HOKKAIDO UNIVERSITY
Faculty of Medicine

HOKKAIDO
UNIVERSITY

北海道大学病院
HOKKAIDO UNIVERSITY HOSPITAL

第12回東京East救急医療研究会

敗血症診療における DIC診断と治療 ～J-SSCGの骨子と DIC研究の今後～

和田　剛志

北海道大学大学院医学研究院
侵襲制御医学講座救急医学教室

May 17, 2023

DICとは何の略でしょう？

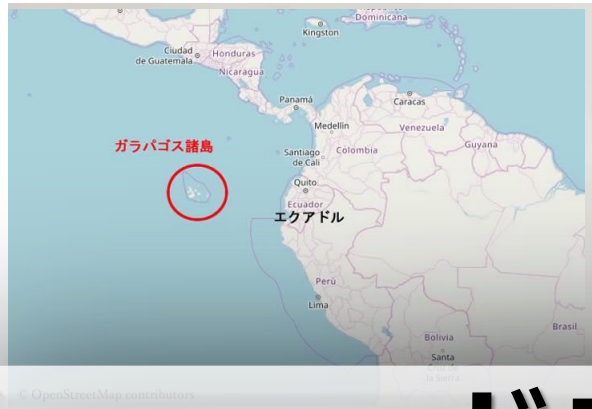
DIC

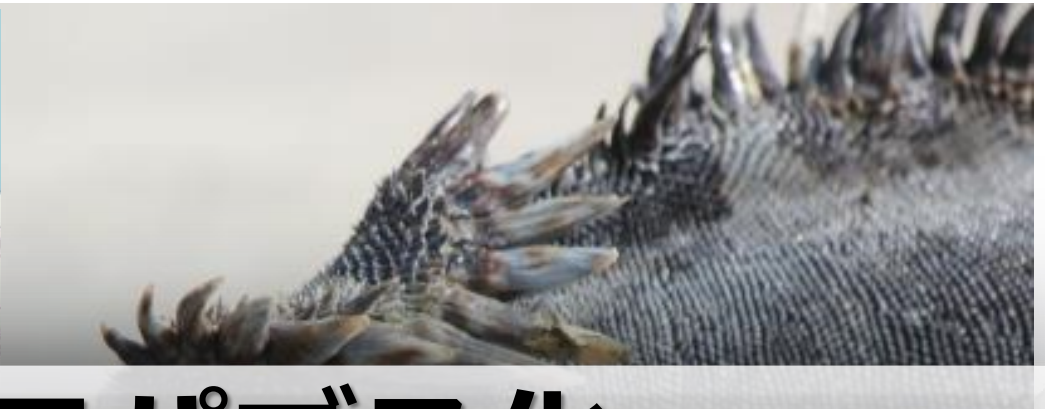
Disseminated

Intravascular

Coagulation

日本の敗血症診療





ガラパゴス化

市場が外界から隔絶された環境下で独自の発展を遂げ、その結果として**世界標準の流れからかけ離れていく状態**を揶揄する表現

日本の敗血症診療

Acute Medicine & Surgery 2020;7:e561 doi: 10.1002/ams2.561

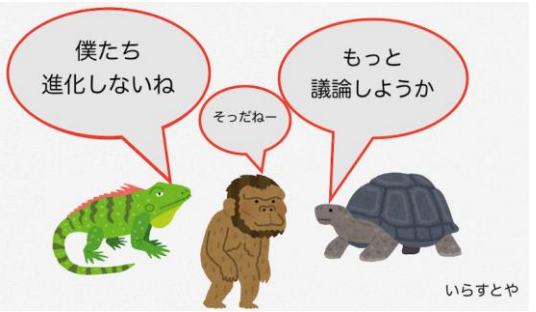
Original Article

Galápagosization of sepsis management in Japan: a nationwide survey of current practices

Kazuma Yamakawa,[1,*] Daisuke Hasegawa,[2,*] Hideto Yasuda,[3] So Sakamoto,[4] Kazuki Nishida,[5] Tomoaki Yatabe,[6] Moritoki Egi,[7] Hiroshi Ogura,[8] Osamu Nishida,[2] and the committee of Japanese Clinical Practice Guidelines for Management of Sepsis, Septic Shock 2016 (J-SSCG 2016)

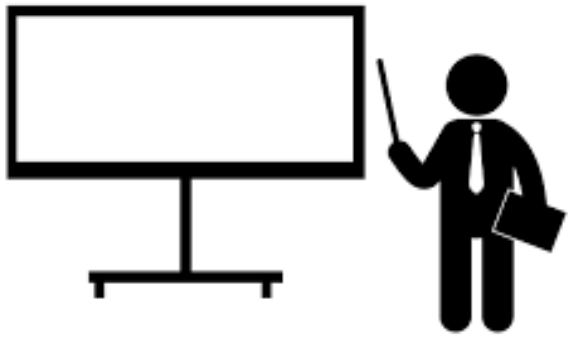
Galapagosization of sepsis management in Japan

- ✓ Antithrombin replacement for DIC
- ✓ Recombinant thrombomodulin for DIC
- ✓ PMX-DHP
- ✓ IVIG
- ✓ RRT with non-renal indications

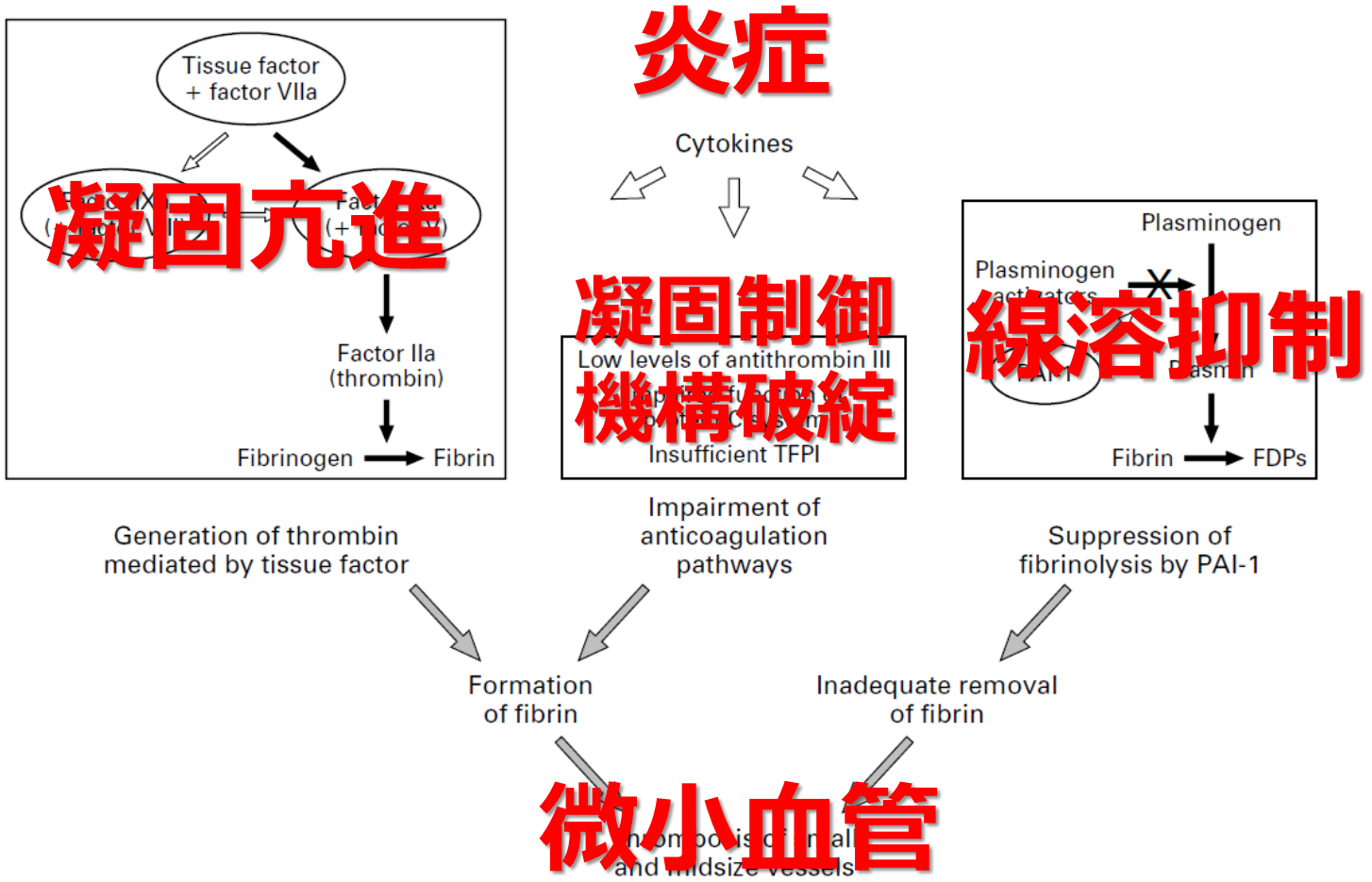


本日の内容

- ◆ DIC診療の国内外の温度差を生んだ過去
- ◆ 本邦がDICを診療対象とする根拠
  - ✓ 確固たる病態概念
  - ✓ 予後への影響
- ◆ J-SSCG2020の骨子
  - ✓ DIC診断
  - ✓ 鑑別
  - ✓ 治療(rhTMを中心に)
- ◆ 今後の展望、まとめ



基本的病態概念: 欧米諸外国も関心はあった



Levi M, et al. ***NEJM*** 1999

2000年前後の欧米

High-Dose Antithrombin III in Severe Sepsis
A Randomized Controlled Trial

Warren, *et al*. ***JAMA*** 2001

KyberSept

Context Activation of the coagulation system and depletion of endogenous anticoagulants are frequently found in patients with severe sepsis and septic shock. Diffuse microthrombus formation may induce organ dysfunction and lead to excess mortality in septic shock. Antithrombin III may provide protection from multiorgan failure and improve survival in severely ill patients.

✓敗血症病態における凝固異常の重要性

✓大規模RCTはどれも失敗に終わった

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C

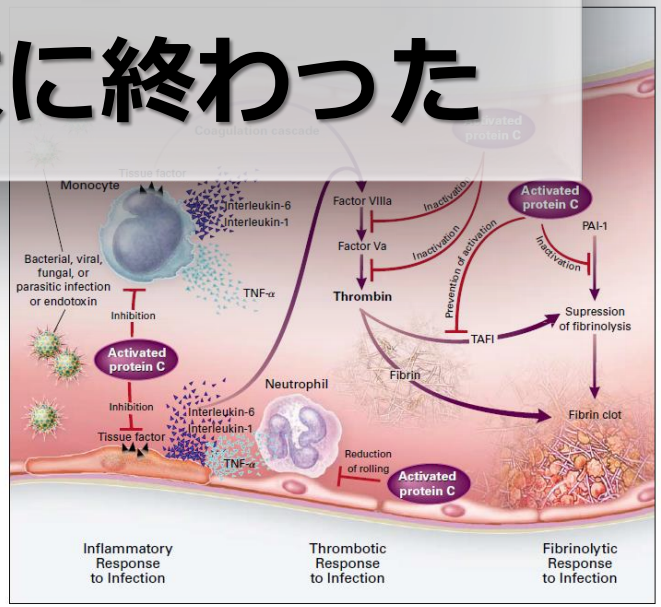
GORDON R. BERNARD, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*

Bernard GR, *et al*. ***NEJM*** 2001

PROWESS

ABSTRACT

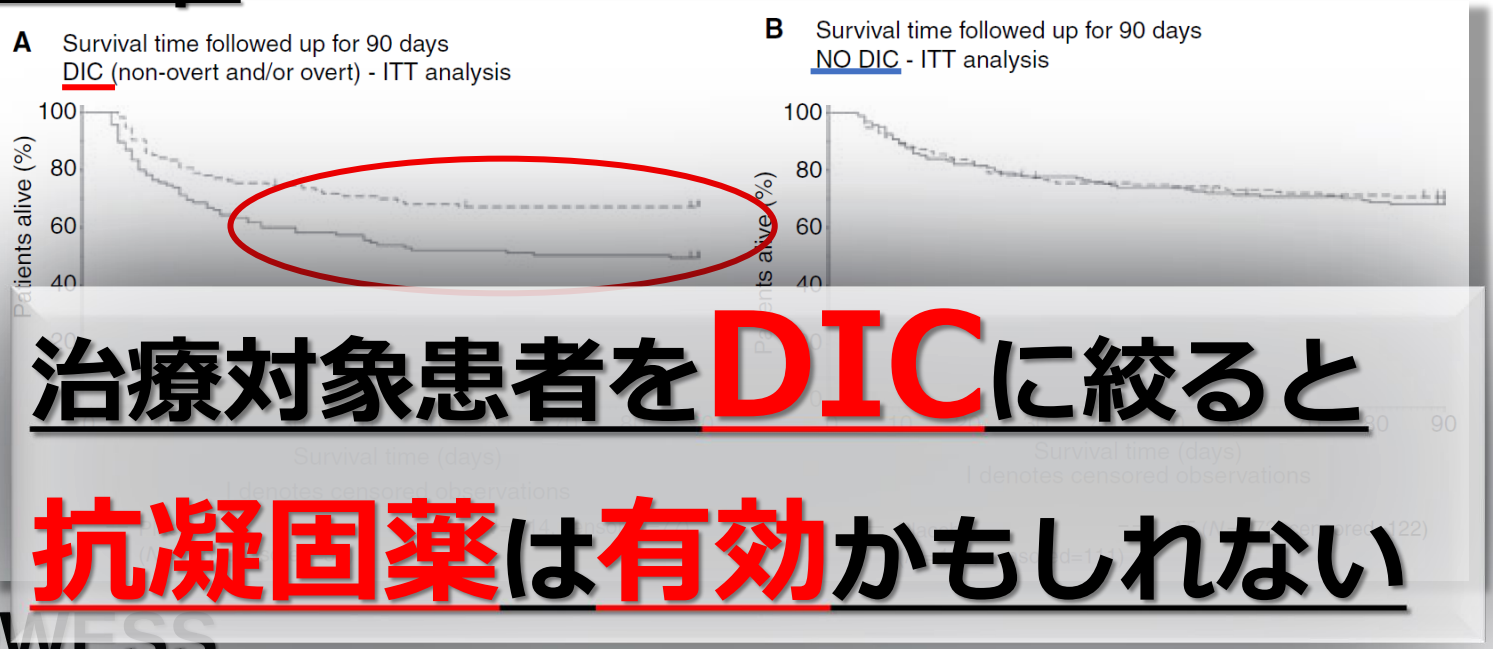
Background Drotrecogin alfa (activated), or recombinant human activated protein C, has antithrombotic, antiinflammatory, and profibrinolytic properties. In a previous study, drotrecogin alfa activated produced dose-dependent reductions in the levels of markers of coagulation and inflammation in patients with severe sepsis. In this phase 3 trial, we assessed whether treatment with drotrecogin alfa activated reduced the rate of death from any cause among patients with severe sepsis.



DICに絞ったサブグループ解析では

KyberSept

※承認外の効能・効果の情報を含みますが、承認外の使用を推奨するものではありません。



治療対象患者をDICに絞ると

抗凝固薬は有効かもしれない

PROWESS

Table 7 Effect of drotrecogin alfa (activated) treatment on mortality by baseline overt DIC status

	Drotrecogin alfa (activated)		Placebo		
Baseline overt DIC status	Number of patients	Percent mortality	Number of patients	Percent mortality	Relative risk (95% CI)
Without ($N = 1114$)	567	22.1	547	27.1	0.81 (0.66–1.00)
With ($N = 454$)	233	30.5	221	43.0	0.71 (0.55–0.91)

Breslow-Day test of homogeneity of odds ratio between patients with or without overt DIC by treatment P-value = 0.261.

