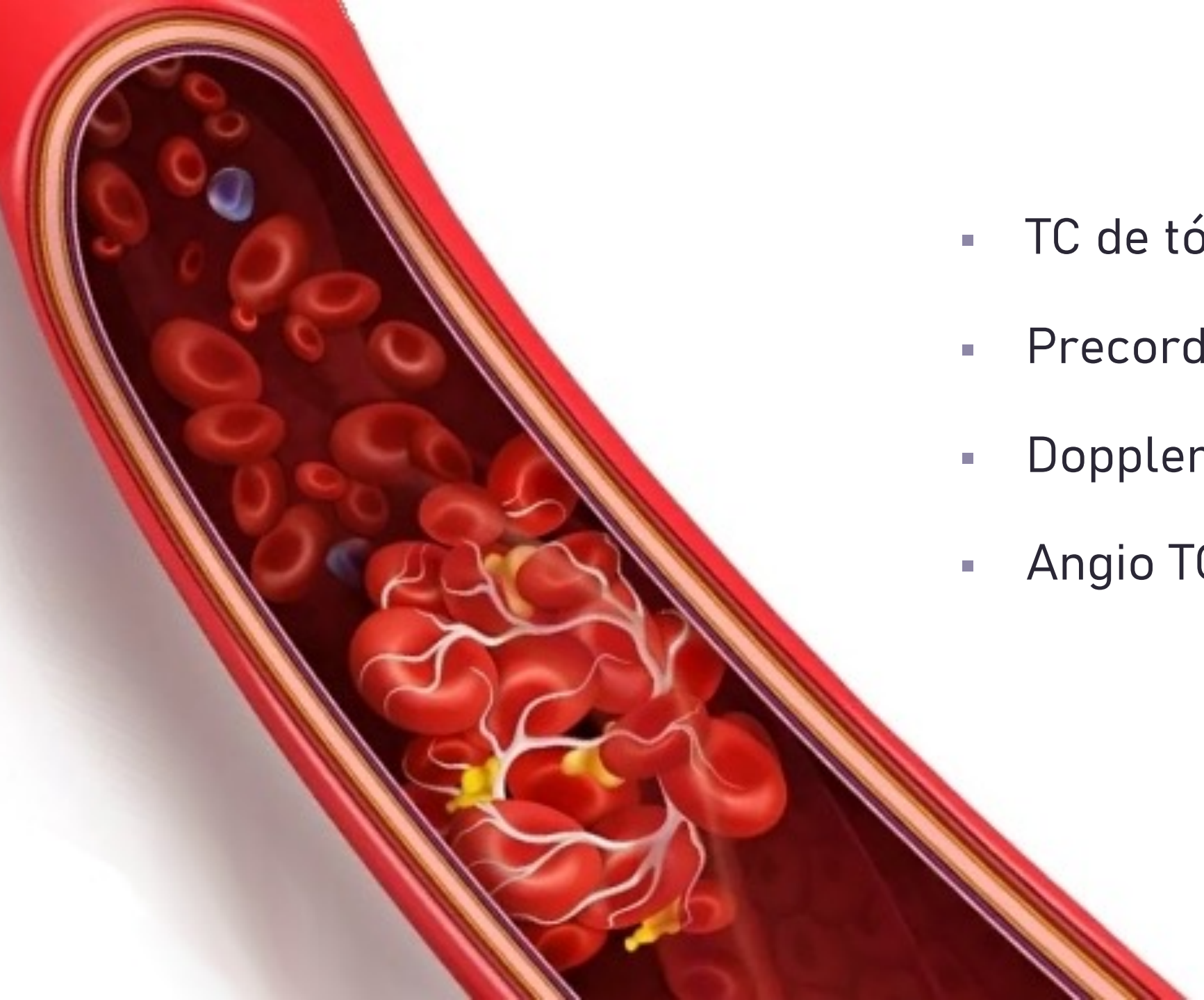
Dra. Raquel Tavares Borba

R2 de Pediatria
Hospital Universitário Antônio Pedro
(HUAP/UFF)

Dr. Leonardo R. Campos

Reumatologista Pediátrico
Hospital Universitário Antônio Pedro
(HUAP/UFF)

- 6 anos
- Trauma em joelho D
- Artrite + febre
- Artrite séptica X Osteomielite
- HMC → CA-MRSA
- Antibióticoterapia – Vancomicina
- Transferência para investigação



- TC de tórax → Consolidações
- Precordialgia + dispneia
- Doppler = Trombose
- Angio TC descartou TEP

Osteomielite em Pediatria

- Epidemiologia:
  - ✓Crianças abaixo de 5 anos e sexo masculino;
  - ✓20% história de trauma local;
  - ✓200 casos a cada 100.000 habitantes.
- Classificação:
  - ✓Aguda (< 2 semanas);
  - ✓Subaguda;
  - ✓Crônica (> 3 meses).

Osteomielite em Pediatria

- Fisiopatologia:
  - ✓ Disseminação hematogênica;
  - ✓ Contiguidade;
  - ✓ Inoculação direta.
- Quadro Clínico:
  - ✓ Dor, calor, edema, hiperemia;
  - ✓ Dificuldade de movimentar membro;
  - ✓ Febre (60 a 80% dos casos).

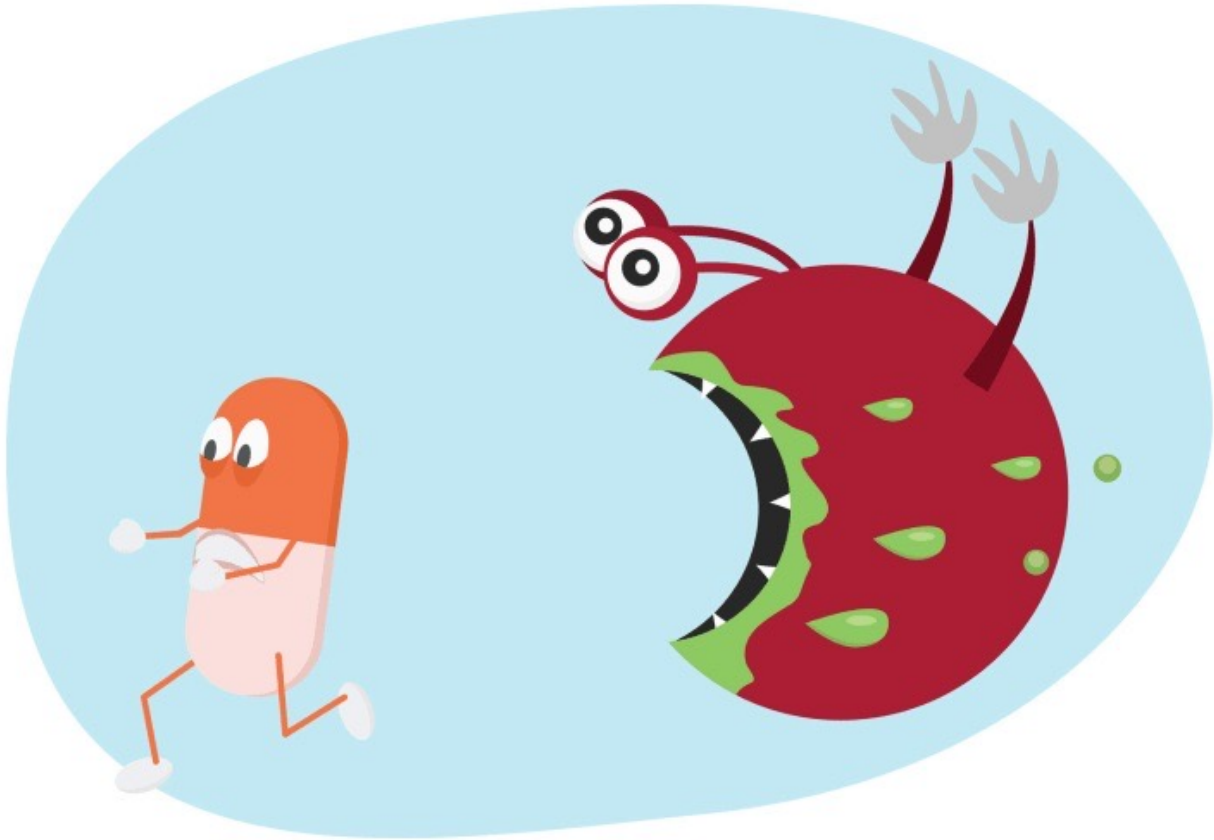
Osteomielite em Pediatria

Etiologia:

Staphylococcus aureus

S. aureus resistente à meticilina adquirido na comunidade (CA-MRSA)

- No Brasil, dois estudos feitos no Estado de São Paulo evidenciaram taxas de resistência à meticilina de 20 a 45% nas IOA em pediatria.



