



***THE ROLE OF EARLY INTERVENTION
WITH METHYLENE BLUE IN
MANAGEMENT OF SEPTIC SHOCK
PATIENTS***

BY

AHMED SALAH EL DIN OMRAN

LECTURER OF ANESTHESIA

AIN SHAMS UNIVERSITY



Corner stones of the inflammatory response initiation

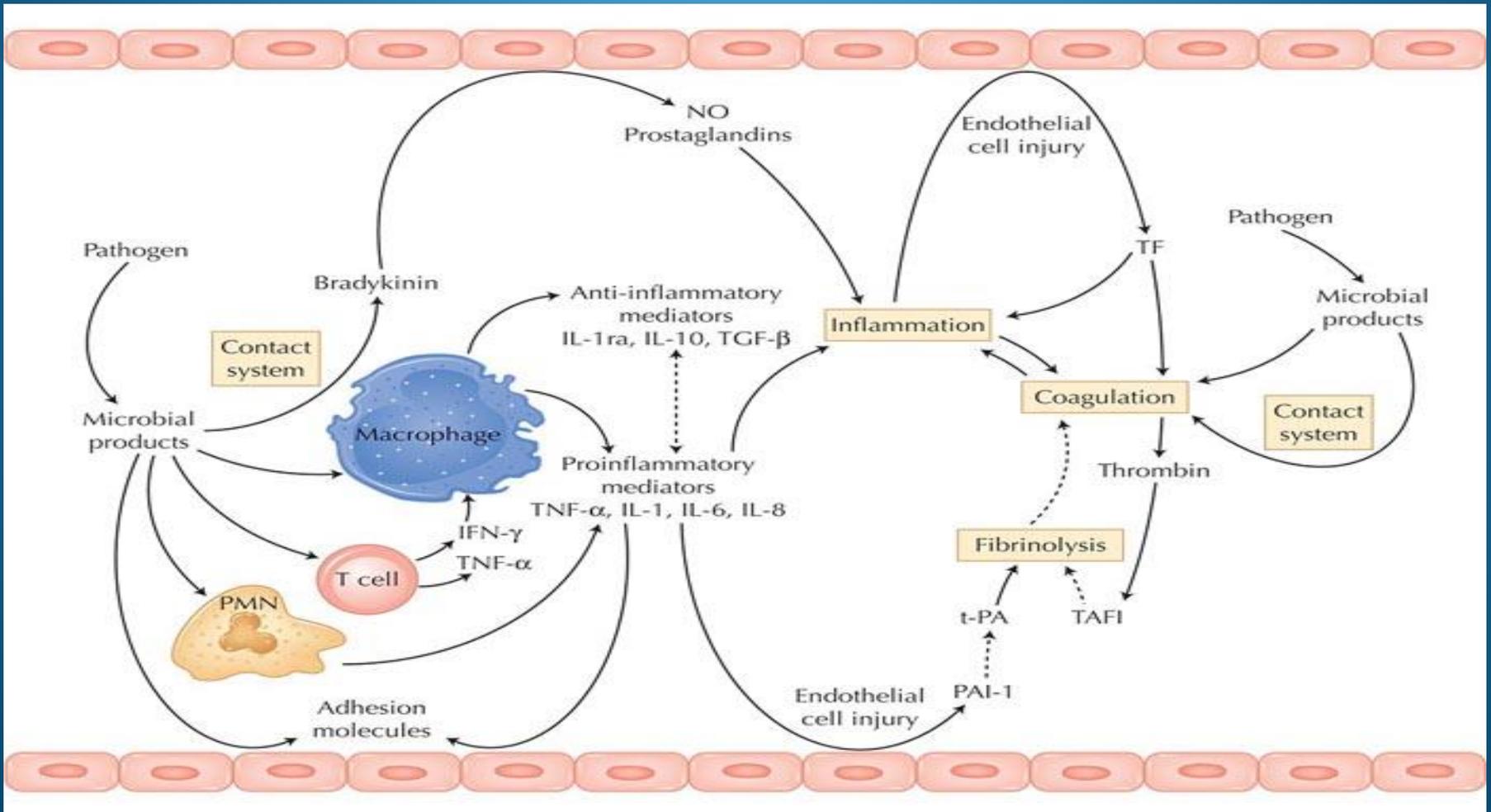
Neutrophil
activation
and oxygen
burst

Endothelial
injury

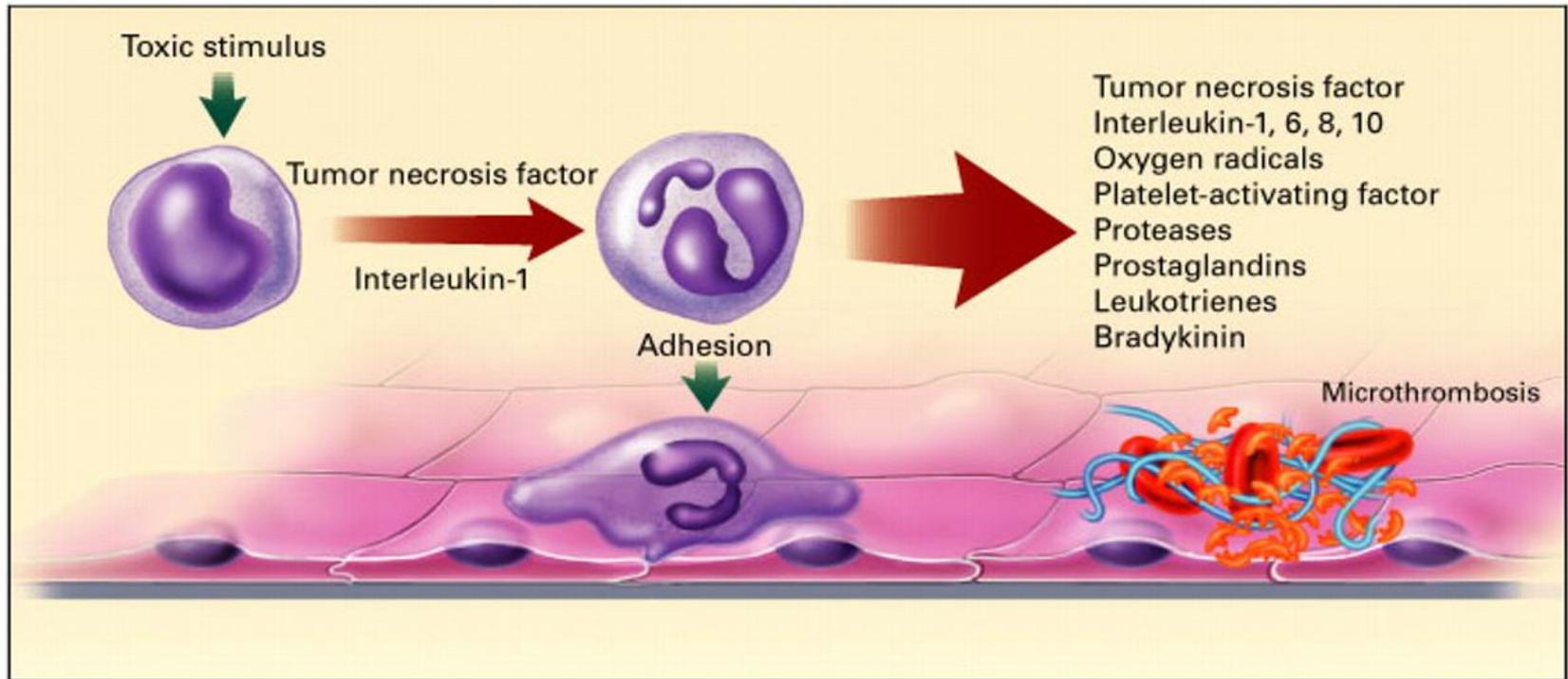
Coagulation
cascade

- Complement activation

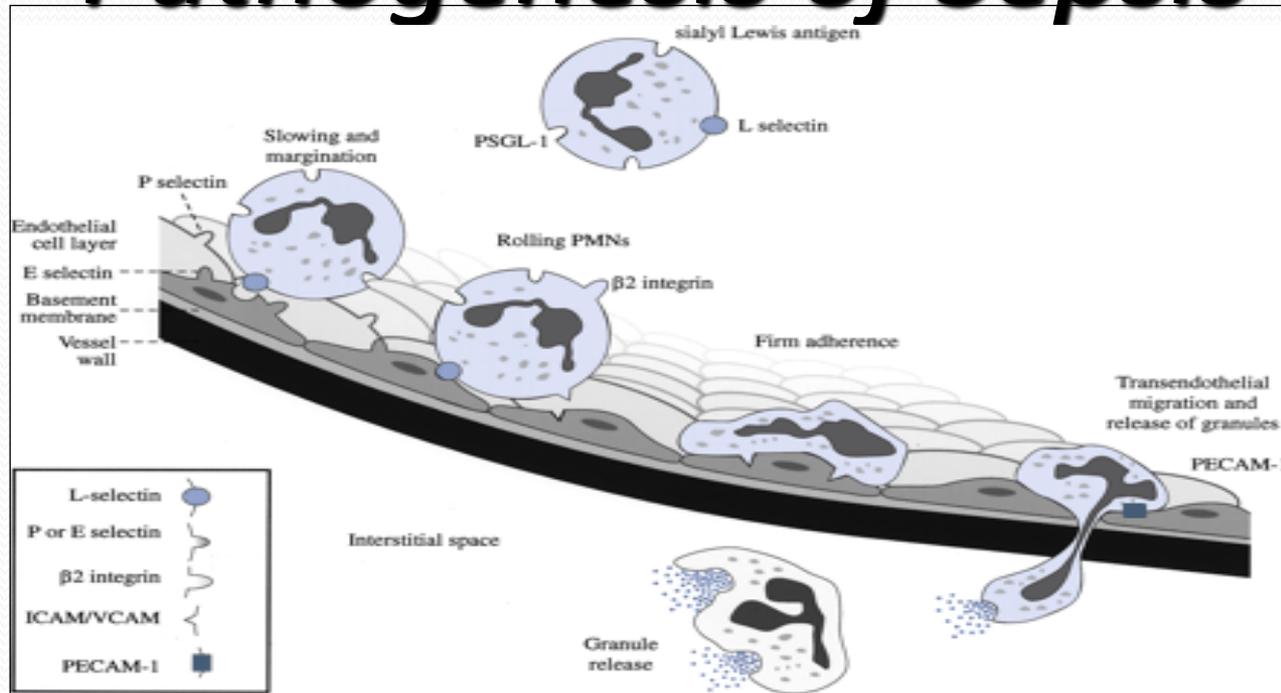
Pathogenesis of Sepsis



Pathogenesis of Sepsis