敗血症に付随する**凝固異常**を、**傍症**とする**欧米**

DICという**治療対象**とする**日本**

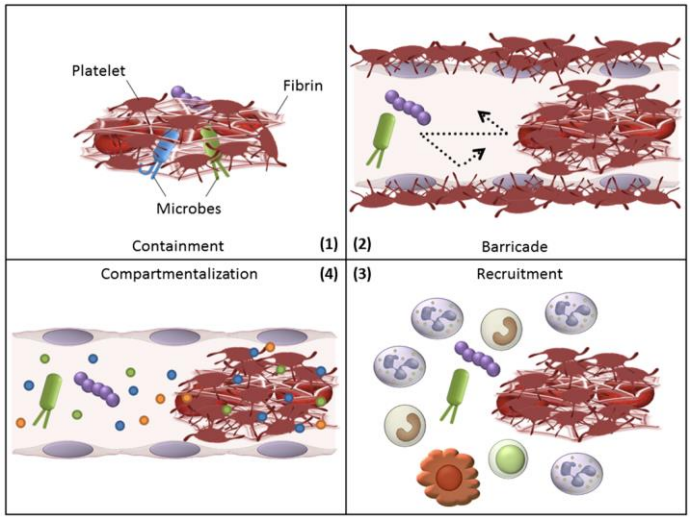
どうして本邦はDICを治療対象と考え研究するのか

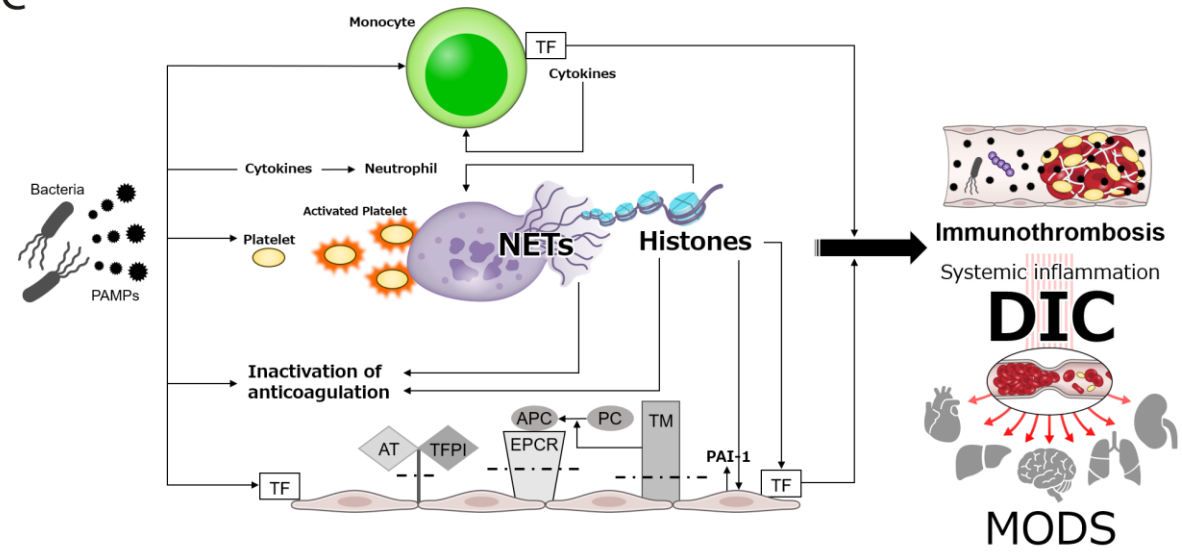
生理的凝固線溶反応(免疫血栓)と病的反応(DIC)

REVIEW Open Access

PAMPs and DAMPs as triggers for DIC

Takashi Ito[1,2]





1）病原体を血栓内に閉じ込める
2）バリアとして病原体の移動を制限
3）感染巣で免疫反応をコーディネート
4）病原体と免疫細胞の接触機会増多

Immunothrombosis/DICの主役

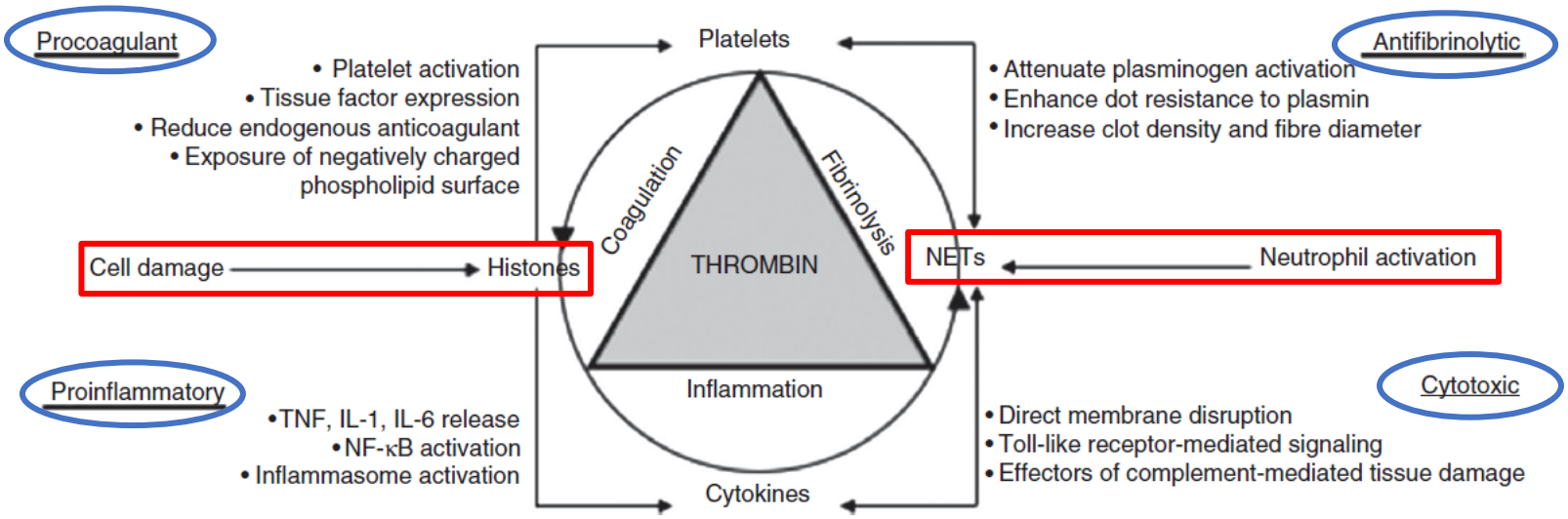
- 活性化好中球由来の**NETs**
- **ヒストン**をはじめとする**DAMPs**

DIC病態の捉え方：病的自然免疫凝固炎症反応

Dysregulated Inflammatory & Coagulofibrinolytic responses

Disseminated intravascular coagulation in cardiac arrest and resuscitation

Wada T *et al.* ***J Thromb Haemost*** 2019



敗血症性DICにおけるヒストン

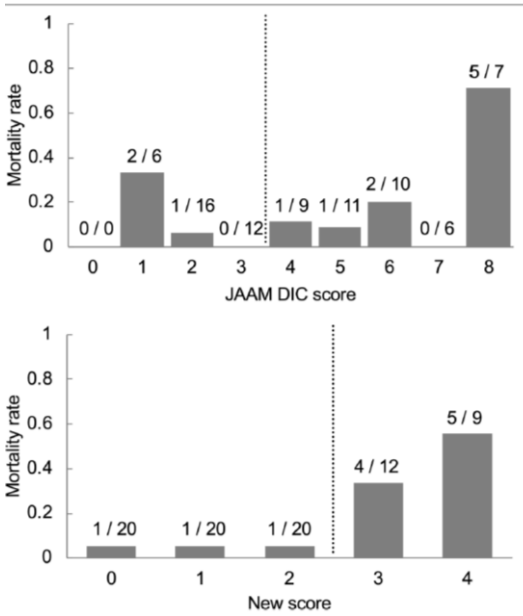
Ito et al. Journal of Intensive Care (2019) 7:63
https://doi.org/10.1186/s40560-019-0420-2

Journal of Intensive Care

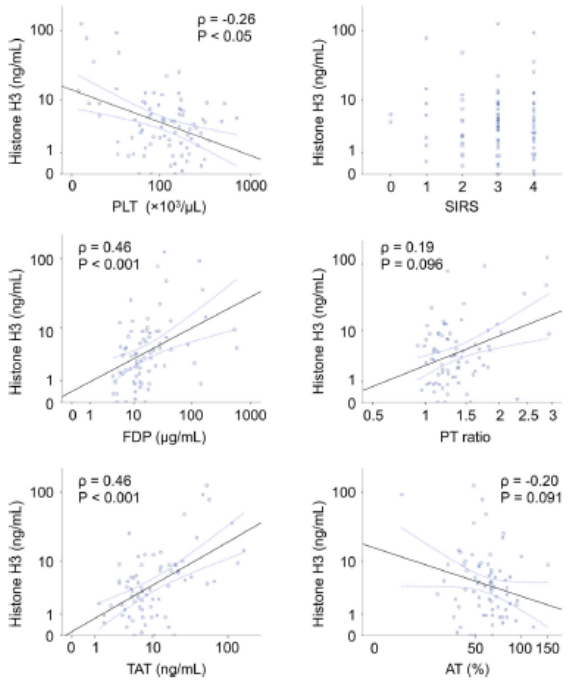
RESEARCH Open Access

Serum histone H3 levels and platelet counts are potential markers for coagulopathy with high risk of death in septic patients: a single-center observational study

Takashi Ito[1,2*†], Takaaki Totoki[1†], Yayoi Yokoyama[1], Tomotsugu Yasuda[1], Hiroaki Furubeppu[1], Shingo Yamada[3], Ikuro Maruyama[2] and Yasuyuki Kakihana[1]



Histone H3 (ng/mL)	
< 3	0
3 ≤ < 9	1
9 ≤	2
Platelet (× 10^3/μL)	
> 120	0
80 ≤ < 120	1
≤ 80	2
Sum score	
3 ≤	Coagulopathy with high risk of death



ヒストンとDIC, 臓器障害

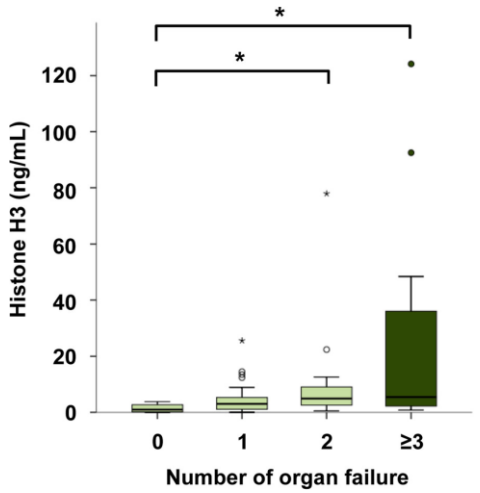
Yokoyama *et al. Thrombosis Journal* (2019) 17:1
https://doi.org/10.1186/s12959-018-0190-4

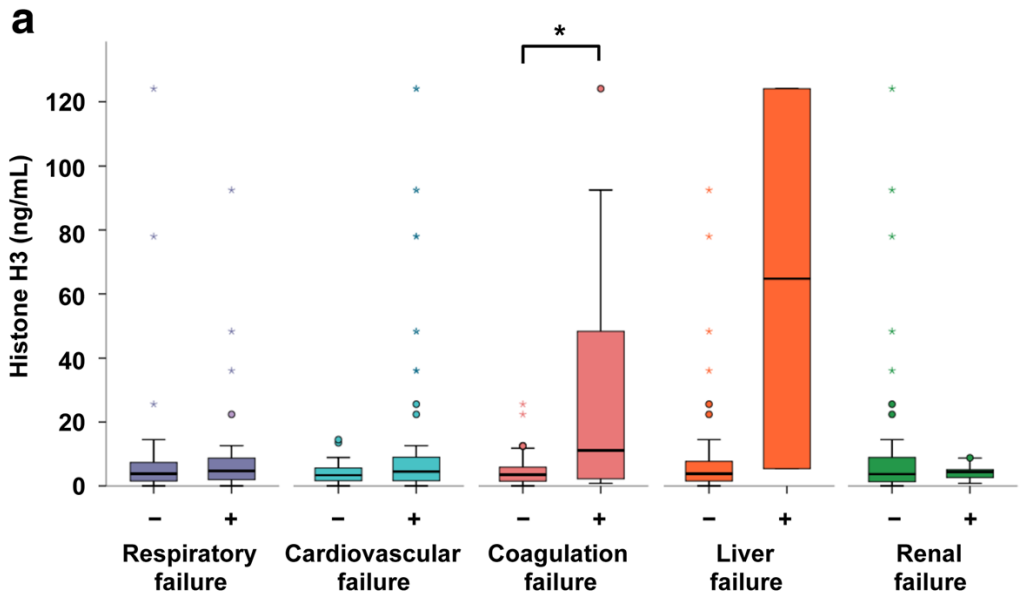
Thrombosis Journal

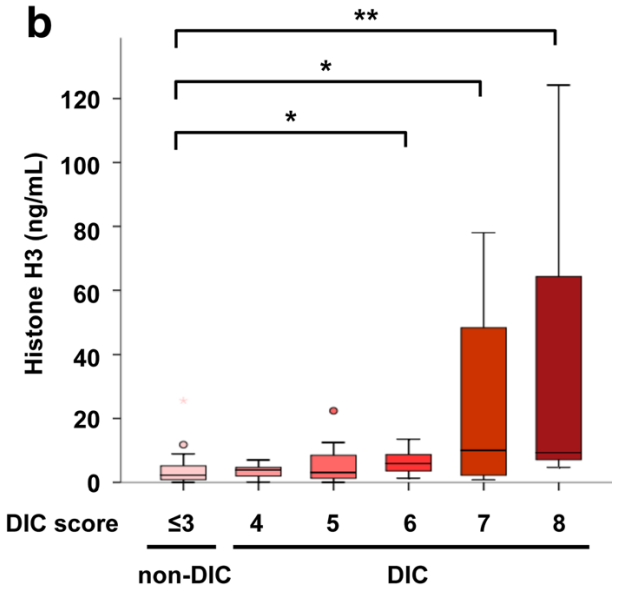
RESEARCH Open Access

Circulating histone H3 levels in septic patients are associated with coagulopathy, multiple organ failure, and death: a single-center observational study

Yayoi Yokoyama[1], Takashi Ito[1,2*], Tomotsugu Yasuda[1], Hiroaki Furubeppu[1], Chinatsu Kamikokuryo[1], Shingo Yamada[3], Ikuro Maruyama[2] and Yasuyuki Kakihana[1]







病的自然免疫凝固炎症反応の病態理解に基づく治療

抗ヒストン

- ✓ 抗ヒストン抗体
- ✓ 活性化プロテインC
- ✓ rTM
- ✓ ヘパリン

抗NETs

- ✓ DNase
- ✓ PAD targeted therapy
- ✓ AT

Extracellular histones are major mediators of death in sepsis

Jun Xu[1], Xiaomei Zhang[2], Rosana Pelayo[3], Marc Monestier[4], Concetta T Ammollo[1], Fabrizio Semeraro[1], Fletcher B Taylor[1], Naomi L Esmon[1], Florea Lupu[1] & Charles T Esmon[1,2]

OPEN ACCESS Freely available online PLOS ONE

Recombinant Thrombomodulin Protects Mice against Histone-Induced Lethal Thromboembolism

Mayumi Nakahara[1☯], Takashi Ito[2☯], Ko-ichi Kawahara[7], Mika Yamamoto[2], Tomoka Nagasato[2], Binita Shrestha[2], Shingo Yamada[8], Takahiro Miyauchi[3], Koji Higuchi[4], Toshihiro Takenaka[4], Tomotsugu Yasuda[5], Akira Matsunaga[1], Yasuyuki Kakihana[5], Teruto Hashiguchi[6], Yuichi Kanmura[1], Ikuro Maruyama[2*]

Nonanticoagulant heparin prevents histone-mediated cytotoxicity in vitro and improves survival in sepsis

Karin C. A. A. Wildhagen,[1] Pablo García de Frutos,[2] Chris P. Reutelingsperger,[1] Roy Schrijver,[1] Cristina Aresté,[2] Almudena Ortega-Gómez,[3] Niko M. Deckers,[1] H. Coenraad Hemker,[4] Oliver Soehnlein,[3,5,6] and Gerry A. F. Nicolaes[1]

Endotoxemia and sepsis mortality reduction by non-anticoagulant–activated protein C

Edward J. Kerschen,[1] José A. Fernandez,[2] Brian C. Cooley,[4] Xia V. Yang,[2] Rashmi Sood,[1] Laurent O. Mosnier,[2] Francis J. Castellino,[5] Nigel Mackman,[3] John H. Griffin,[2] and Hartmut Weiler[1]

Antithrombin III improved neutrophil extracellular traps in lung after the onset of endotoxemia

Michiko Ishikawa, PhD,[a,] Hayato Yamashita, MS,[b] Nobuki Oka, MS,[b] Takahiro Ueda, MD, PhD,[a] Keisuke Kohama, MD, PhD,[a,c] Atsunori Nakao, MD, PhD,[d] and Joji Kotani, MD, PhD[a]*