De onde veio o trombo?

REVIEW ARTICLE

Staphylococcus aureus, master manipulator of the human hemostatic system

L. LIESENBORGHS, P. VERHAMME and T. VANASSCHE
Department of Cardiovascular Sciences, Center for Molecular and Vascular Biology, KULeuven - University Hospitals Leuven, Leuven, Belgium

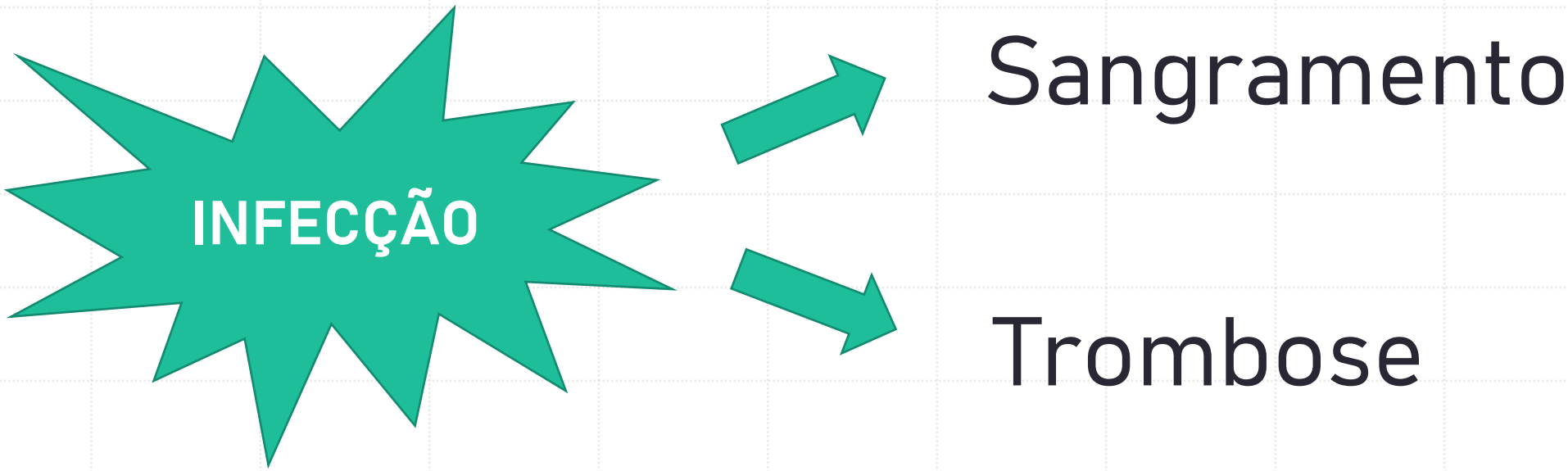
To cite this article: Liesenborghs L, Verhamme P, Vanassche T. *Staphylococcus aureus*, master manipulator of the human hemostatic system. *J Thromb Haemost* 2018; **16**: 441–54.

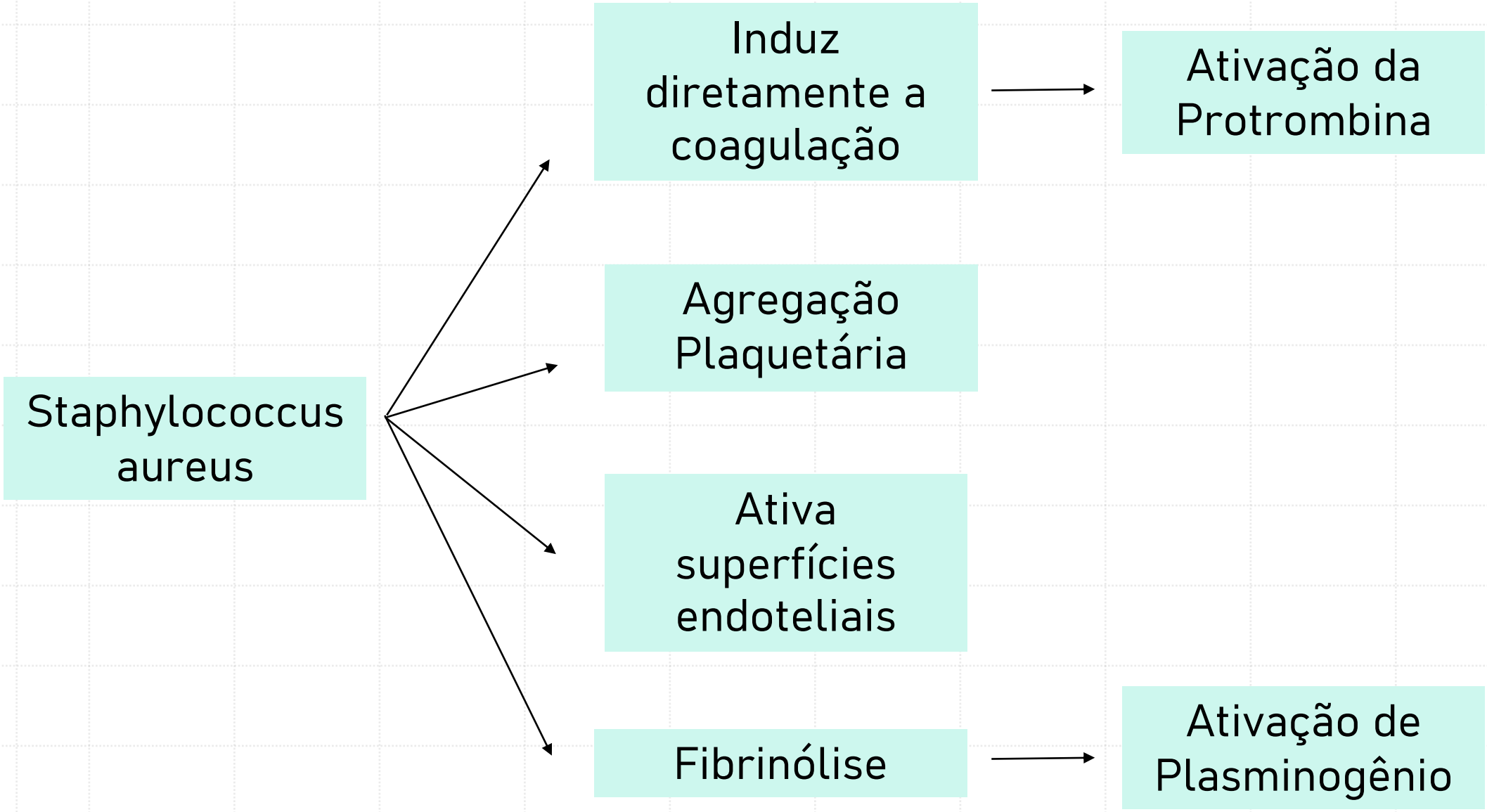
Summary. The coagulation system does not only offer protection against bleeding, but also aids in our defense against invading microorganisms. The hemostatic system and innate immunity are strongly entangled, which explains why so many infections are complicated by either bleeding or thrombosis. *Staphylococcus aureus* (*S. aureus*), currently the most deadly infectious agent in the developed world, causes devastating intravascular infections such as sepsis and infective endocarditis. During these infections *S. aureus* comes in close contact with the host hemostatic system and proves to be a master in manipulating coagulation. The coagulases of *S. aureus* directly induce coagulation by activating prothrombin. *S. aureus* also manipulates fibrinolysis by triggering plasminogen activation via staphylokinase. Furthermore, *S. aureus* binds and activates platelets and interacts with key coagulation proteins such as fibrin(ogen), fibronectin and von Willebrand factor. By manipulating the coagulation system *S. aureus* gains a significant advantage over the host defense mechanisms. Studying the interplay between *S. aureus* and the hemostatic system can therefore lead to new innovative therapies for battling *S. aureus* infections.