敗血症性腎障害に対する抗ヒストンを介したrTMの効果

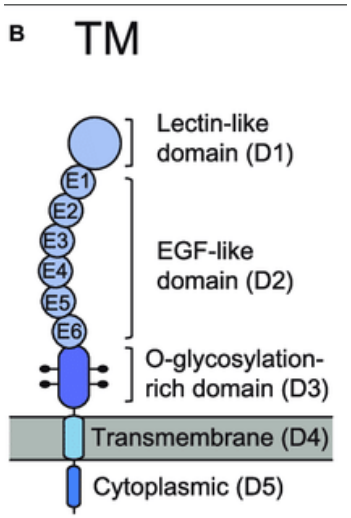
RESEARCH ARTICLE

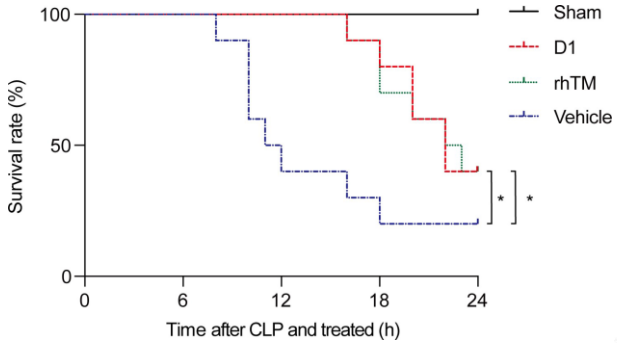
PLOS ONE 2020;15:e0228093

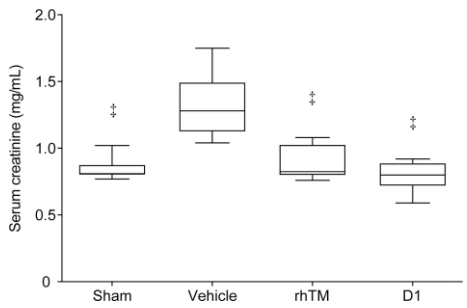
Recombinant human soluble thrombomodulin is associated with attenuation of sepsis-induced renal impairment by inhibition of extracellular histone release

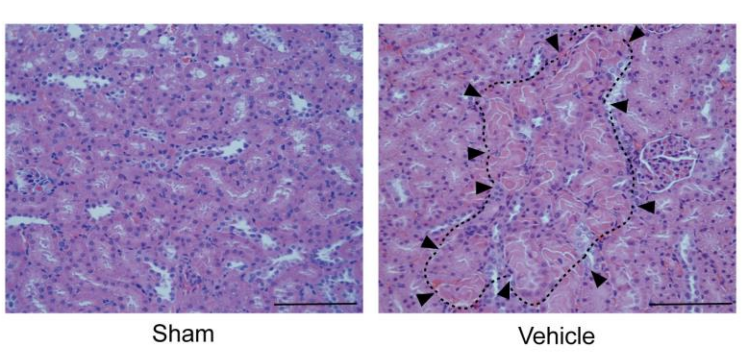
Masayuki Akatsuka[1,2]*, Yoshiki Masuda[2], Hiroomi Tatsumi[2], Michiaki Yamakage[1]

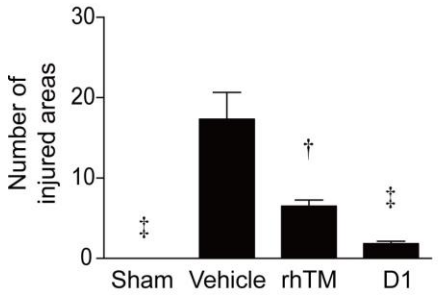
1 Department of Anesthesiology, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan, 2 Department of Intensive Care Medicine, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan

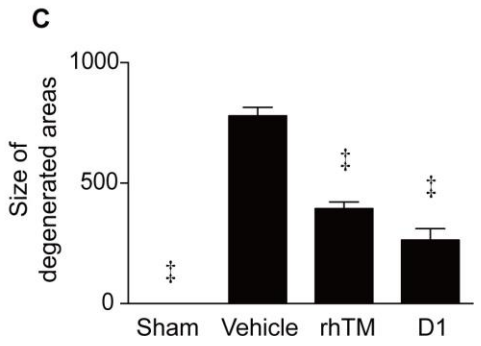












DICの転帰への影響①

ORIGINAL ARTICLE

Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation

Kienast *et al.* ***J Thromb Haemost***. 2006

28-day mortality
DIC vs. non-DIC

40.0% vs. 22.2%

ORIGINAL ARTICLE

Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation[1]

Dhainaut, *et al*. ***J Thromb Haemost*** 2004

43.0% vs. 27.0%

Sakr *et al. Critical Care* 2012, **16**:R222
http://ccforum.com/content/16/6/R222

CRITICAL CARE

RESEARCH Open Access

Patterns and early evolution of organ failure in the intensive care unit and their relation to outcome

Yasser Sakr[1], Suzana M Lobo[2], Rui P Moreno[3], Herwig Gerlach[4], V Marco Ranieri[5], Argyris Michalopoulos[6], Jean-Louis Vincent[7*] and the SOAP Investigators

多臓器不全の中で凝固異常を含む症例は特に予後が悪い

Table 2 ICU and hospital mortality rates according to the number, type, and combinations of failed organs

	On admission to the ICU			At any time during ICU stay		
	Incidence (%)	Mortality (%)		Incidence (%)	Mortality (%)	
		ICU	Hospital		ICU	Hospital
Combinations of two organ failures						
Respiratory + cardiovascular	274 (9)	39	46	726 (25)	39	46
Respiratory + renal	120 (4)	42	49	543 (19)	41	48
Respiratory + CNS	197 (7)	38	47	488 (17)	43	50
Hepatic + renal	24 (1)	38	46	98 (3)	47	51
Respiratory + hepatic	22 (1)	50	50	109 (4)	47	53
Renal + cardiovascular	24 (1)	38	46	481 (16)	47	55
CNS + cardiovascular	220 (8)	39	48	390 (13)	50	55
CNS + renal	109 (4)	39	51	308 (11)	49	57
Hepatic + cardiovascular	29 (1)	48	52	97 (3)	55	59
Respiratory + coagulation	34 (1)	47	53	203 (7)	53	63
Coagulation + cardiovascular	51 (2)	47	59	201 (7)	56	65
Coagulation + renal	25 (1)	52	68	159 (5)	59	67
Coagulation + hepatic	15 (1)	67	80	64 (2)	63	70
Hepatic + CNS	29 (1)	58	67	97 (3)	66	71
Coagulation + CNS	23 (1)	65	74	113 (4)	69	79

†Alone or in combination with other organs.

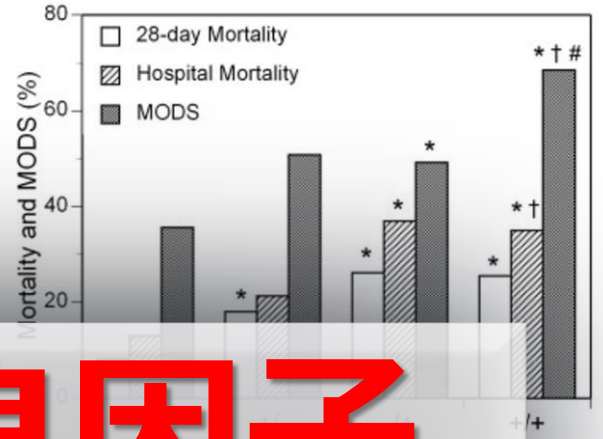
DICの転帰への影響②

RESEARCH Open Acces

A multicenter, prospective validation study of the Japanese Association for Acute Medicine disseminated intravascular coagulation scoring system in patients with severe sepsis

Satoshi Gando[1*†], Daizoh Saitoh[2†], Hiroshi Ogura[3], Seitaro [illegible]
Hiroto Ikeda[7], Joji Kot[illegible], Yasuo Mik[illegible]
Yasushi Suzuki[13], Nao[illegible]
Norio Yama[illegible]

DICは予後不良因子



Gando S, *et al. Crit Care* 2013

prevalence of multiple organ dysfunction syndrome on day 4.

Contents lists available at ScienceDirect

Thrombosis Research

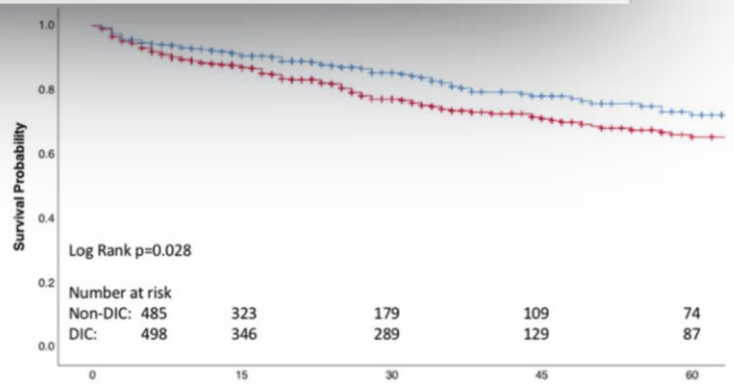
journal homepage: www.elsevier.com/locate/thromres

ELSEVIER

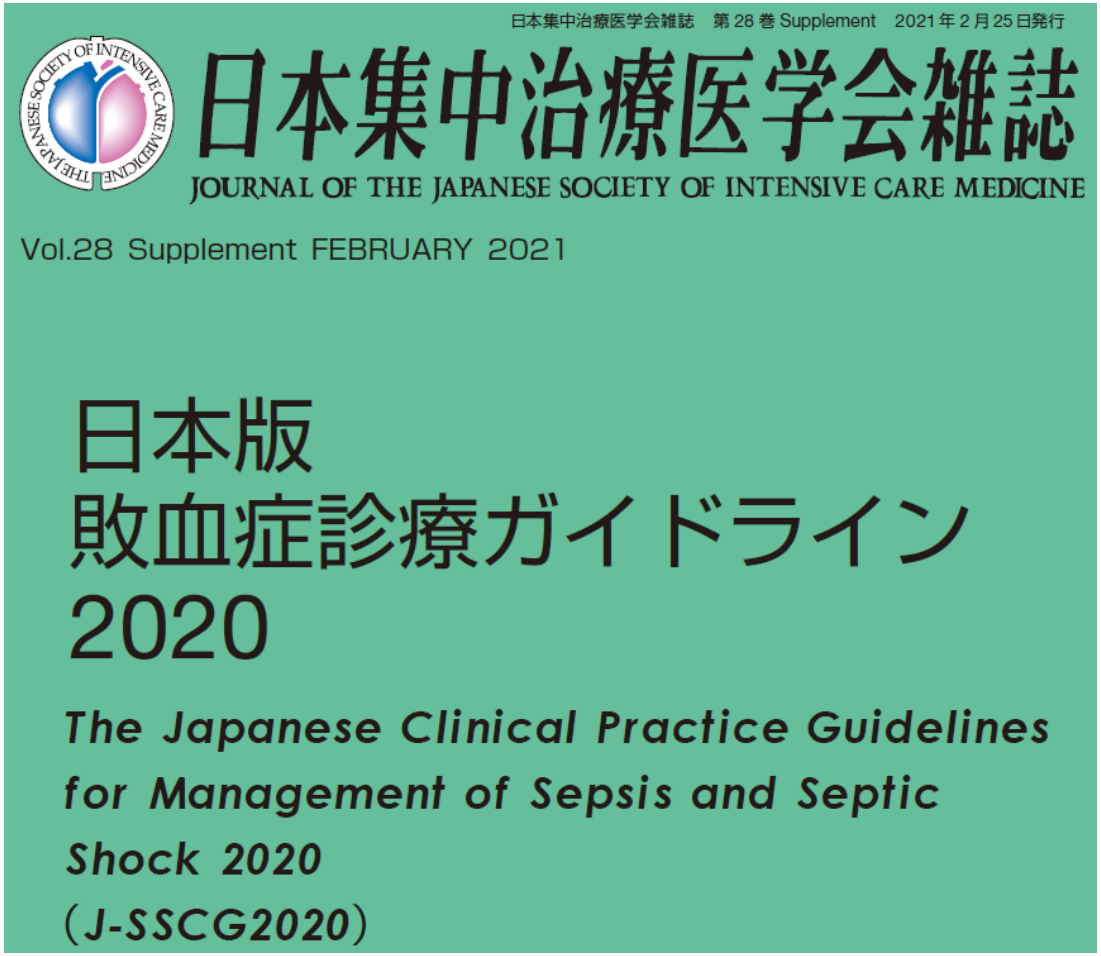
Full length article

Role of disseminated intravascular coagulation in severe sepsis

Gando S, *et al.* ***Thromb Res*** 2019



J-SSCG2020からDIC診療について



日本救急医学会

THE JAPANESE SOCIETY OF INTENSIVE CARE MEDICINE

J-SSCG2020での「DIC診断基準」

日本版敗血症診療ガイドライン 2020
The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020（J-SSCG 2020）

CQ15-1: 敗血症性 DIC の診断方法は？

Answer: DIC の診断を行うために複数の診断基準が存在する。国内では急性期 DIC 診断基準が広く用いられており、海外では ISTH overt-DIC が標準として使用されている。診断基準間の優劣を判断することは困難であり、目的に応じて使い分ける。

DIC診断の意義

Contents lists available at ScienceDirect

Thrombosis Research

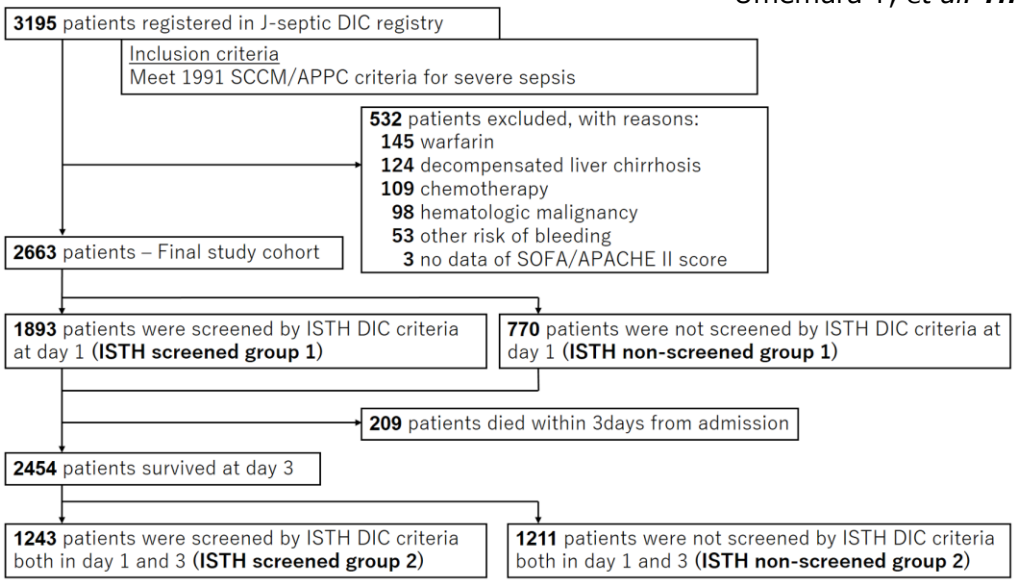
journal homepage: www.elsevier.com/locate/thromres

Full Length Article

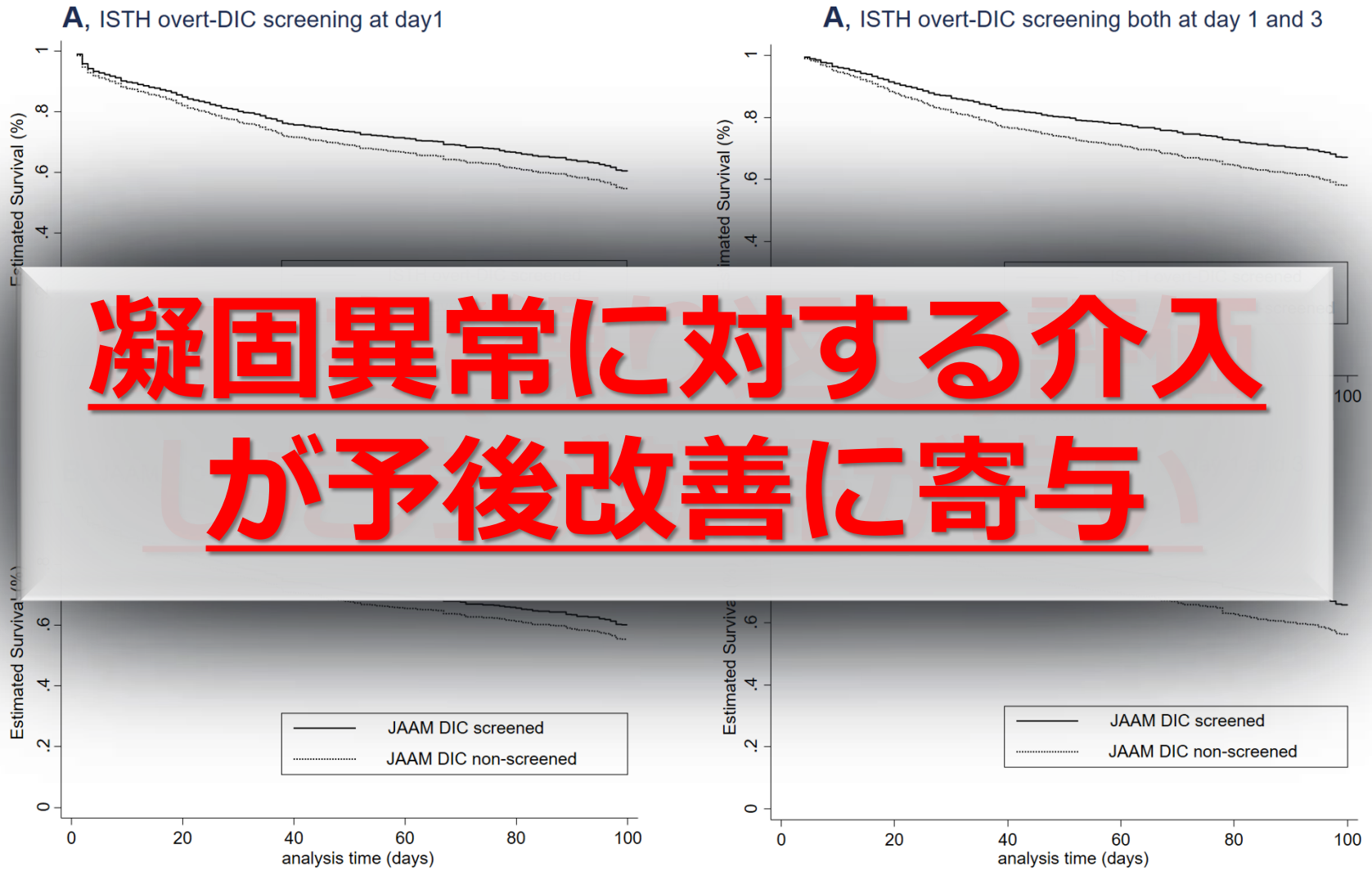
Screening itself for disseminated intravascular coagulation may reduce mortality in sepsis: A nationwide multicenter registry in Japan

Yutaka Umemura[a], Kazuma Yamakawa[b,*], Mineji Hayakawa[c], Toshimitsu Hamasaki[d], Satoshi Fujimi[b], for the Japan Septic Disseminated Intravascular Coagulation (J-Septic DIC) study group

Umemura Y, *et al.* ***Thromb Res*** 2018



DIC診断の意義



凝固異常に対する介入が予後改善に寄与

DIC診断基準

	旧厚生省	ISTH	急性期
基礎疾患 臨床症状	有　：1点 出血症状：1点 臓器症状：1点	必須項目 — —	必須項目、要除外診断 SIRS(3項目以上)：1点
血小板数 ($X10^4/\mu L$)	8＜ ≦12 ：1点 5＜ ≦8 ：2点 ≦5 ：3点	5-10 ：1点 ＜5 ：2点	8≦ ＜12 or 30%以上減少/24h：1点 ＜8 or 50%以上減少/24h：3点
FDP (μg/ml)	10≦ ＜20：1点 20≦ ＜40：2点 40≦ ：3点	FDP、DD、SF 中等度増加：2点 著明増加：3点	10≦ ＜25：1点 25≦ ：3点
フィブリノゲン (mg/dl)	100＜ ≦150：1点 ≦100：2点	＜100：1点	—
PT	PT比 1.25≦ ＜1.67：1点 1.67≦：2点	PT秒 3-6秒延長：1点、 6秒以上延長：2点	PT比 1.2≦：1点
DIC診断	7点以上	5点以上	4点以上

ISTH(国際血栓止血学会)：国際的標準基準、感度が低く診断されたときには病期進行

急性期(日本救急医学会)：感度が高く治療開始基準として有用、敗血症に高い有用性

DIC診断の意味合い　本邦と欧米の違い

我が国の臨床家の多くは、敗血症性DICを、
抗凝固療法の対象と考えている。

→ 早期治療介入の指標が必要

諸外国では一般的に敗血症性DICは
特異的な治療の対象とされていない

→ 正確な病態評価を目的とした厳密な診断基準が必要

Sepsis-induced coagulopathy(SIC)

Proposal of a two-step process for the diagnosis of sepsis-induced disseminated intravascular coagulation

Toshiaki Iba[1] | Jerrold H. Levy[2] | Kazuma Yamakawa[3] | Jecko Thachil[4] | Theodore E. Warkentin[5] | Marcel Levi[6] | The Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis

J Thromb Haemost 2019

TABLE 1 SIC and ISTH overt-DIC scoring systems

	Points	SIC	Overt-DIC
Platelet count ($\times 10^9$ L^{-1})	2	<100	<50
	1	≧100, <150	≧50, <100
FDP or D-dimer	3	—	Strong increase
	2	—	Moderate increase
	1	—	—
PT-INR	2	>1.4	≧6 s
	1	>1.2, ≦1.4	≧3, <6 s
Fibrinogen (g mL^{-1})	1	—	<100
Total SOFA score	≧2	2	—
	1	1	—

Box 4. qSOFA (Quick SOFA) Criteria

Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

Step 1

Yes

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

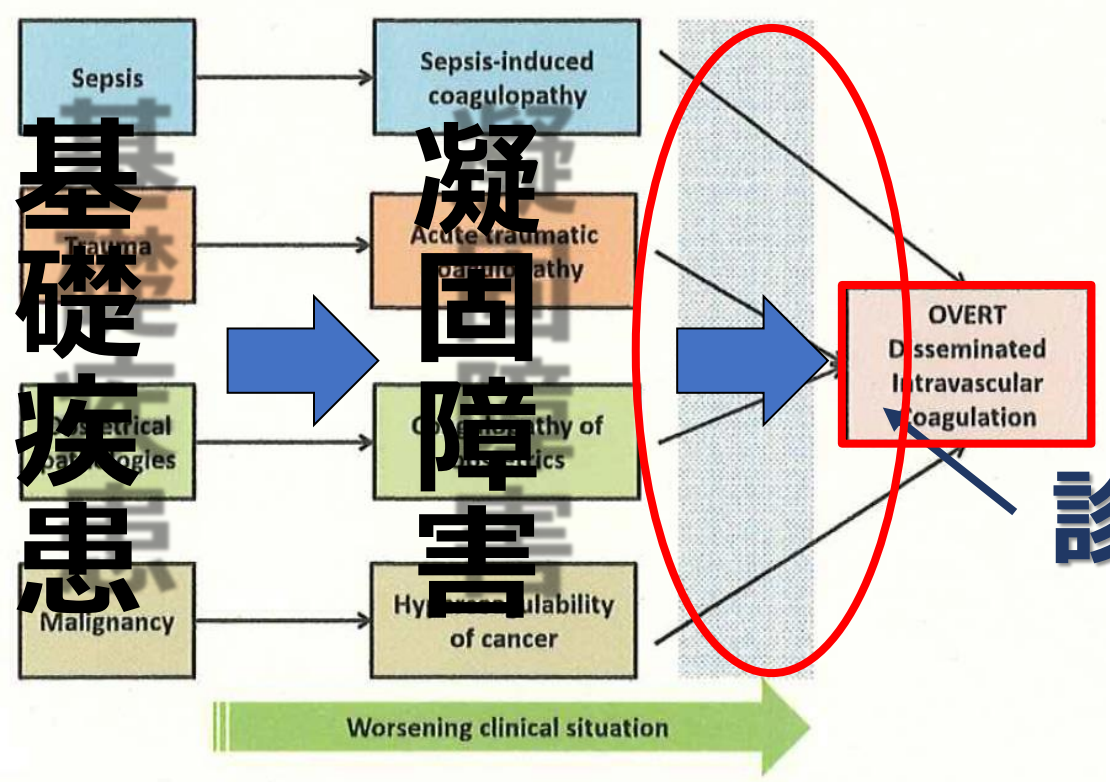
診断基準はどうあるべきか？

Review

Disseminated intravascular coagulation – new pathophysiological concepts and impact on management

Jecko Thachil

Thachil J. ***Exp Rev Hematol*** 2016



診断基準とはどうあるべきか？

Intensive Care Med (2016) 42:1062–1064
DOI 10.1007/s00134-016-4257-z

WHAT'S NEW IN INTENSIVE CARE

What's new in the diagnostic criteria of disseminated intravascular coagulation?

Satoshi Gando[1*], Ferhat Meziani[2,3] and Marcel Levi[4]

診断基準の2つの目的

- ✓ 同一の症状・症候を持つ他と異なる独立した患者集団を拾い上げる
- ✓ その患者集団に治療介入を行い、その予後を改善する事

診断基準が満たすべき条件

- ✓ どこでも使用できて使いやすい
- ✓ 診断精度
- ✓ 予後を予測

余談：Sepsis-3を提唱したDr. Vincent(若き日)

Dear SIRS, I'm sorry to say that I don't like you

Vincent, Jean-Louis MD, PhD, FCCM

Crit Care Med 1997; 15: 372-374

Dear SIRS, you're too sensitive
Dear SIRS, you don't help us understand the pathophysiology
Dear SIRS, you're not helping our clinical trials
Dear SIRS, you're not helping us in our practice
Dear SIRS, I'm afraid we don't need you

Dear SIRS, I am afraid you're not only useless, you are potentially harmful

余談：Sepsis-1(SIRS)でDr. Roger C. Boneは言いました

CRITICAL CARE MEDICINE
Copyright © 1991 by Williams & Wilkins

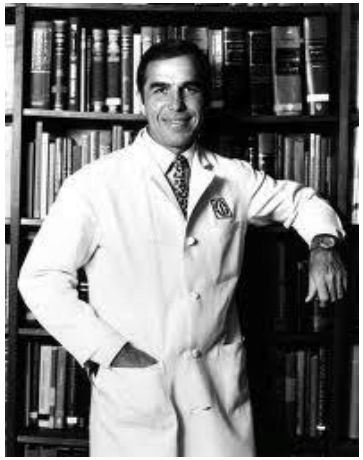
Vol. 19, No. 7
Printed in U.S.A.

Special Article

Let's agree on terminology: Definitions of sepsis

ROGER C. BONE, MD, FCCM

"Words mean what I say they mean."
—Humpty Dumpty, from *Alice in Wonderland*



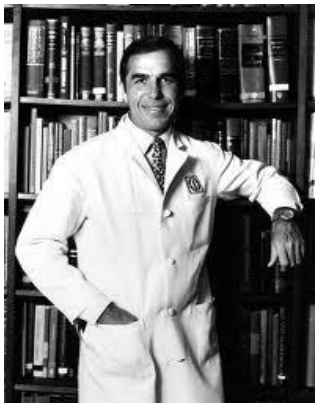
"Words mean what I say they mean."
—Humpty Dumpty, from *Alice in Wonderland*

「僕が言葉を使うときはね」とハンプティ・ダンプティはあざけるように言いました
「**その言葉は、僕がその言葉のために選んだ意味を持つようになるんだよ。僕が選んだものとぴったり、同じ意味にね**」

Aliceの世界での診断基準　SIRSとqSOFA

疾患

診断基準



治療介入

予後改善

Sepsis-1 (SIRS)

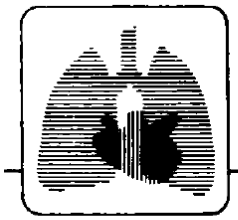
sensitivity

Sepsis-3 (qSOFA)

specificity

Words mean what I say they mean.

SIRSすなわちSepsis-1とDIC



Special Article

ed 1992; 20: 864-874
.992; 101: 1644-1655

Let's agree on terminology: Definitions of sepsis

ROGER C. BONE, MD, FCCM

"Words mean what I say they mean."
—Humpty Dumpty, from *Alice in Wonderland*

Table 2. Variables of multiorgan failure

Disseminated intravascular coagulation	A confirmatory test is positive (FDP >1:40 or D-Dimers >2.0) and there are abnormally low values for platelets (or there is a >25% decrease from a previously documented value) and either prolonged prothrombin time or partial thromboplastin time or clinical evidence of bleeding.These abnormalities must occur in the absence of medically significant confounding factors such as liver failure, major hematoma, or anticoagulant therapy.
Adult respiratory distress syndrome	Unexplained hypoxemia in the presence of a predisposing factor such as sepsis. Bilateral pulmonary infiltrates consistent with pulmonary edema *and* Pao_2/FIo_2 <175. These factors must occur in the absence of congestive heart failure or primary lung disease such as pulmonary embolus or bilateral pneumonia. Pulmonary artery occlusion pressure, when measured, must be <18 mm Hg.
Acute renal failure	Serum creatinine becomes abnormal and urinary sodium is >40 mmol/L in a spot specimen, *or* serum creatinine increases by 2.0 mg/dL (176 µmol/L) in a patient with previous renal insufficiency, and is not prerenal in nature (e.g., associated with dehydration or gastrointestinal bleeding) or due to rhabdomyolysis. (It is preferable if no diuretics are given within 2 hrs before obtaining urinary sodium levels.)
Hepatobiliary dysfunction	Serum bilirubin exceeds 2.0 mg/dL (34 µmol/L), and alkaline phosphatase, gamma glutamyl transpeptidase (GGT), SGOT, or SGPT exceed twice the upper limit of normal, in the absence of confounding disease.
Central nervous system (CNS) dysfunction	Glasgow Coma Scale score is <15 in patients with normal baseline CNS function, or at least one point lower than a baseline Glasgow Coma Scale score in patients with baseline CNS impairment. To assess Glasgow Coma Scale scores, patients cannot be treated with paralyzing or sedating agents in sufficient dose to alter their Glasgow Coma Scale scores.

FDP, fibrin degradation products; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

BLOOD-BORI

Figure 1. Inte
sponse syndrom

F.C.C.P.
I.D.
n, M.D.
M.D., F.C.C.P.

e of the
nfection

20 breaths

,000/mm³,

Sepsis, Severe Sepsis, Septic Shock

敗血症性DICが疑われる症例での鑑別疾患は？

日本版敗血症診療ガイドライン 2020
The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020（J-SSCG 2020）

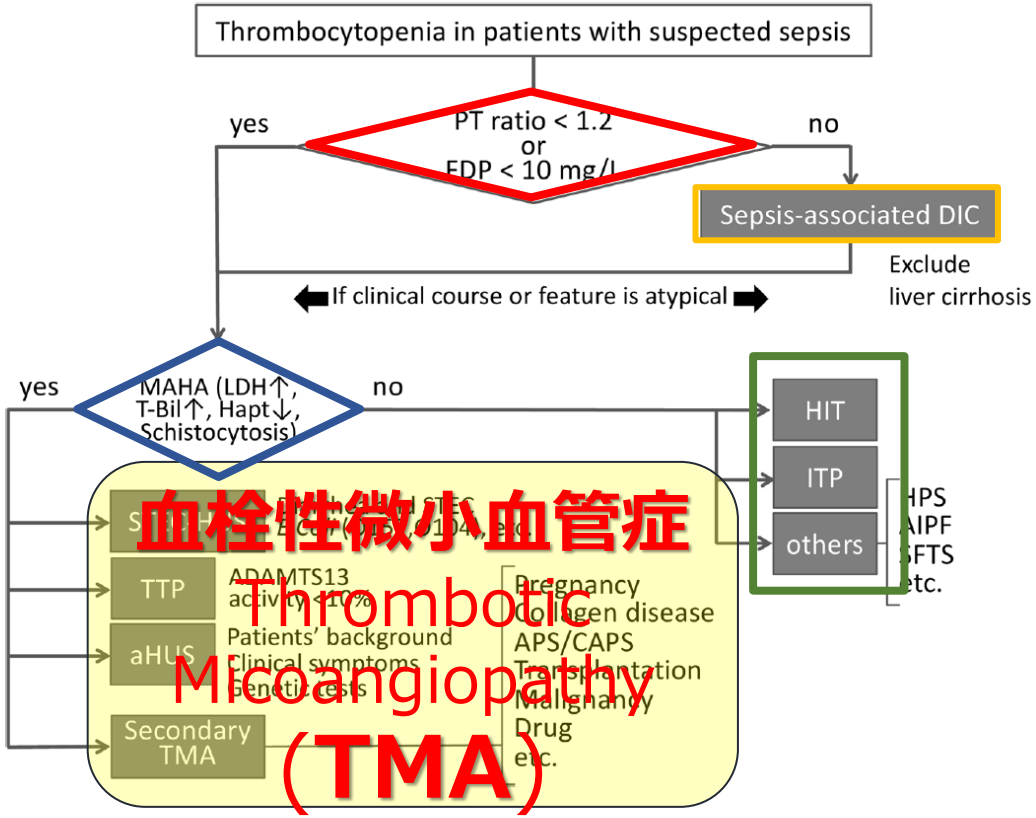
CQ15-2: 敗血症性 DIC が疑われる症例での鑑別疾患は？

Answer: DIC 類似病態として血栓性血小板減少性紫斑病 (thrombotic thrombocytopenic purpura: TTP) や溶血性尿毒症症候群 (hemolytic uremic syndrome: HUS)、ヘパリン起因性血小板減少症 (HIT) などが存在し、鑑別を要するこれらの疾患においては DIC とは異なる対応が必要になる。