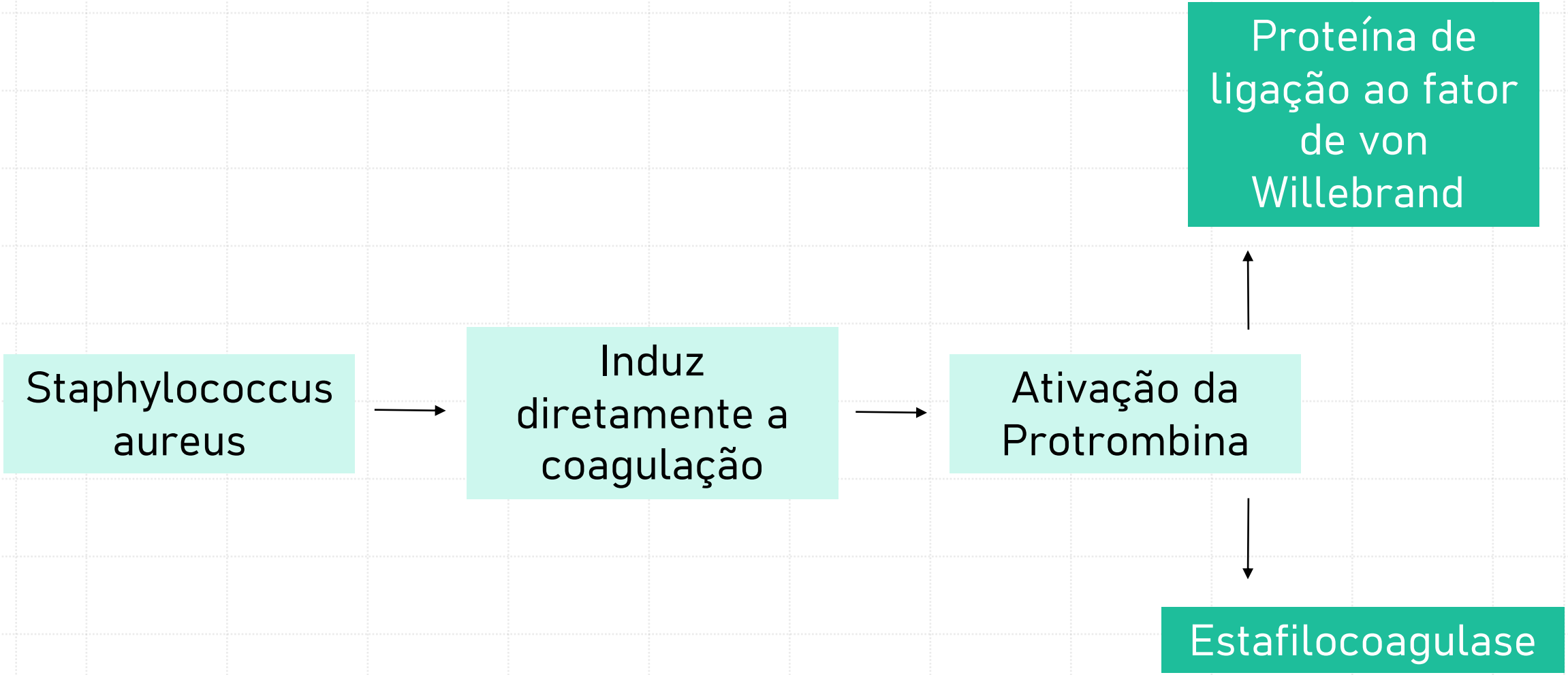
Keywords: infective endocarditis; sepsis; staphylocoagulase; staphylococcus aureus; staphylokinase.

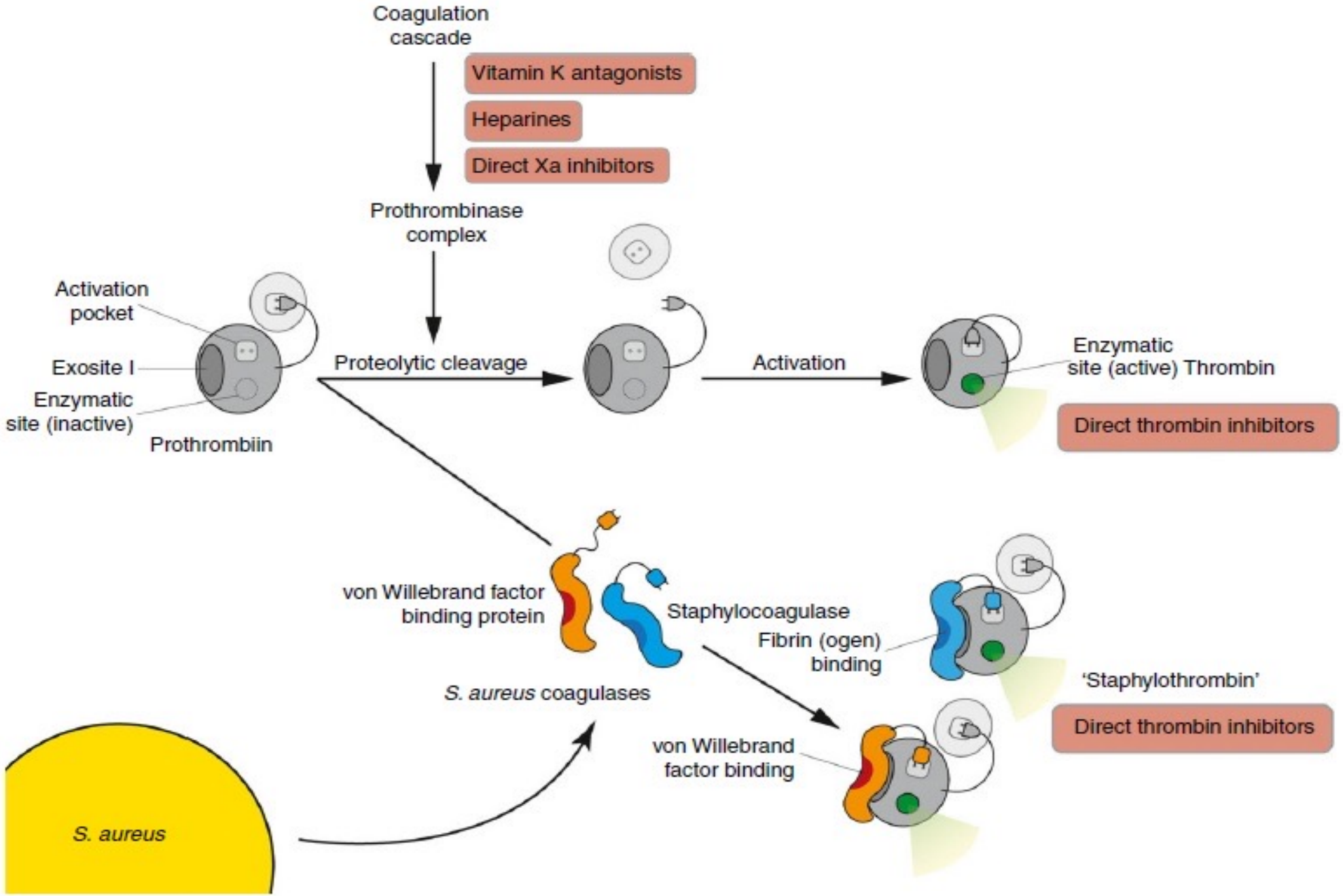
The role of hypervirulent Staphylococcus aureus infections in the development of deep vein thrombosis. Eric Martin, Cihan Cevik., Kenneth Nugent. Thrombosis Research 130 (2012) 302–308.