敗血症性DIC類似疾患鑑別のアルゴリズム　J-SSCG

REVIEW Open Access

Sepsis-associated disseminated intravascular coagulation and its differential diagnoses

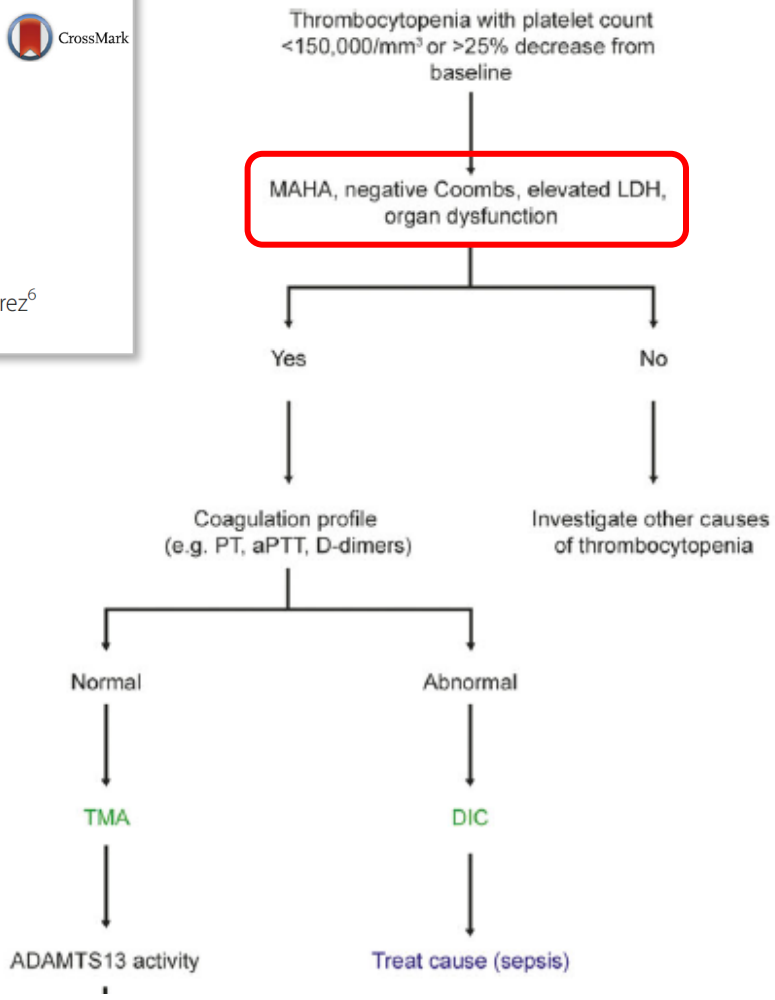


敗血症性DIC類似疾患鑑別のアルゴリズム　欧米

EDITORIAL Open Access

Thrombocytopenia in the ICU: disseminated intravascular coagulation and thrombotic microangiopathies—what intensivists need to know

Jean-Louis Vincent[1*], Pedro Castro[2], Beverley J. Hunt[3], Achim Jörres[4], Manuel Praga[5], Jose Rojas-Suarez[6] and Eizo Watanabe[7]



- 最初にMAHAの評価

→凝固・線溶の評価

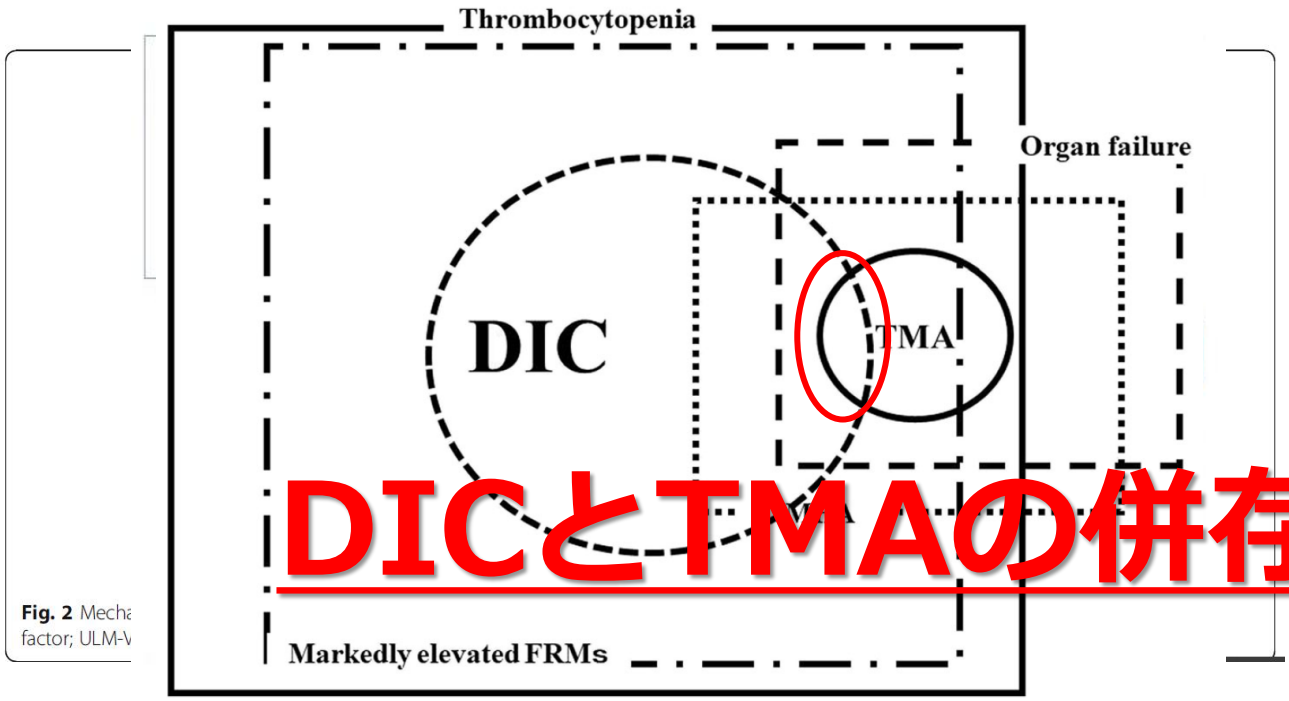
- DICが特異的治療対象ではなく診断を急ぐ必要がないという背景

DICとTMAの関係

REVIEW Open Access

Differences and similarities between disseminated intravascular coagulation and thrombotic microangiopathy

Hideo Wada[1*], Takeshi Matsumoto[2], Kei Suzuki[3], Hiroshi Imai[3], Naoyuki Katayama[4], Toshiaki Iba[5] and Masanori Matsumoto[6]



DICとTMAの併存

Fig. 2 Mecha
factor; ULM-V

DICとTMA(aHUS)の併存

Clinical Case Report

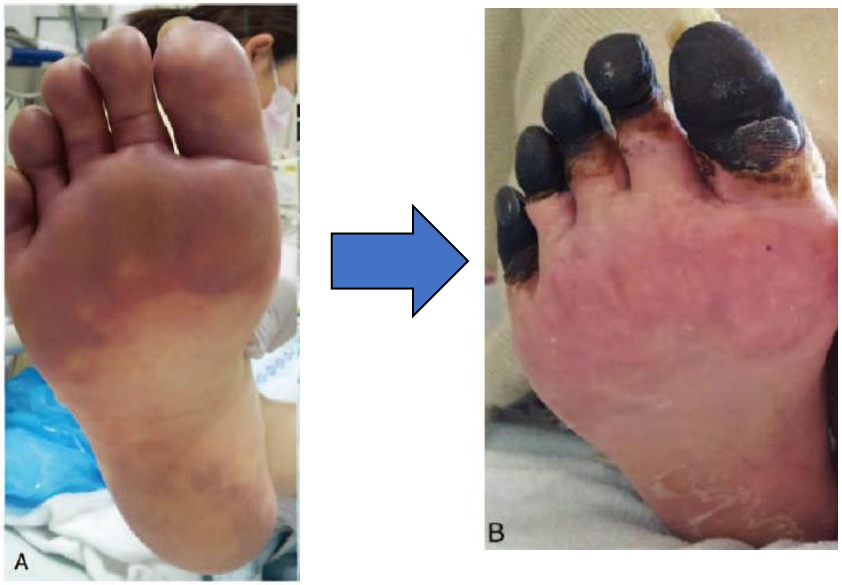
Medicine

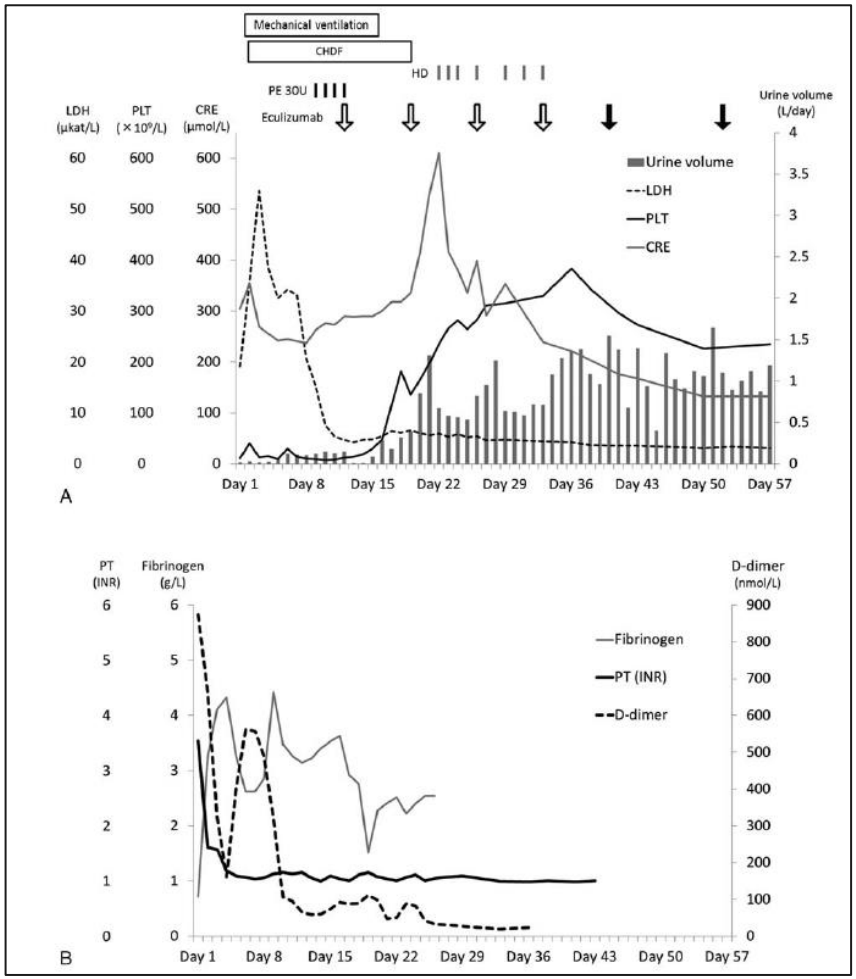
OPEN

Complement-mediated thrombotic microangiopathy secondary to sepsis-induced disseminated intravascular coagulation successfully treated with eculizumab

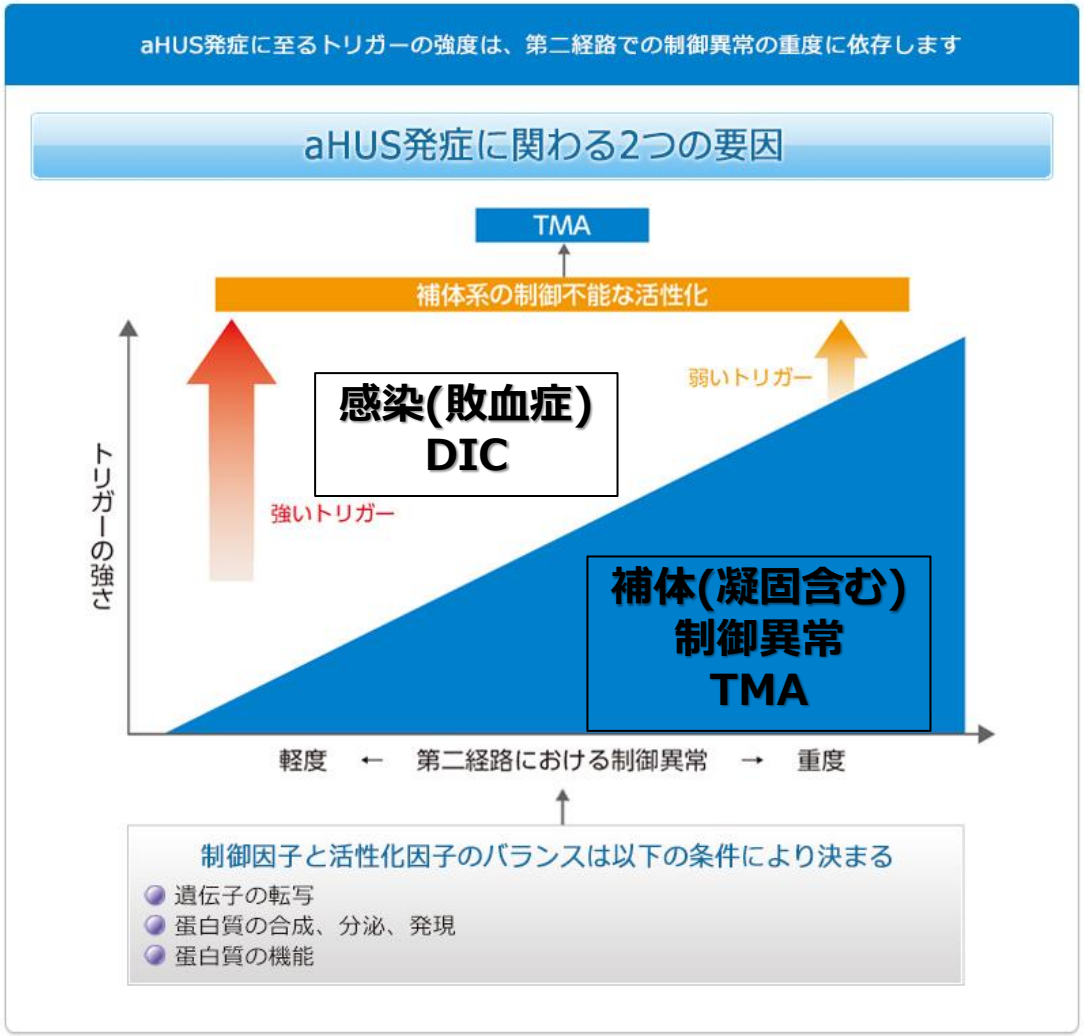
A case report

Tomohiro Abe, MD[a,*], Akira Sasaki, MD[a], Taichiro Ueda, MD[a], Yoshitaka Miyakawa, MD, PhD[b], Hidenobu Ochiai, MD, PhD[a]





aHUS発症に関わる要因



アレクシオンファーマHPより

DICとaHUSの併存

From Lecture Slides of Wai Lim, MD

Asif, A et al. *J Nephrol.* 2017;30:347-362.

- DICとaHUSの併存
- Key mediatorはトロンボモジュリン

補体制御遺伝子の機能異常に補体を活性化させる
CAC(Complement-Amplifying Condition)が加わりTMA発症

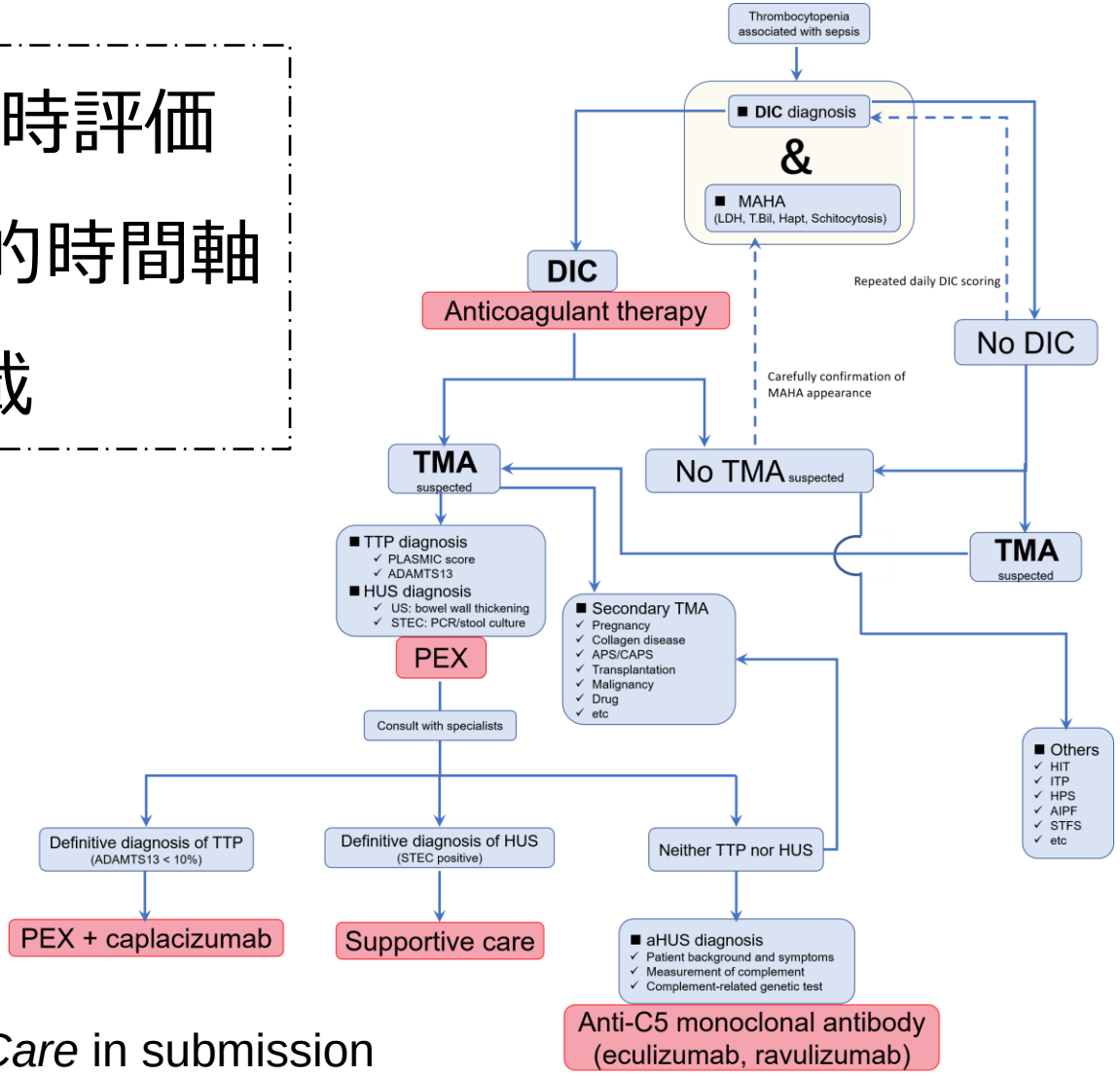
TTP：ADAMTS13

ADAMTS-13はトロンビンや好中球エラスターゼにより分解される

DICとTTPの併存？

総括：DIC診療中は常にTMAを疑う

- DIC & MAHA 同時評価
- TMA診断に臨床的時間軸
- 特異的治療の記載



Journal of Intensive Care in submission

J-SSCG2020: CQ15-3～6の推奨

CQ15-3 敗血症性 DIC にアンチトロンビンの補充を行うか？

Answer: 敗血症性 DIC 患者に対してアンチトロンビンの補充療法を行うことを弱く推奨する（GRADE2C エビデンスの確実性＝低）

CQ15-4 敗血症性 DIC にヘパリン，ヘパリン類の投与を行うか？

Answer: 敗血症性 DIC 患者に対してヘパリン・ヘパリン類投与を標準治療として行わないことを弱く推奨する（GRADE 2D :エビデンスの確実性＝非常に低）。

CQ15-6 敗血症性 DIC にタンパク分解酵素阻害薬の投与を行うか？

Answer: 敗血症性 DIC 患者に対してタンパク分解酵素阻害薬投与を標準治療としては行わないことを弱く推奨する（GRADE2D エビデンスの確実性＝非常に低）

CQ15-5 敗血症性 DIC にリコンビナント・トロンボモジュリン投与を行うか？

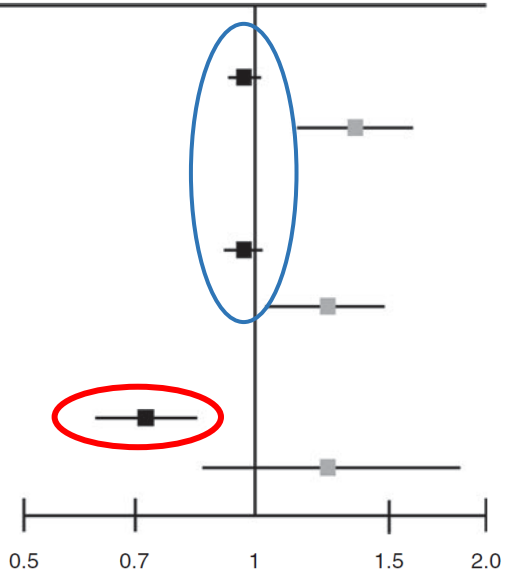
Answer: 敗血症性 DIC 患者に対してリコンビナント・トロンボモジュリン製剤を投与することを弱く推奨する（GRADE2C エビデンスの確実性＝低）

抗凝固療法の効果を検証した研究のメタ解析

Efficacy and safety of anticoagulant therapy in three specific populations with sepsis: a meta-analysis of randomized controlled trials

Umemura Y, *et al.* ***J Thromb Haemost*** 2016

Outcomes	Illustrative comparative risks [95% CI] Assumed risk Control	Corresponding risk Anticoagulant	Risk ratio M-H, Random, 95% CI	No. of participants [No. of studies]	NNT or NNH [95% CI]
Overall population of sepsis					
All-cause mortality	337 per 1000	327 per 1000 [310, 344]	0.97 [0.92, 1.02]	14767 [24 studies]	not calculated
Bleeding complications	57 per 1000	76 per 1000 [64, 89]	1.33 [1.12, 1.57]	14359 [20 studies]	44 [24, 222]
Population of sepsis-induced coagulopathy					
All-cause mortality	387 per 1000	375 per 1000 [348, 411]	0.97 [0.88, 1.08]	2629 [5 studies]	not calculated
Bleeding complications	155 per 1000	195 per 1000 [164, 232]	1.26 [1.06, 1.50]	1854 [2 studies]	22 [11, ∞]
Population of sepsis-induced DIC					
All-cause mortality	400 per 1000	288 per 1000 [248, 340]	0.72 [0.62, 0.85]	1603 [7 studies]	13 [8, 27]
Bleeding complications	61 per 1000	77 per 1000 [52, 113]	1.26 [0.86, 1.85]	1566 [6 studies]	not calculated



治療すべき対象は”Sepsis”ではなく、”Sepsis with DIC”

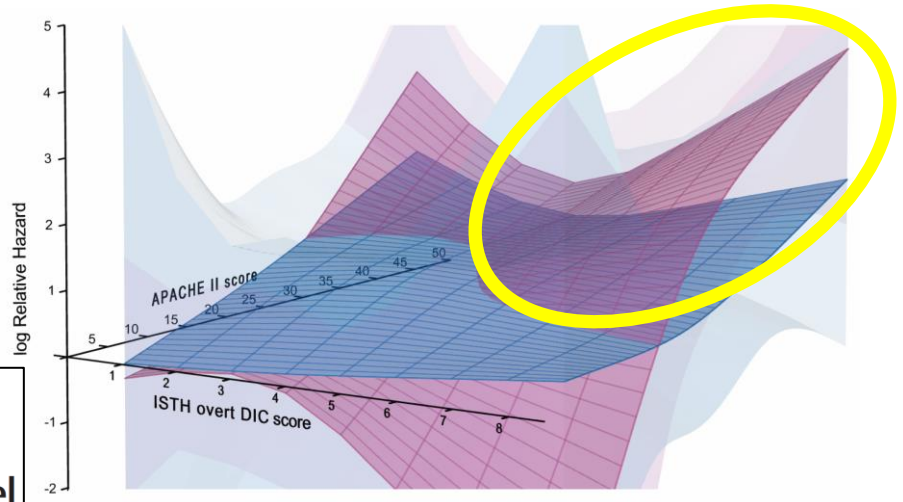
抗凝固療法を受けるべき患者は? JAAM FORECAST

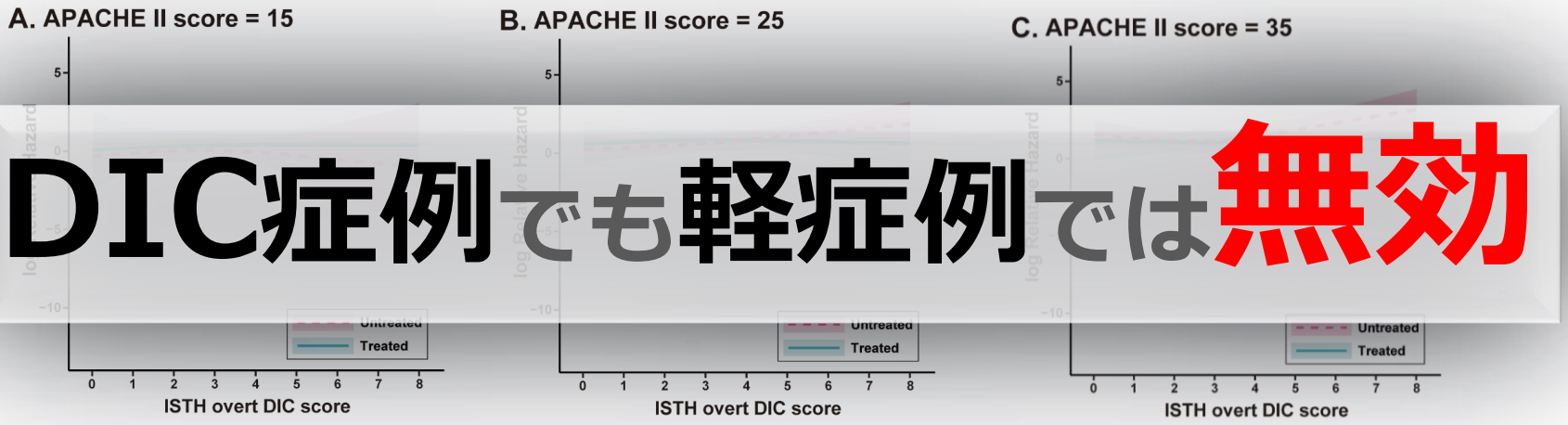
The Japanese Association for Acute Medicine Focused Outcomes Research in Emergency Care in ARDS, Sepsis, Trauma

- Multicenter, involving 59 ICUs in Japan
- Prospective cohort study
- 1,184 severe sepsis patients

Identifying Sepsis Populations Benefitting from Anticoagulant Therapy: A Prospective Cohort Study Incorporating a Restricted Cubic Spline Regression Model

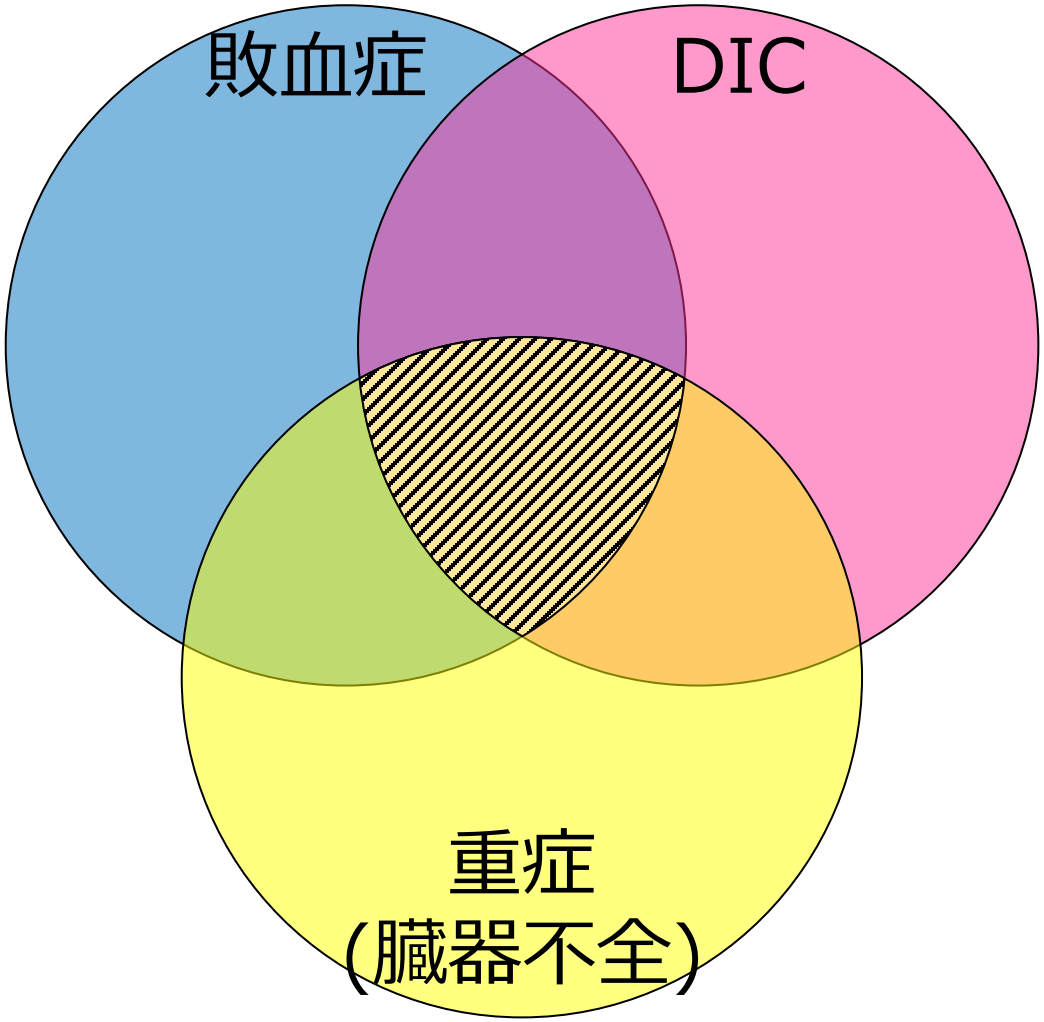
K. Yamakawa, *et al.* ***Thromb Haemost*** 2019





DIC症例でも軽症例では無効

抗凝固療法を受けるべき患者は?