Sistema Imune ⟷ **Sistema Hemostático**

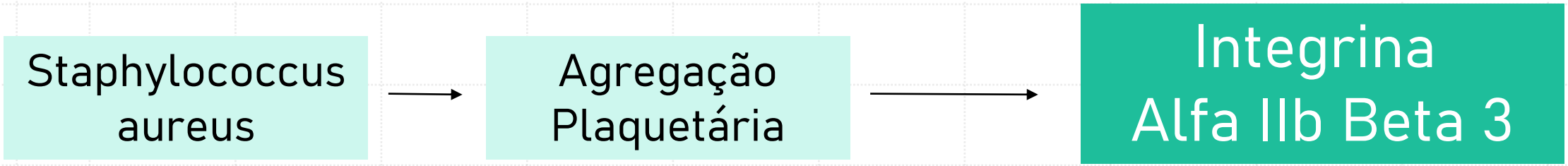


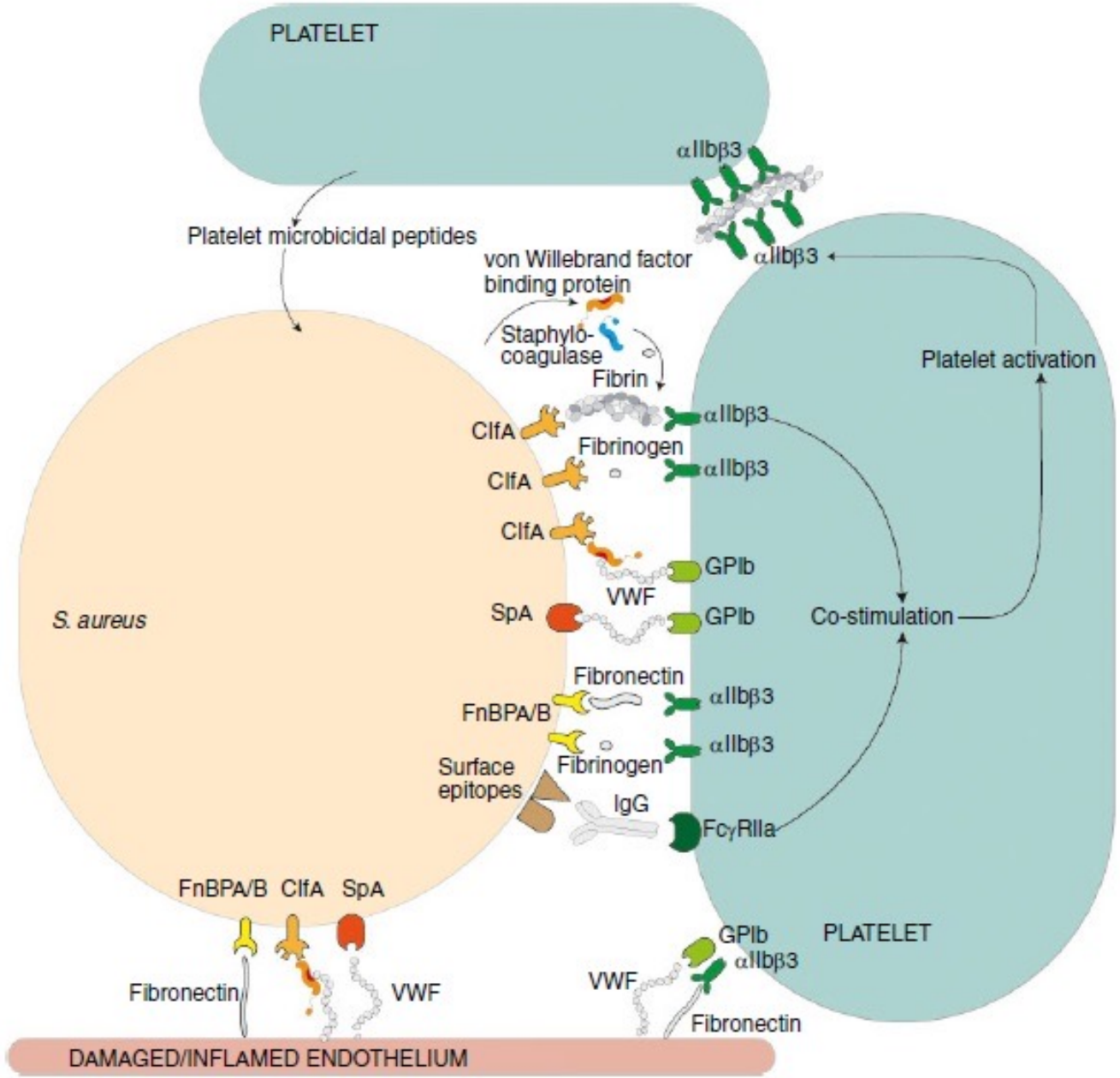

Staphylococcus aureus
Induz diretamente a coagulação
Ativação da Protrombina
Agregação Plaquetária
Ativa superfícies endoteliais
Fibrinólise
Ativação de Plasminogênio

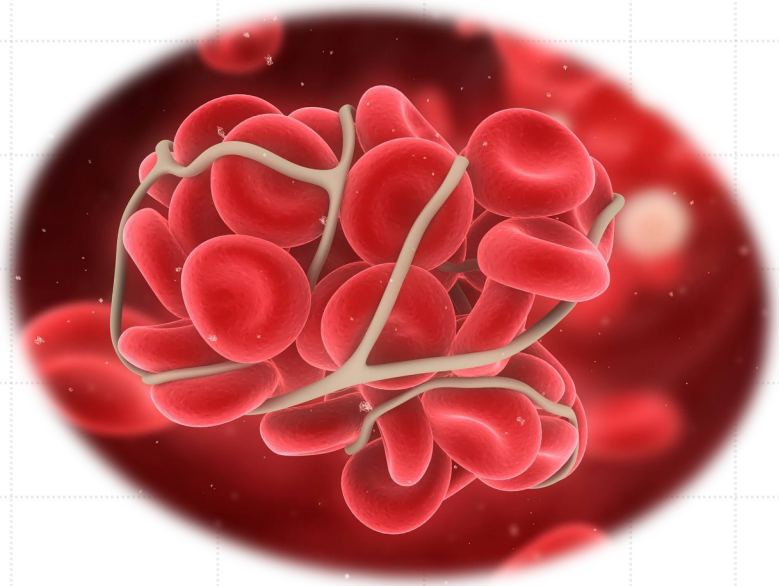

Proteína de ligação ao fator de von Willebrand
Staphylococcus aureus
Induz diretamente a coagulação
Ativação da Protrombina
Estafilocoagulase



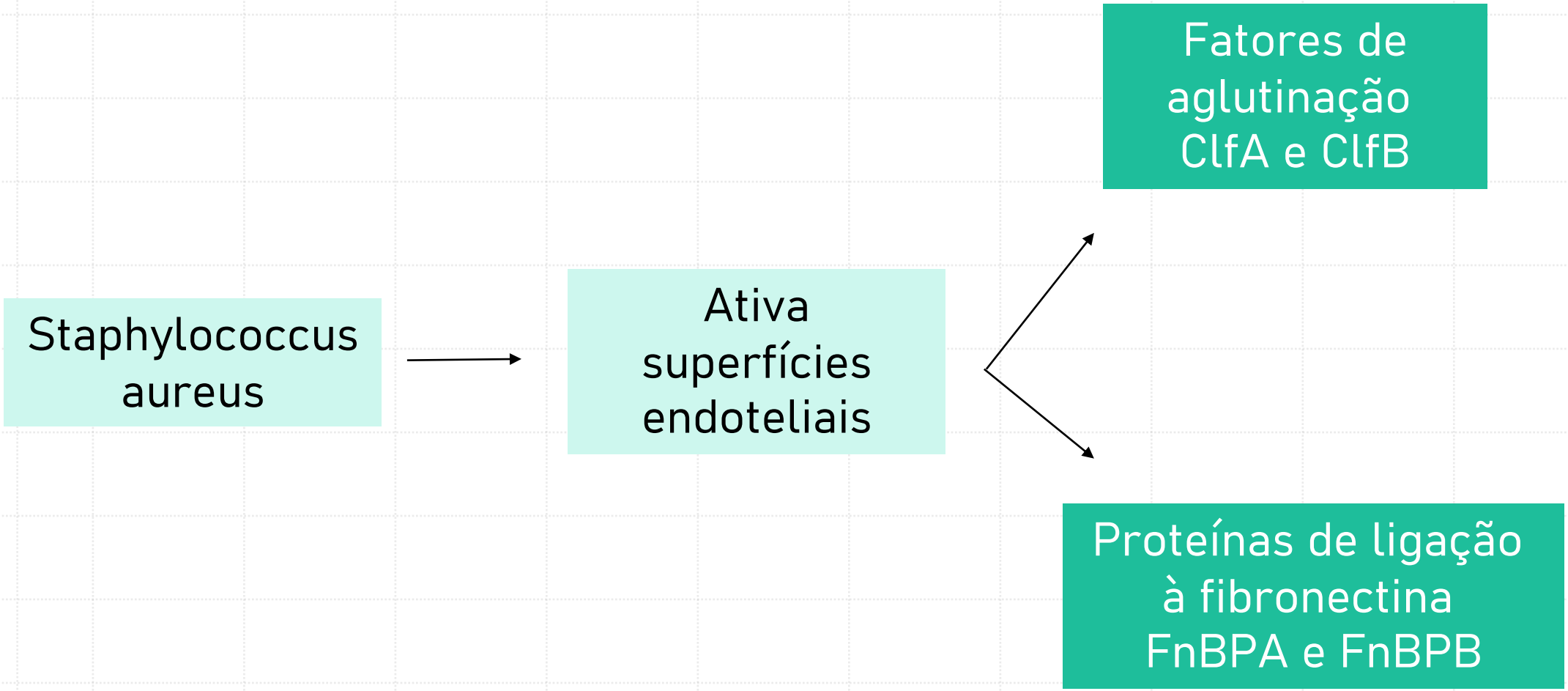
The role of hypervirulent Staphylococcus aureus infections in the development of deep vein thrombosis. Eric Martin, Cihan Cevik., Kenneth Nugent. Thrombosis Research 130 (2012) 302–308.