遺伝子組換えトロンボモジュリン

この視点で

SCARLET trial

をみてみよう

SCARLET trial

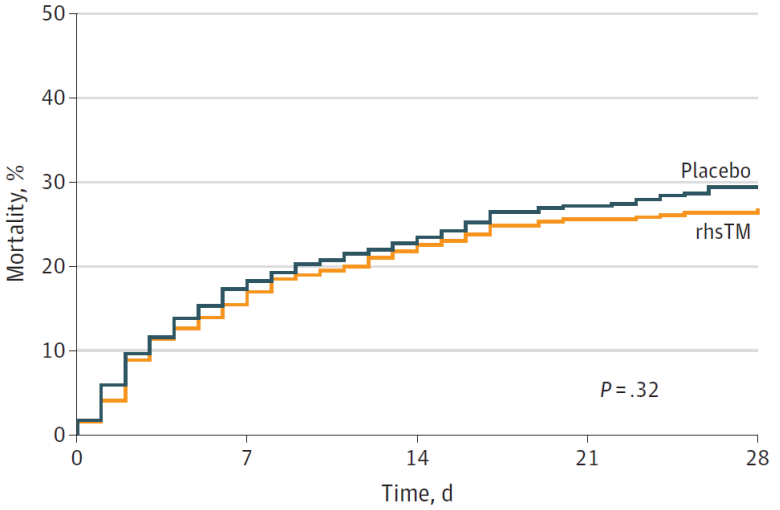
Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy

The SCARLET Randomized Clinical Trial

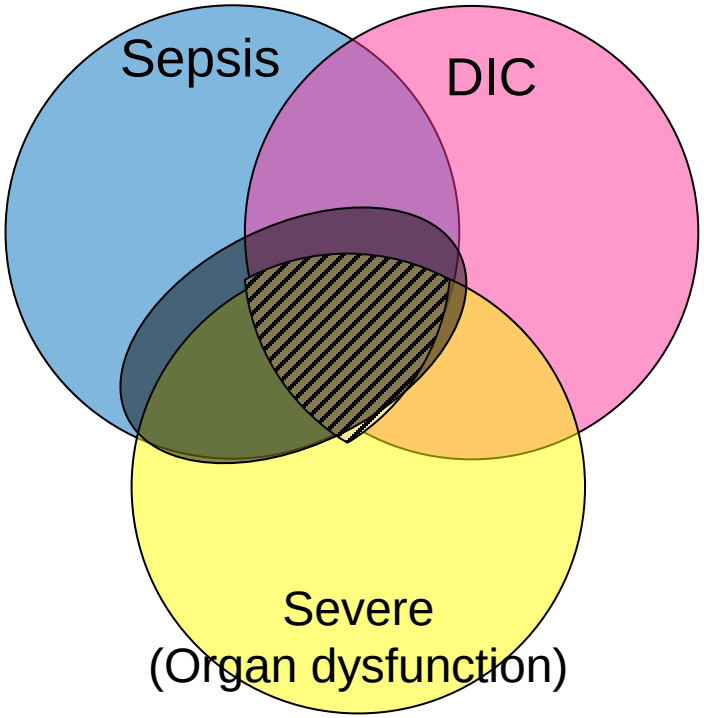
Vincent JL, *et al.* ***JAMA*** 2019



SCARLET trialの解釈をもう少し詳細に

◆Inclusion criteria

- ➢Bacterial infection and a known site of infection
- ➢Cardiovascular dysfunction or respiratory failure due to sepsis
- ➢Coagulopathy: PT-INR>1.4 and 30,000mm^3<Plt<150,000mm^3



	JAAM DIC (n = 292)	Non-DIC (n = 332)	P value
Age (years)	69 ± 18	69 ± 15	0.575
Gender (male/female)	181/111	210/122	0.744
Septic shock (%)	56.2	35.5	<0.001
Positive blood culture (%)	49.5	33.9	<0.001
JAAM DIC score	5.6 ± 1.3	1.9 ± 0.9	<0.001
Platelet counts (× 10^9/l)	89 ± 88	215 ± 111	<0.001
Prothrombin time (seconds)	19.5 ± 9.5	16.1 ± 5.1	<0.001
Prothrombin time ratio	1.63 ± 0.64	1.40 ± 0.56	<0.001
Fibrinogen (g/l)	3.96 ± 1.96	4.83 ± 1.99	<0.001
FDP (mg/l)	62.5 ± 104.7	10.6 ± 6.7	<0.001
SIRS score	3.3 ± 0.8	3.1 ± 0.9	0.007
APACHE II score	25.2 ± 8.5	21.9 ± 7.9	<0.001
SOFA score	10.6 ± 3.8	6.7 ± 3.3	<0.001
MODS (%)	65.4	40.4	<0.001
28-day outcome (death/%)	91/31.2	53/16.0	<0.001
Hospital outcome (death/%)	112/38.4	72/21.7	<0.001

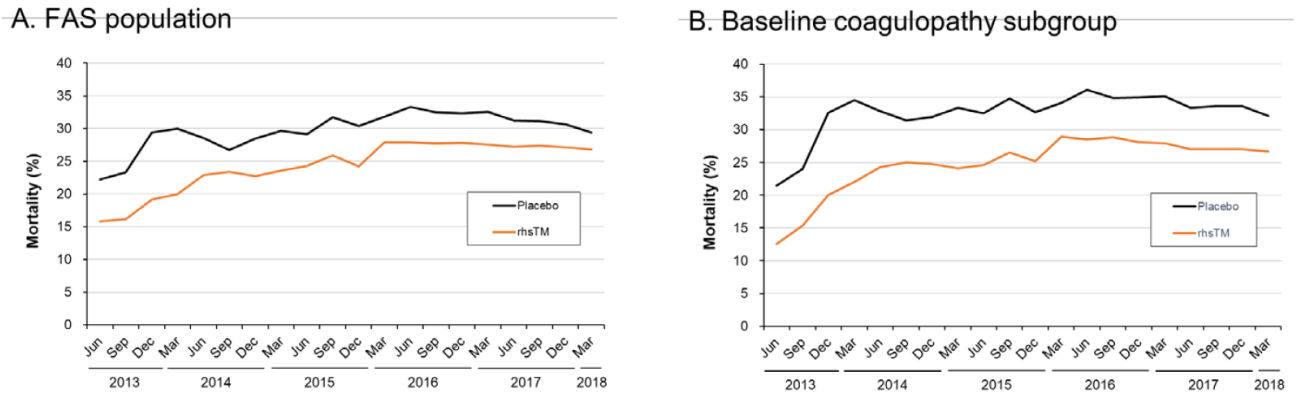
Gando S, *et al.* ***Crit Care*** 2013

Supplemental contentもきっちりみてみよう

eFigure 1. Subgroup analysis of 28-day mortality rate stratified by baseline characteristics

Subgroup	No. of patients		Mortality No.(%)		Favors Placebo	Favors rhsTM	Difference of mortality % (95% CI)
	Placebo	rhsTM	Placebo	rhsTM			
All patients	405	395	119 (29.4)	106 (26.8)			2.55 (-3.68 - 8.77)
Baseline coagulopathy *							
Yes	327	307	105 (32.1)	82 (26.7)			5.40 (-1.68 - 12.48)
No (1)	70	76	10 (14.3)	15 (19.7)			-5.45 (-17.59 - 6.68)
No (2)	11	13	4 (36.4)	9 (69.2)			-32.87 (-70.78 - 5.05)
Baseline PT-INR							
> 1.4	335	319	109 (32.5)	91 (28.5)			4.01 (-3.04 - 11.06)
≤ 1.4	70	76	10 (14.3)	15 (19.7)			-5.45 (-17.59 - 6.68)

eFigure 2. Transition of 28-day mortality rate through the trial for the 2 treatment arms in the full analysis set (FAS) population (panel A) and in the baseline coagulopathy subgroup (panel B).



プロトコルの修正

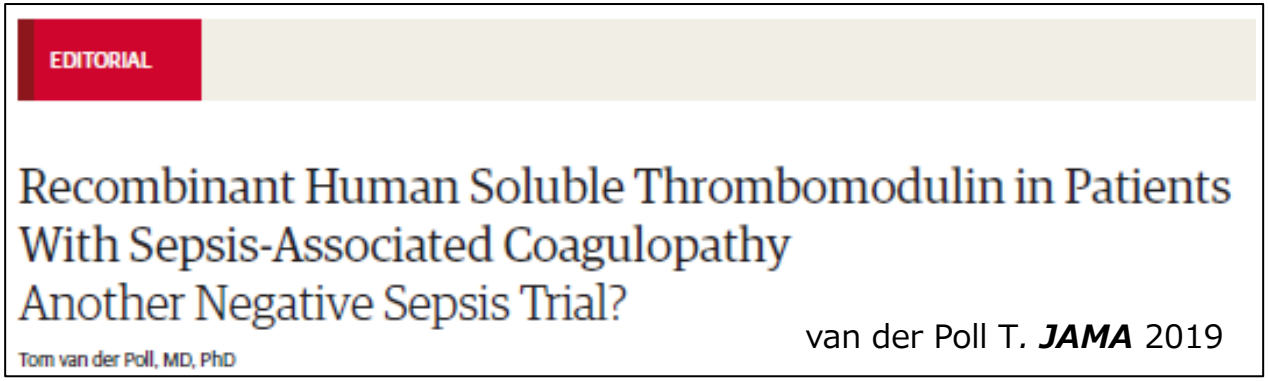
The time limit for the confirmation of inclusion criteria was modified during the study after protocol version 4.0 was implemented, substantially lengthening the maximum time between the first qualifying INR measure and the first dose of rhsTM or placebo from 15 hours to 40 hours. The purpose of this change was to provide more time for investigators to enroll participants because the 15-hour restriction affected the ability to identify and enroll patients in a timely manner. The

- 治験登録時から治験薬投与開始までの間に凝固異常が改善した患者⇒軽症？？
- 6回の投与予定に対して半分以下の投与しかできなかった患者

⇒軽すぎて退院（ICU退室）した？？

重症過ぎて死亡？？

SCARLET trialの解釈



EDITORIAL

Recombinant Human Soluble Thrombomodulin in Patients With Sepsis-Associated Coagulopathy
Another Negative Sepsis Trial?

Tom van der Poll, MD, PhD

van der Poll T. ***JAMA*** 2019

It may be important to consider **modifying enrollment criteria.**

rTM seemed to be most beneficial for patients who **did not receive heparin**.

SCARLETのサブ解析 フランス

François et al. Ann. Intensive Care (2021) 11:53
https://doi.org/10.1186/s13613-021-00842-4

Annals of Intensive Care

RESEARCH Open Access

Efficacy and safety of human soluble thrombomodulin (ART-123) for treatment of patients in France with sepsis-associated coagulopathy: post hoc analysis of SCARLET

Table 3 Efficacy of ART-123 vs placebo in France and ROW

Mortality rate, %	Subpopulation	ART-123	Placebo	ARR (95% CI)
FAS	Global	26.8	29.4	2.55 (−3.68, 8.77)
	France	17.3	25.7	8.3 (−4.79, 21.47)
	ROW	29.1	30.2	1.1 (−5.87, 8.16)
Baseline coagulopathy[a]	France	15.6	29.0	13.4 (−0.97, 27.79)
	ROW	29.6	32.8	3.2 (−4.86, 11.26)
No baseline heparin	France	13.0	29.5	16.6 (0.4, 32.77)
	ROW	29.7	31.8	2.0 (−8.65, 12.74)

ARR absolute risk reduction, *CI* confidence interval, *FAS* full analysis set, *INR* international normalized ratio, *ROW* rest of world

[a] Coagulopathy was defined as INR > 1.4 without other known etiology and platelet count > 30×10^9/L at baseline

SCARLETのサブ解析　凝固線溶パラメーター

Effect of a Recombinant Human Soluble Thrombomodulin on Baseline Coagulation Biomarker Levels and Mortality Outcome in Patients With Sepsis-Associated Coagulopathy

Marcel Levi, MD, PhD, FRCP[1]; Jean-Louis Vincent, MD, PhD, FCCM[2]; Kosuke Tanaka, MEng[3]; Amanda H. Radford, MS, RD[3]; Toshihiko Kayanoki, BS[3]; David A. Fineberg, MD, MBA[3]; Debra Hoppensteadt, PhD[4]; Jawed Fareed, PhD, FAHA[4]

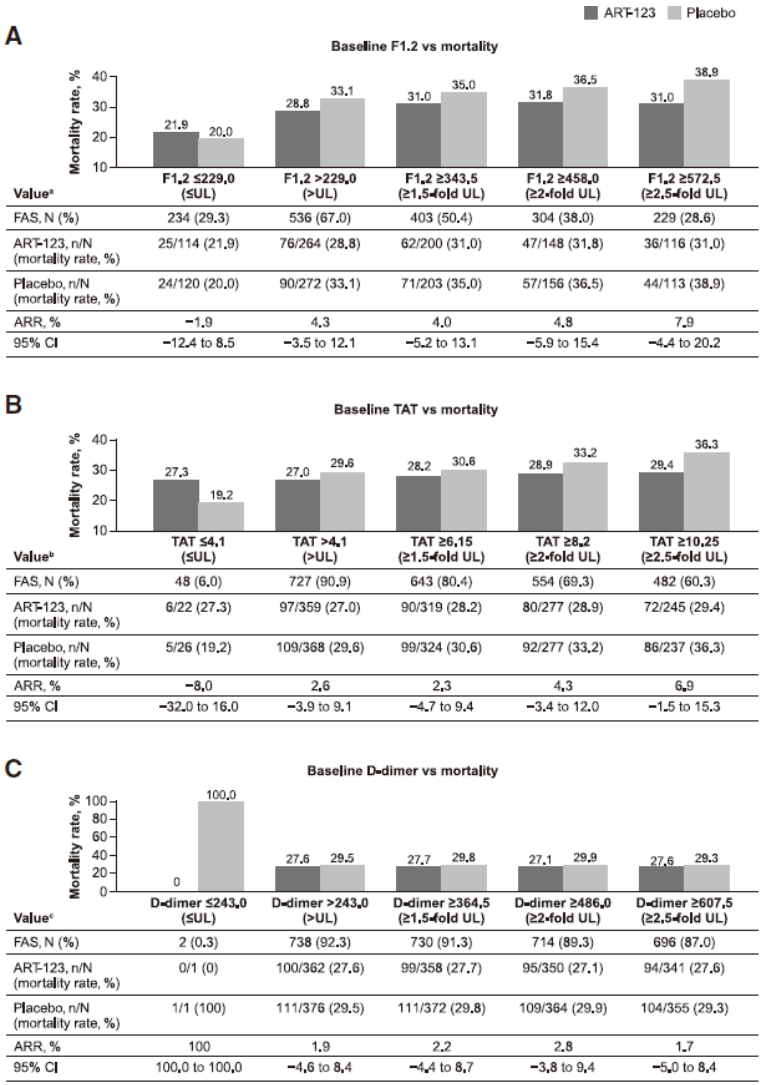
Levi, M et al. *Crit Care Med*. 2020

TABLE 3. Association of Baseline Coagulation Biomarkers With 28-Day All-Cause Mortality in the Post Hoc Analysis in the Full Analysis Set Population of the Sepsis Coagulopathy Asahi Recombinant LE Thrombomodulin Trial

Biomarker	Subgroup Concentration Relative to Median Value in Full Analysis Set[a]	Recombinant Human Soluble Thrombomodulin ($n = 395$) n (%)[b]	Placebo ($n = 405$) n (%)[b]	Absolute Risk Reduction (%) of 28-d All-Cause Mortality	(95% CI)
Prothrombin fragment 1.2, pmol/L[c]	< 358.9	42/187 (22.5)	45/198 (22.7)	0.3	(−8.1 to 8.6)
	≥ 358.9	59/191 (30.9)	69/194 (35.6)	4.7	(−4.7 to 14.1)
Thrombin-antithrombin complex, ng/mL[d]	< 14.2	41/187 (21.9)	41/199 (20.6)	−1.3	(−9.5 to 6.9)
	≥ 14.2	62/194 (32.0)	73/195 (37.4)	5.5	(−4.0 to 14.9)
D-dimer, ng/mL[e]	< 3,030	50/173 (28.9)	57/197 (28.9)	0.0	(−9.2 to 9.3)
	≥ 3,030	50/190 (26.3)	55/180 (30.6)	4.2	(−5.0 to 13.4)

[a]Median values were calculated from baseline values in full analysis set.
[b]Ratio is number of patients with a particular biomarker result who were deceased by day 28 to number of patients with data for the particular biomarker.
[c]Data were unavailable for 30 patients.
[d]Data were unavailable for 25 patients.
[e]Data were unavailable for 60 patients.