Staphylococcus aureus
Agregação Plaquetária
Integrina Alfa IIb Beta 3

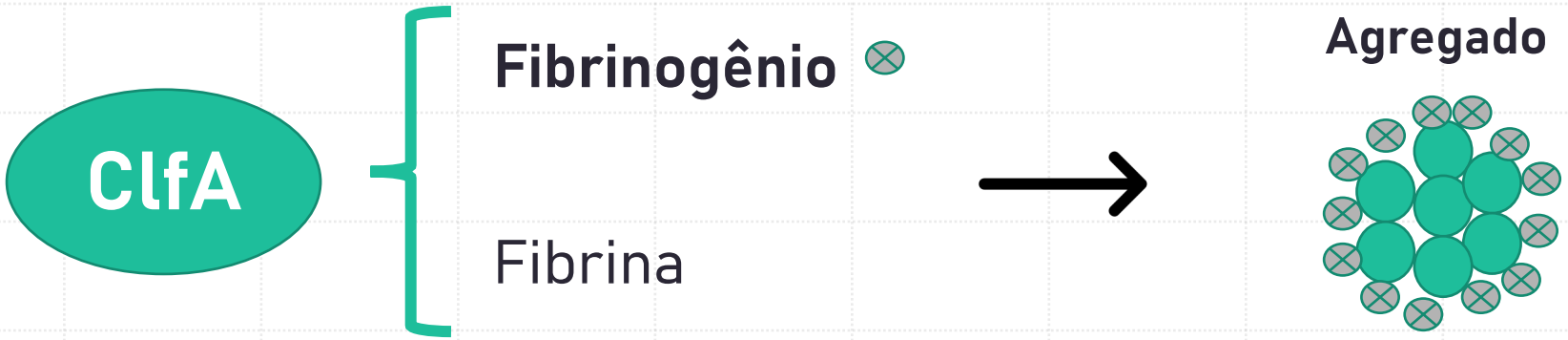




The role of hypervirulent Staphylococcus aureus infections in the development of deep vein thrombosis. Eric Martin, Cihan Cevik., Kenneth Nugent. Thrombosis Research 130 (2012) 302–308.

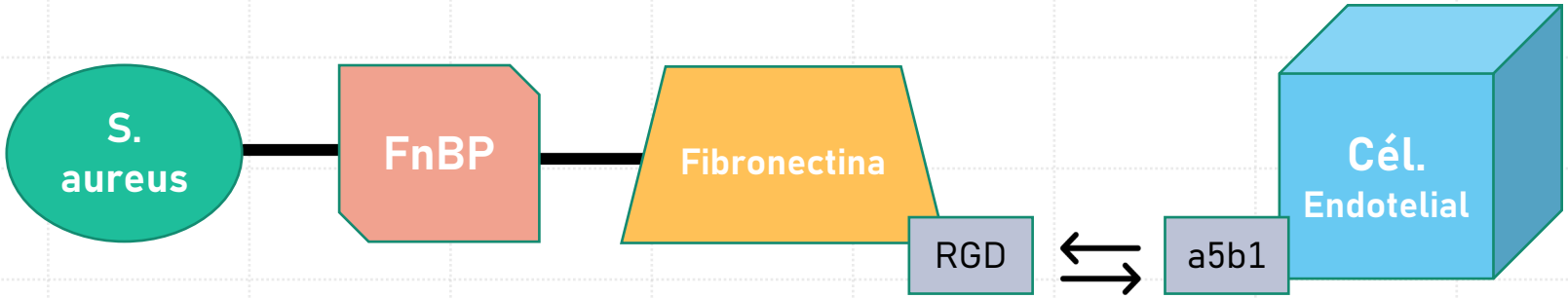

Staphylococcus aureus
Ativa superfícies endoteliais
Fatores de aglutinação ClfA e ClfB
Proteínas de ligação à fibronectina FnBPA e FnBPB

Fatores de aglutinação **ClfA** e ClfB

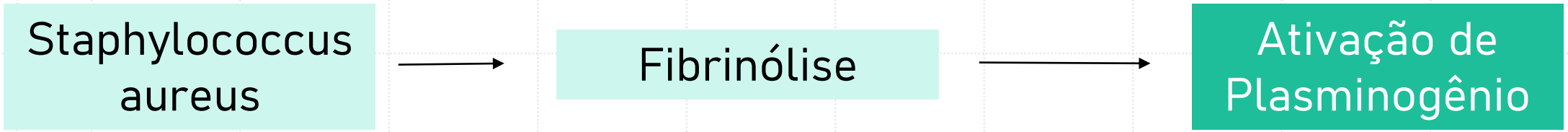


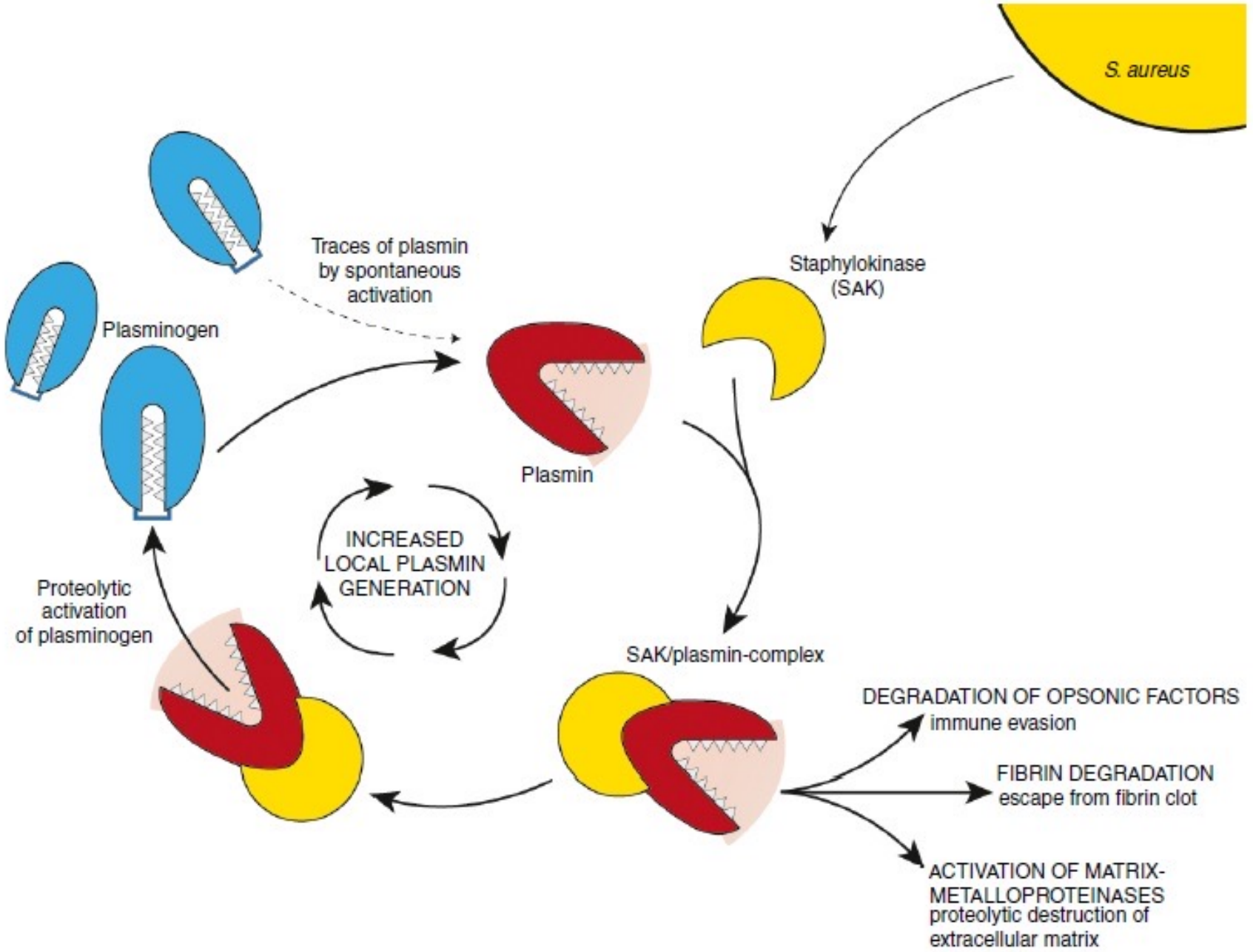
- Dentro desses agregados S. aureus é protegido do sistema imunológico da fagocitose.
- É mais provável que esses agregados sejam retidos na microcirculação e, assim, promovam metástases da infecção.
- ClfA também aumenta sua adesão a corpos estranhos revestidos de fibrinogênio, portanto, é provável que promova infecções de cateter ou dispositivo intracardíacos.