凝固亢進が顕著な症例(厳密な**DIC**)ではrhTMは効きそう



機械学習を用いた敗血症性DICと抗凝固療法(rTM)の研究

RESEARCH Open Access

Coagulation phenotypes in sepsis and effects of recombinant human thrombomodulin: an analysis of three multicentre observational studies

Table 1 Characteristics of patients in the derivation cohort according to clusters

Variables	Overall n = 3694	Cluster dA n = 323	Cluster dB n = 629	Cluster dC n = 1147	Cluster dD n = 1595	P*
Platelet (10^3/μL), median (IQR)	122.0 (65.0, 194.0)	59.5 (32.0, 92.0)	78.0 (46.5, 128.0)	103.0 (54.0, 162.0)	178.0 (121.0, 252.0)	< 0.001
PT-INR, median (IQR)	1.3 (1.2, 1.6)	1.6 (1.4, 2.1)	1.7 (1.5, 2.2)	1.3 (1.2, 1.5)	1.2 (1.1, 1.4)	< 0.001
Fibrinogen (mg/mL), median (IQR)	421.0 (296.0, 528.0)	231.0 (151.0, 311.0)	245.3 (157.0, 350.0)	452.0 (367.0, 563.0)	476.9 (395.3, 576.0)	< 0.001
FDP (μg/mL), median (IQR)	17.6 (10.1, 36.2)	120.2 (79.2, 266.0)	16.0 (10.4, 24.0)	34.3 (22.8, 55.1)	10.0 (7.6, 13.8)	< 0.001

dA群
凝固障害が重度
臓器障害＋
死亡率高い

dA群のみ
rTMで
死亡率低下

SSCG2021発表

Intensive Care Med
https://doi.org/10.1007/s00134-021-06506-y

GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

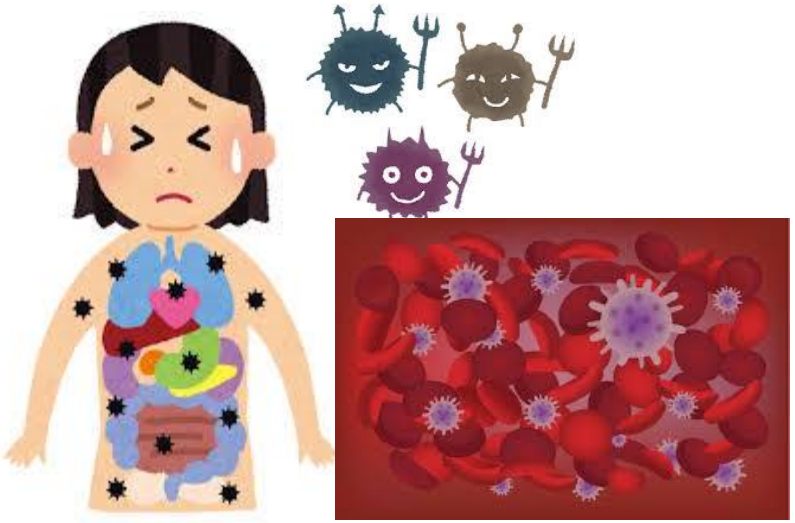
rhTM, antithrombinはおろか、
”DIC”も消滅

Laura Evans[1*], Andrew Rhodes[2], Waleed Alhazzani[3], Massimo Antonelli[4], Ruth M. Coopersmith[5], Craig French[6], Flávia R. Machado[7], Lauralyn Mcintyre[8], Marlies Ostermann[9], Hallie C. Prescott[10], Christa Schorr[11], Steven Simpson[12], W. Joost Wiersinga[13], Fayez Alshamsi[14], Derek C. Angus[15], Yaseen Arabi[16], Luciano Azevedo[17], Richard Beale[9], Gregory Beilman[18], Emilie Belley-Cote[19], Lisa Burry[20], Maurizio Cecconi[21,22], John Centofanti[23], Angel Coz Yataco[24], Jan De Waele[25], R. Phillip Dellinger[11], Kent Doi[26], Bin Du[27], Elisa Estenssoro[28], Ricard Ferrer[29], Charles Gomersall[30], Carol Hodgson[31], Morten Hylander Møller[32], Theodore Iwashyna[33], Shevin Jacob[34], Ruth Kleinpell[35], Michael Klompas[36,37], Younsuck Koh[38], Anand Kumar[39], Arthur Kwizera[40], Suzana Lobo[41], Henry Masur[42], Steven McGloughlin[43], Sangeeta Mehta[44], Yatin Mehta[45], Mervyn Mer[46], Mark Nunnally[47], Simon Oczkowski[3], Tiffany Osborn[48], Elizabeth Papathanassoglou[49], Anders Perner[50], Michael Puskarich[51], Jason Roberts[52,53,54,55], William Schweickert[56], Maureen Seckel[57], Jonathan Sevransky[5], Charles L. Sprung[58,59], Tobias Welte[60], Janice Zimmerman[61] and Mitchell Levy[62]

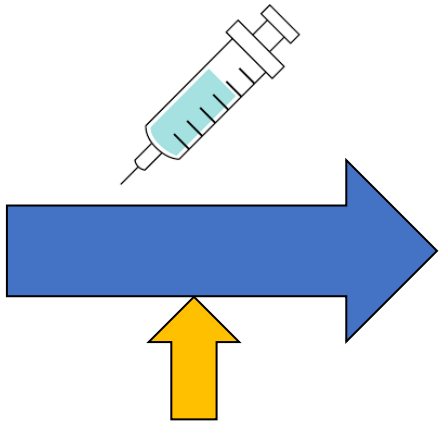
今後は、、、

敗血症では
DICは
治療する必要はない

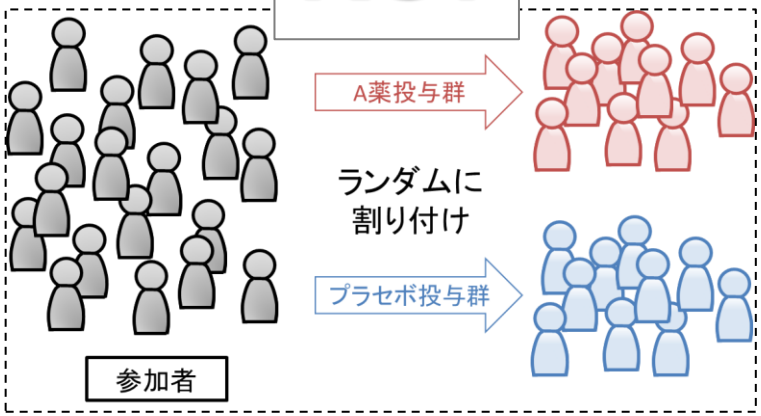
薬剤の効果検証の図式



「敗血症性DIC」



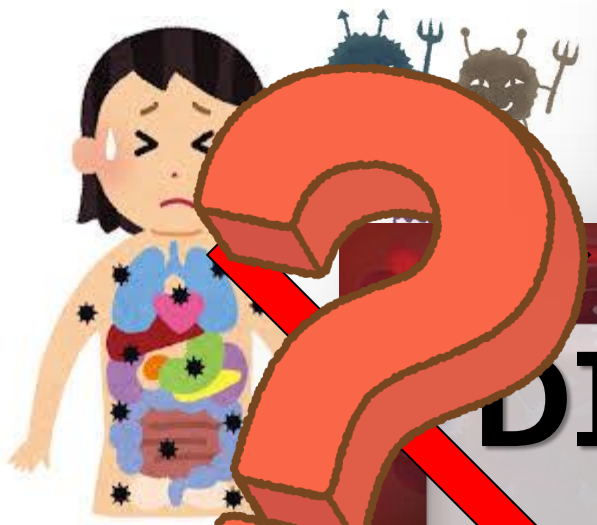
RCT



生

死

RCTで薬剤の効果が否定された場合



「敗　症性DIC」

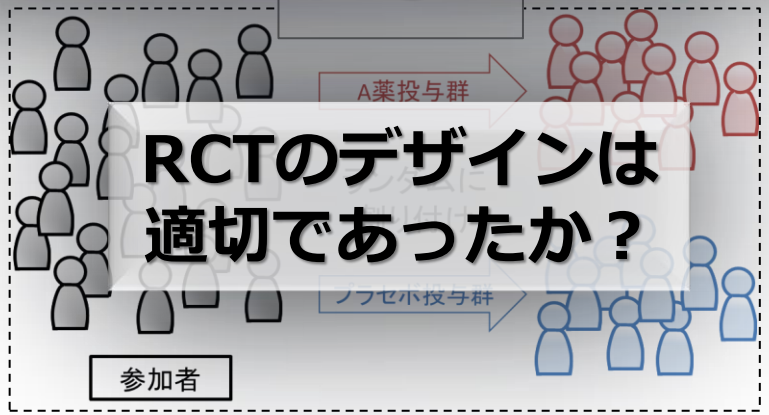
薬剤〇〇は敗血症性DICに効果がない

DICは治療する必要がない

生

生死で薬剤の効果を判定してよい？

RCT



RCTのデザインは適切であったか？

敗血症臨床研究における”outcome”

- **Mortalityのみのoutcomeで薬剤が「効く」「効かない」は判断できないのでは？**
- **適切なoutcomeを評価していない研究から得られた結果で治療可否を判断するのは危険**

➢ Morbidityと併せた”mortality”の予後としての指標

➢ 臓器不全(SOFA)やDIC離脱率、PICSなど

重症敗血症症例の生存率向上のために

敗血症症例でのDIC診療・治療

A promising “sword” to confront the “formidable adversary”

- **正しい病態理解**に基づく治療戦略構築
- 適切な研究デザインでの治療効果評価

P: Patients

I : Intervention

C: Comparison

O: Outcome

今後の敗血症性DIC治療研究の方向性

Research design: PICO

P: Patient

I : Interve

C: Compa

O: Outcome

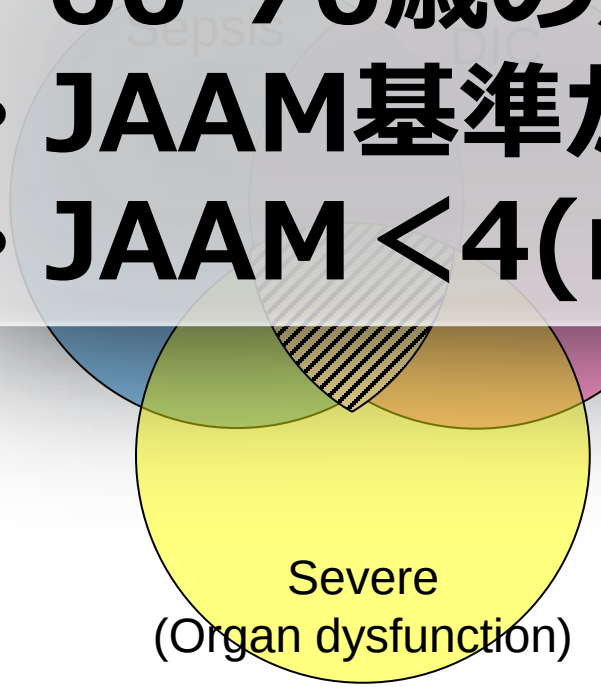
- この患者群をdetectする手法
- **簡便、どこででも使用可能**
- ATとの併用

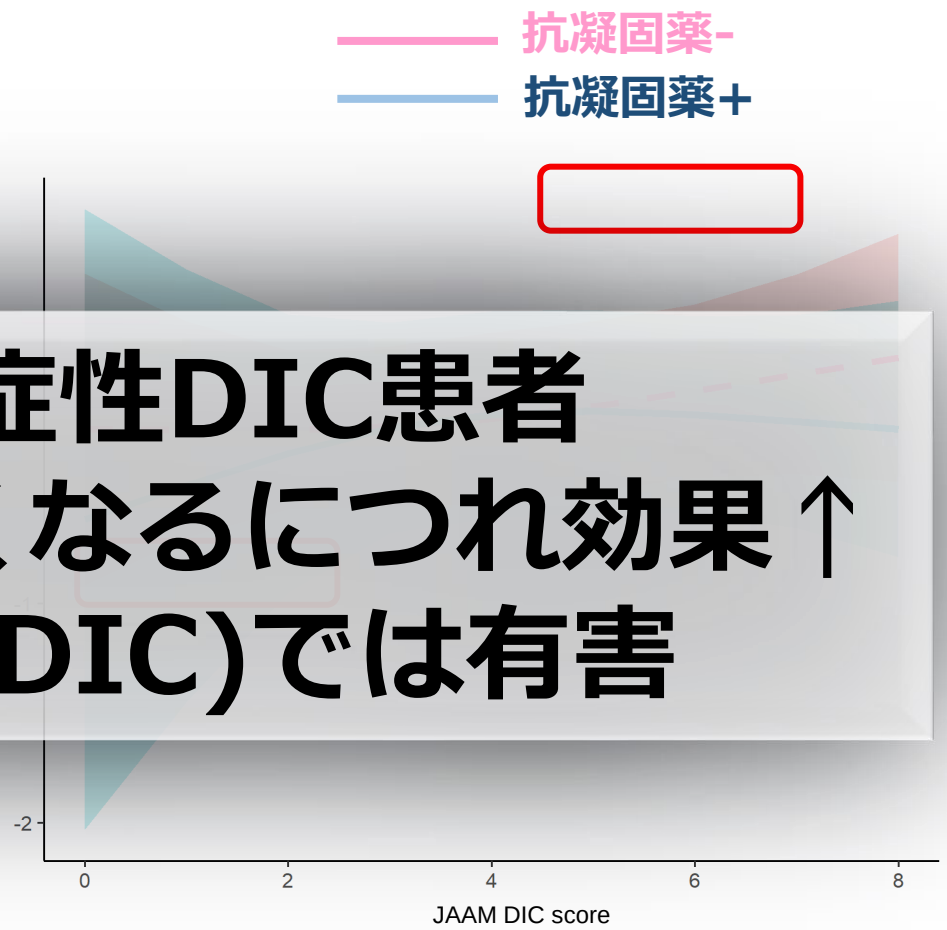
JAAM FORECAST sepsis①

OPEN **Age-related differences in the survival benefit of the administration of antithrombin, recombinant human thrombomodulin, or their combination in sepsis**

Wada T et al. Sci Rep;12:9304, 2022

- **60-70歳の敗血症性DIC患者**
- **JAAM基準が高くなるにつれ効果↑**
- **JAAM＜4(non-DIC)では有害**





Global P-value for anticoagulant=0.773
Global P-value for JAAM DIC score=0.777
P-value for 2-way interaction=0.687

JAAM FORECAST sepsis②

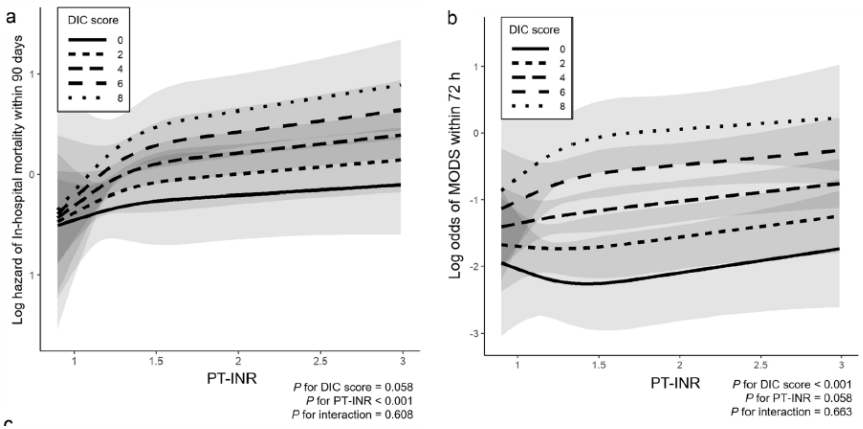
Wada et al. Journal of Intensive Care (2023) 11:8
https://doi.org/10.1186/s40560-023-00656-5

Journal of Intensive Care

RESEARCH Open Access

Sepsis-related coagulopathy treatment based on the disseminated intravascular coagulation diagnostic criteria: a post-hoc analysis of a prospective multicenter observational study

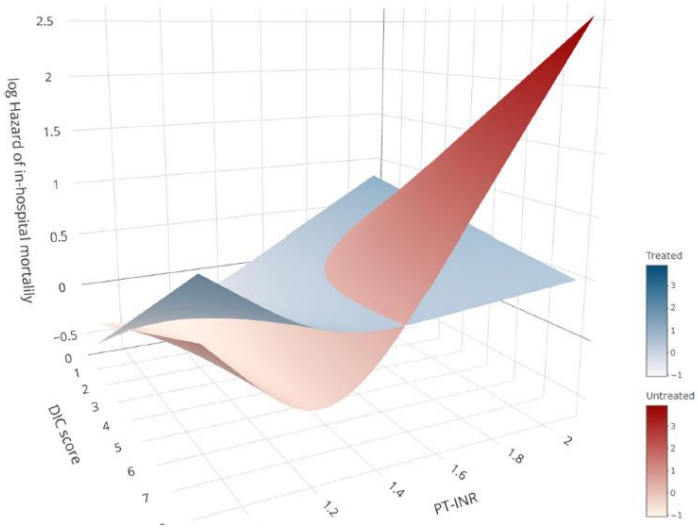
Takeshi Wada[1*], Kazuma Yamakawa[2], Daijiro Kabata[3], Toshikazu Abe[4,5], Seitaro Fujishima[6], Shigeki Kushimoto[7], Toshihiko Mayumi[8], Hiroshi Ogura[9], Daizoh Saitoh[10], Atsushi Shiraishi[11], Yasuhiro Otomo[12] and Satoshi Gando[1,13] on behalf of the JAAM FORECAST Group



Target: DICでかつ重症

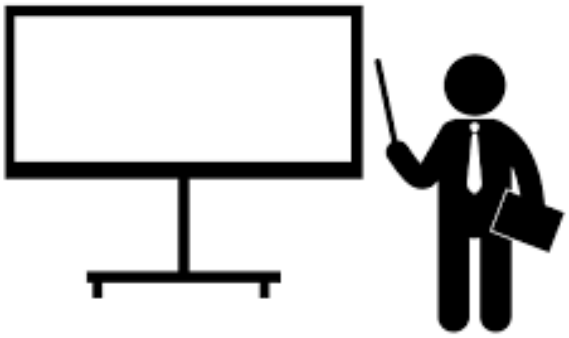
→JAAM基準+PTで評価できないか

- PTが高値でDICが重症になるほど死亡、多臓器不全↑
  (PT-INR1.5あたりまでが顕著)
- DIC重症かつPT-INR高くになるにつれ抗凝固療法の生存率改善効果が顕著
- その閾値は、**JAAM 5かつPT-INT 1.5**



本日の内容

- ◆ DIC診療の国内外の温度差を生んだ過去
- ◆ 本邦がDICを診療対象とする根拠
  - ✓ 確固たる病態概念
  - ✓ 予後への影響
- ◆ J-SSCG2020の骨子
  - ✓ DIC診断
  - ✓ 鑑別
  - ✓ 治療(rhTMを中心に)
- ◆ 今後の展望、まとめ



Take home message

DIC治療はガラパゴス？

→正し へ！

ご清聴ありがとうございました