Proteínas de ligação à fibronectina **FnBPs**



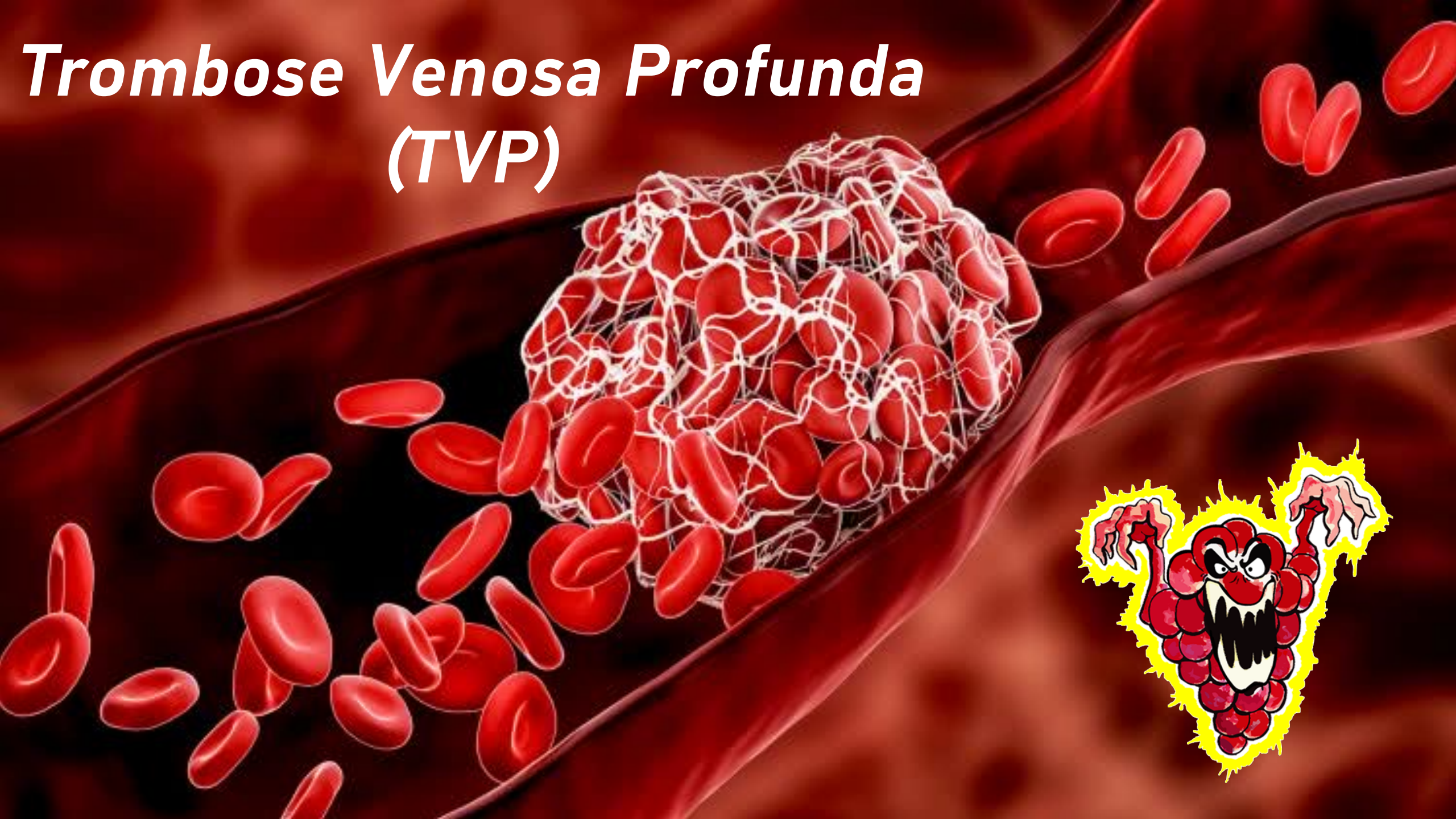
- A ligação do complexo S. aureus- FnBP-fibronectina leva a um agrupamento com alfa5beta1, que induz **endocitose**.
- Isso permite o S. aureus sobreviver no intracelularmente, onde é protegido do sistema imunológico ou antibióticos.


Staphylococcus aureus
Fibrinólise
Ativação de Plasminogênio



The role of hypervirulent Staphylococcus aureus infections in the development of deep vein thrombosis. Eric Martin, Cihan Cevik., Kenneth Nugent. Thrombosis Research 130 (2012) 302–308.

Trombose Venosa Profunda (TVP)



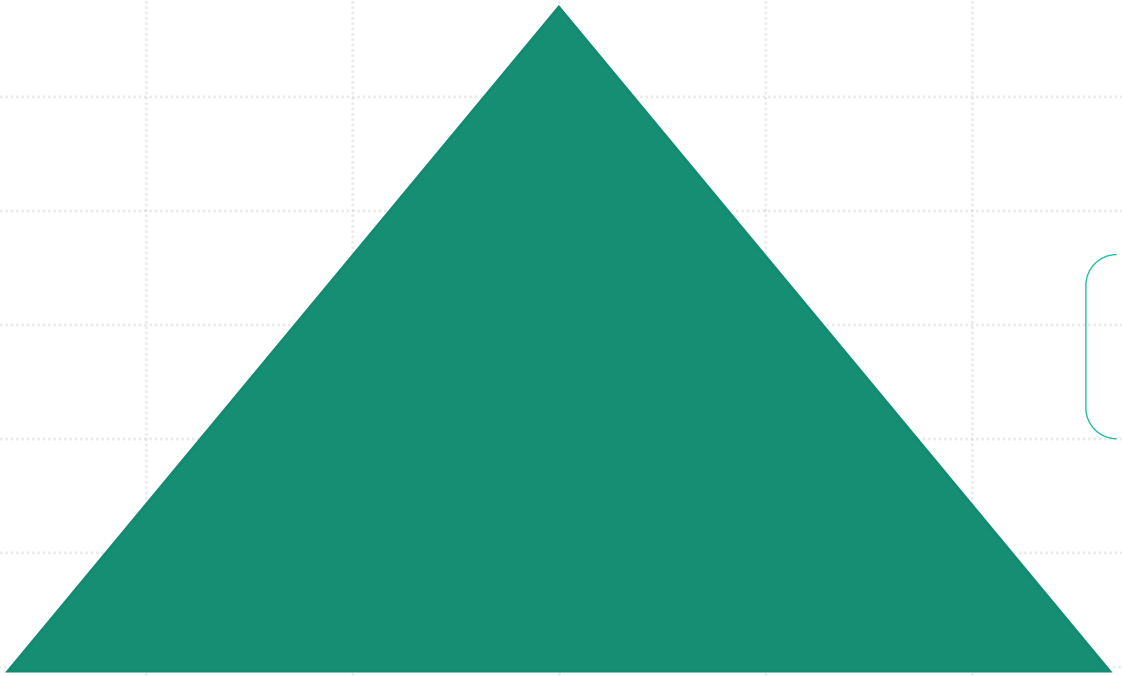
Fatores de risco para TVP

Hipercoagulabilidade

Cateter

Infecção

Lesão endotelial



Restrição de movimento

Estase venosa

When should DVT be suspected in children with osteomyelitis?

abstract

BACKGROUND: There is increasing recognition that deep venous thrombosis (DVT) is a complicating factor in some children with acute hematogenous osteomyelitis. The similarity in signs and symptoms of osteomyelitis and DVT make clinical recognition of this complicating condition difficult. It would be helpful to the clinician to identify by other means which children with osteomyelitis are at greatest risk for DVT. We reviewed the available literature regarding osteomyelitis and DVT in children to identify potential characteristics of children with osteomyelitis that puts them at risk for concurrent DVT.

METHODS: We performed searches of the PubMed, Cochrane, CINAHL, and National Guideline Clearinghouse databases on the topic of osteomyelitis and thrombosis in children 0 to 18 years of age from 2001 to the present.

RESULTS: Four studies were included: 3 retrospective and 1 prospective. Studies varied in terms of clinical, laboratory, and imaging parameters evaluated. Overall they suggest trends toward increased incidence of DVT in children who were critically ill at presentation, had positive blood cultures, were infected with methicillin-resistant *Staphylococcus aureus*, had an elevated C-reactive protein, and had central venous catheters placed.

CONCLUSIONS: Strong consideration should be given to evaluating children with osteomyelitis for DVT if they are critically ill at presentation, particularly if they have pulmonary findings, are persistently bacteremic, especially with methicillin-resistant *S aureus*.

- Revisão de literatura sobre TVP em crianças com osteomielite no período de 2001 e 2012.
- TVP foi observada em maior frequência nos pacientes:
  - ✓ Disseminação hematogênica
  - ✓ Internados em UTI
  - ✓ Hemocultura positiva
  - ✓ Aumento PCR
  - ✓ Uso de CVC
  - ✓ Acometimento pulmonar (embolia séptica)
- Diagnóstico incidental (baixa suspeição e sobreposição de sintomas – eritema, dor e aumento de volume na perna, p. ex)

When should DVT be suspected in children with osteomyelitis? Mary G. Altobelli, MD and Ricardo A. Quinonez, MD. JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS. March 13, 2015.

TVP (%)

9/180 (5%)

10/35 (28,5%)

11/212 (5%)

7/70 (10%)

TABLE 1 Characteristics of the Studies Reviewed

Study	Type	Inclusions	Exclusions	No. with DVT	Organisms	Clinical Findings	Blood Culture Positive	Mean CRP, mg/dL	Comparison with Patients Without DVT[a]
Gonzales[8]	Retrospective	180 patients with *S aureus* osteomyelitis	Not documented	9	7 MRSA, 2 MSSA	Septic pulmonary emboli (4), bilateral air space disease (1), pleural effusions (1)	9/9 (100%)	"elevated"	Not addressed
Crary[11]	Retrospective	35 patients with osteomyelitis of proximal upper & lower extremities pelvis, or vertebra	17 patients with excluded sites: ankle, foot, distal upper extremities, cranium	10	7 MRSA, 2 MSSA, 1 *C tropicalis*	Septic pulmonary emboli (6), 1 also had cerebral abscess and 1 also had endocarditis	10/10 (100%)	22.6	No difference in age, ESR, WBC, platelets; higher CRP values approached significant difference
Hollmig[12]	Retrospective	212 children with osteomyelitis of spine, pelvis, extremities	Not documented	11	8 MRSA, 3 MSSA	Septic pulmonary emboli (6), pleural effusions (1)	Not addressed	16.9	Older, shorter symptom duration before admission, higher temp, higher rates of *S aureus* infection
Bouchoucha[13]	Prospective	70 patients with osteomyelitis	Neonates, nosocomial, direct inoculation / infection	7	3 MRSA, 4 MSSA	Deteriorated health on admission (5), diffuse alveolar lesions (3)	6/7 (86%)	25.1	Higher ESR, higher blood culture positivity, more febrile days

[a] Findings listed are those for patients with DVT in comparison with those without DVT (when available).

When should DVT be suspected in children with osteomyelitis? Mary G. Altobelli, MD and Ricardo A. Quinonez, MD. JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS. March 13, 2015.

Thrombosis in central catheter–associated *Staphylococcus aureus* bacteremia: Always scan the site?*

- Incidência de 71% de tromboses venosas associadas em uma série de pacientes com bacteremia relacionada ao cateter devido a S. aureus.
- Falta de sensibilidade e especificidade dos achados do exame físico para detectar tromboses venosas profundas dos membros superiores.
- O doppler da veia previamente cateterizada deve ser realizado em todos os pacientes com bacteremia relacionada ao S. aureus na qual um achado positivo de trombose levaria a uma alteração na terapia.
- Em relação a terapia anticoagulante, o American College of Chest Physicians recomenda anticoagulação total para pacientes com trombose venosa de membros superiores.
- Pacientes com bacteremia por S. Aureus ativa pode apresentar risco aumentado de complicações da anticoagulação.

Thrombosis in central catheter–associated Staphylococcus aureus bacteremia: Always scan the site? Adam B. Keene, MD. Montefiore Medical Center Bronx, NY. Crit Care Med 2008 Vol. 36, No. 2

Open Forum Infectious Diseases

MAJOR ARTICLE

Catheter-Related *Staphylococcus aureus* Bacteremia and Septic Thrombosis: The Role of Anticoagulation Therapy and Duration of Intravenous Antibiotic Therapy

Rita Wilson Dib,[1] Anne-Marie Chaftari,[1] Ray Y. Hachem,[1] Ying Yuan,[1] Dima Dandachi,[1,2] and Issam I. Raad[1]

[1]Department of Infectious Diseases, Infection Control & Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas; [2]Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, Houston, Texas

Background. Catheter-related septic thrombosis is suspected in patients with persistent central line–associated bloodstream infection (CLABSI) after 72 hours of appropriate antimicrobial therapy. The clinical diagnosis and management of this entity can be challenging as limited data are available. We retrospectively studied the clinical characteristics of patients with *Staphylococcus aureus* catheter-related septic thrombosis and the outcomes related to different management strategies.

Methods. This retrospective study included patients with CLABSI due to *S. aureus* who had concomitant radiographic evidence of catheter site thrombosis treated at our institution between the years 2005 and 2016. We collected data pertaining to patients' medical history, clinical presentation, management, and outcome within 3 months of bacteremia onset.

Results. A total of 128 patients were included. We found no significant difference in overall outcome between patients who had deep vs superficial thrombosis. Patients with superficial thrombosis were found to have a higher rate of pulmonary complications (25% vs 6%; $P = .01$) compared with those with deep thrombosis. Patients who received less than 28 days of intravascular antibiotic therapy had higher all-cause mortality (31 vs 5%; $P = .001$). A multivariate logistic regression analysis identified 2 predictors of treatment failure: ICU admission during their illness (odds ratio [OR], 2.74; 95% confidence interval [CI], 1.08–6.99; $P = .034$) and not receiving anticoagulation therapy (OR, 0.24; 95% CI, 0.11–0.54; $P < .001$).

Conclusions. Our findings suggest that the presence of *S. aureus* CLABSI in the setting of catheter-related thrombosis may warrant prolonged intravascular antimicrobial therapy and administration of anticoagulation therapy in critically ill cancer patients.

Keywords. anticoagulation; bacteremia; catheter-related bloodstream infection; septic thrombophlebitis; *Staphylococcus aureus*.

- Estudo retrospectivo com 128 pacientes entre os anos de 2005 e 2016.
- Em 55% dos pacientes, os sinais locais indicativos de trombose estavam presentes
- 79% apresentaram febre
- 47% das infecções foram causadas por MRSA
- Tratamento por 28 dias (4 semanas) ou mais com antibióticos IV teve vantagem sobre a duração mais curta (14–27 dias)
- Deve-se considerar seriamente a inclusão de anticoagulação no manejo de TV por S. aureus relacionada ao cateter.

Catheter-Related Staphylococcus aureus Bacteremia and Septic Thrombosis: The Role of Anticoagulation Therapy and Duration of Intravenous Antibiotic Therapy. Rita Wilson Dib. Open Forum Infectious Diseases. September 2018.

Table 2. Comparison of Patients with Superficial vs Deep Venous Thrombosis

Characteristic	Superficial Thrombosis (n = 20)	Deep Thrombosis (n = 108)	*P* Value
Age, median (range), y	54 (4–67)	55 (7–88)	.55
Male sex, No. (%)	11 (55)	70 (65)	.40
Underlying condition, No. (%)			.41
Hematological malignancy	12 (60)	54 (50)	
Solid tumor	8 (40)	54 (50)	
Risk factors (within 30 d of bacteremia), No. (%)			
Chemotherapy	18 (90)	81 (75)	.24
Steroids	9 (45)	33 (31)	.21
Radiation	0 (0)	14/106 (13)	.12
Surgery	0 (0)	6 (6)	.59
MRSA, No. (%)	11 (55)	49 (45)	.43
ANC <500 cells/μL at bacteremia, No. (%)	8 (40)	21 (19)	.08
Catheter type, No. (%)			.96
PICC	13 (65)	73 (68)	
Central venous catheter	5 (25)	25 (23)	
Surgically implanted (port-a-cath)	2 (10)	10 (9)	
Catheter lumens, No. (%)			.32
Single	2/19 (11)	26/107 (24)	
Double	17/19 (89)	76/107 (71)	
Triple	0/19 (0)	5/107 (5)	
Clinical presentation, No. (%)			
Fever (temperature ≥38°C)	19 (95)	82 (76)	.07
Type of sepsis on presentation	11 (55)	68 (63)	.96
Required ICU admission	5 (25)	22 (20)	.77
Local signs of inflammation	10 (50)	61 (56)	.59
Management			
Duration of IV antibiotic therapy, median (range), d	27 (1–49)	24 (1–69)	.83
Total duration of antibiotic (IV and oral), median (range), d	33 (14–62)	29 (3–161)	.27
Catheter removed/exchanged, No. (%)	20 (100)	105 (97)	>.99
Time to first negative blood culture, median (range), d	3 (1–14)	4 (1–16)	.11
Time to fever resolution, median (range), d	5 (1–14)	2 (1–11)	<.001
Anticoagulation, No. (%)	9 (45)	79 (73)	.013
Outcome, No. (%)			
Development of deep-seated infection	7 (35)	17[a] (16)	.06
Septic arthritis	0 (0)	1 (1)	>.99
Deep tissue abscess	1 (5)	4 (4)	.59
Osteomyelitis	0 (0)	1 (1)	>.99
Pulmonary complications	5 (25)	6 (6)	.01
Chest wall abscess	0	1 (1)	>.99
Endocarditis	1 (5)	6/105 (6)	>.99
Overall outcome,[b] No. (%)			.63
Success	11 (55)	65/107 (61)	
Failure	9 (45)	42/107 (39)	

Case Report

Deep-vein thrombosis and septic pulmonary emboli in methicillin-sensitive *Staphylococcus aureus* infection

Banani Poddar, Jyoti Narayan Sahoo, Mohan Gurjar, Ratender Singh, Afzal Azim

Department of Critical Care Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

- TVP e êmbolos pulmonares sépticos na infecção estafilocócica foram descritos mais frequentemente em Staphylococcus aureus resistentes à meticilina (MRSA).

Table 1 Presenting complaints and sites of involvement

	Case 1*	Case 2	Case 3	Case 4
Age, yrs	14	10	14	8
Gender	M	M	M	M
History of boils	Yes	No	No	No
History of trauma	No	No	No	Yes
Onset of illness to hospital admission, days	8	5	8	6
Symptoms, days	Left lower limb pain and swelling (8) Fever (7) Resp. distress (1)	Right lower limb pain and swelling (5) Fever (3) Resp. distress (2)	Left upper limb pain and swelling (8) Fever (7) Resp. distress (2)	Right lower limb pain and swelling (6) Fever (1) Resp. distress (1)
Primary site of infection	Left thigh	Right thigh	Left upper limb	Right foot ulcer
Bone or joint involvement	No	Right hip, left elbow, Osteomyelitis – right femur	Myositis around left shoulder joint	No

- A TVP em crianças é mais frequentemente secundária a uma causa predisponente (ex. CVC).
- Nos países industrializados, quase todas essas infecções são por MSSA.
- O diagnóstico de infecção por S. aureus com lesões pulmonares deve levar o médico a pesquisar TVP como fonte de êmbolos sépticos.

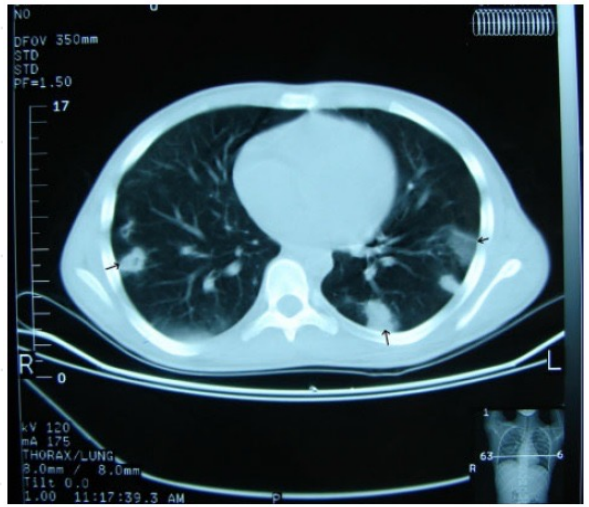


Figure 1 CT chest: multiple septic pulmonary emboli (arrows)

Deep-vein thrombosis and septic pulmonary emboli in methicillin-sensitive Staphylococcus aureus infection. Banani Poddar. Paediatrics and International Child Health 2013 VOL. 33 NO. 1

Observational Study

Medicine®

OPEN

Severe infections of Panton-Valentine leukocidin positive *Staphylococcus aureus* in children

- Estudo retrospectivo que incluiu 75 crianças tratadas por infecções por Staphylococcus aureus Panton-Valentine leucocidina positivo (PVL-SA) entre 2012 e 2017.
- As infecções por PVL-SA são caracterizadas por furúnculos múltiplos ou recorrentes, abscessos ou infecções periorbitárias.
- PVL-SA causa infecções graves a potencialmente fatais que requerem longos tratamentos no hospital em uma porcentagem substancial de crianças sintomáticas colonizadas.
- Leucocidina Panton-Valentine pode ser expressa por cepas MSSA e MRSA.
- A TVP está cada vez mais sendo detectada em pacientes com infecções causadas por PVL-AS.

Severe infections of Panton-Valentine leukocidin positive Staphylococcus aureus in children. Hoppe et al. Medicine (2019)

- Ainda não está claro se é a maior virulência do PVL-SA em geral ou se os mecanismos específicos do patógeno contribuem para a formação de trombo.

- Necessidade de investigar se a tromboprofilaxia com heparina de baixo peso molecular deve ser administrada rotineiramente em crianças com infecção grave de PVL-SA.

- Mais de 50% das infecções graves podem ser evitadas pelo teste imediato para PVL-SA em indivíduos com história de abscessos ou furunculose, seguido por medidas de descolonização.

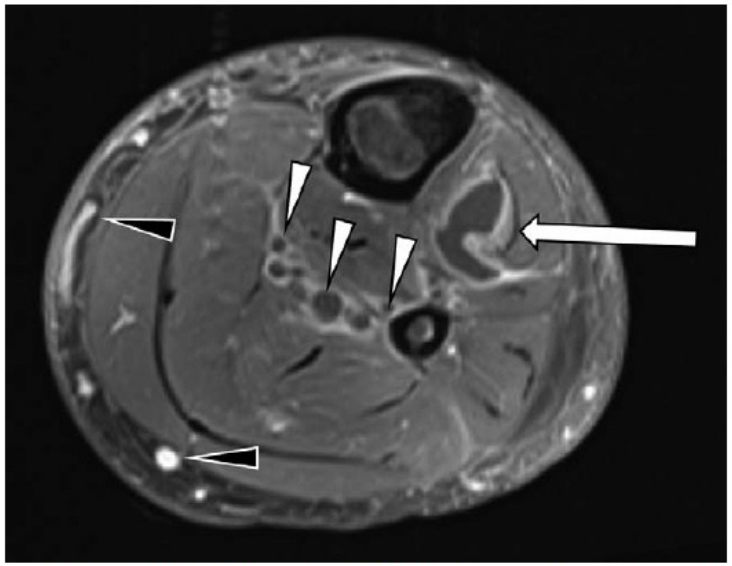


Figure 7. Patient 1 at 3 days after admission. Axial contrast-enhanced T1-weighted MRI with fat suppression of the proximal left lower thigh. Large arrow: abscess formation with circular contrast enhancement in the ventral compartment. Small arrows: thrombosis of deep veins. Small black arrows: subcutaneous veins with contrast. MRI = magnetic resonance imaging.

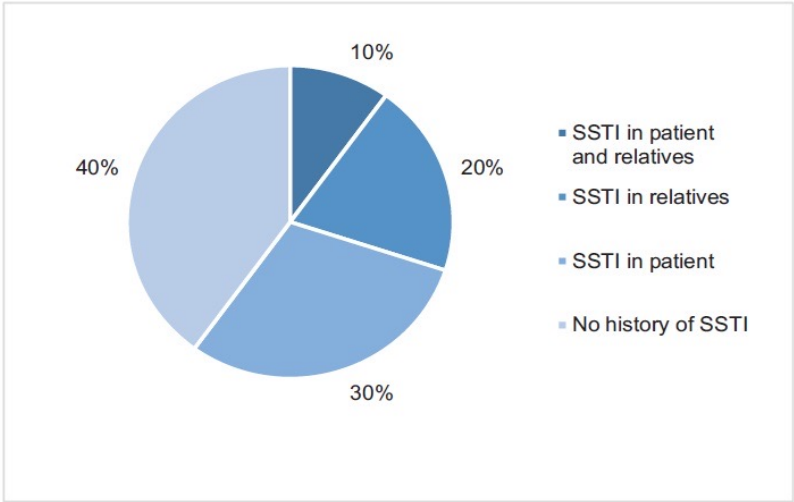


Figure 9. History of SSTI in patients and relatives of our cohort before admission for serious infection (n=10). SSTI = skin and soft tissue infections.

Severe infections of Panton-Valentine leukocidin positive Staphylococcus aureus in children. Hoppe et al. Medicine (2019)

Mensagens Finais

Infecção por Staphilococcus aureus e Trombose

- Fatores de risco:

Infecção por CA-MRSA

Acometimento pulmonar

Cateter venoso profundo

Infecções por PVL-SA

Infecção por Staphilococcus aureus e Trombose

O doppler da veia previamente cateterizada deve ser realizado em todos os pacientes com bacteremia relacionada ao S. aureus.


Obrigada