Pathogenesis of Sepsis



Mechanism of arrest and transmigration of neutrophils into the interstitial space. Neutrophils constitutively express L-selectin, which binds to endothelial cell glycoprotein ligands. Simultaneously, early response cytokines stimulate endothelial cells to rapidly express Pselectin and later E-selectin receptors, which weakly bind neutrophil

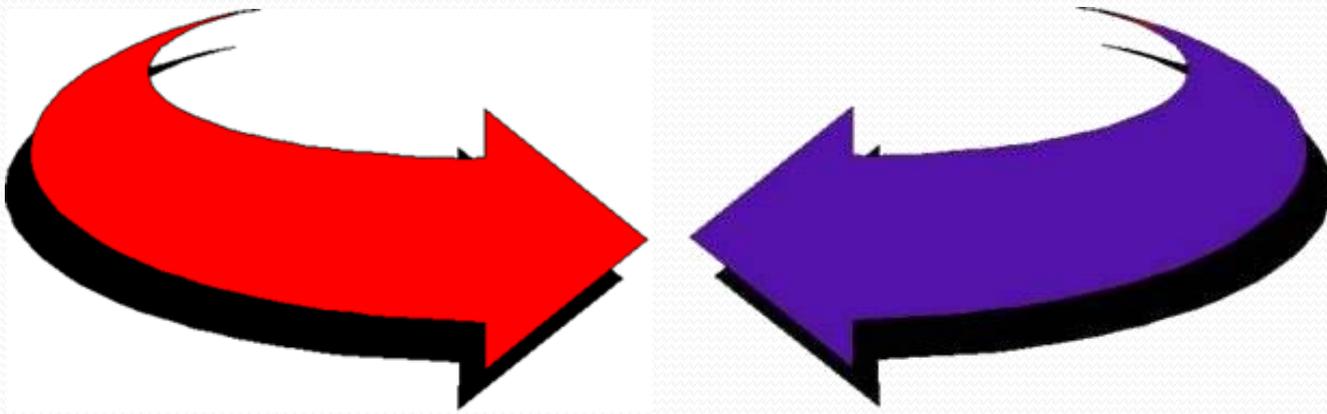


MODS is the failure of the balance

Uncontrolled inflammatory response

Anti-inflammatory reaction

IL-10, IL-4,
IL-1ra, Lipoxin
Cell elimination



Pro-inflammatory reaction

TNF- α , IL-1, IL-6, IFN
TXA₂, PAF
Cell activation

Systemic Inflammatory Response Syndrome (SIRS)

【Definition】

Anti-inflammatory reaction

IL-10, IL-4, TGF- β

IL-1ra, Lipoxin

Cell eliminate

- An uncontrolled inflammatory response
- Pro-inflammatory signals exceed normal domain or degree

Pro-inflammatory reaction

TNF- α , IL-1, IL-6, IFN

TXA₂, PAF

- Result in **Cell activation** and organ damage and multi-system failure.

Infection

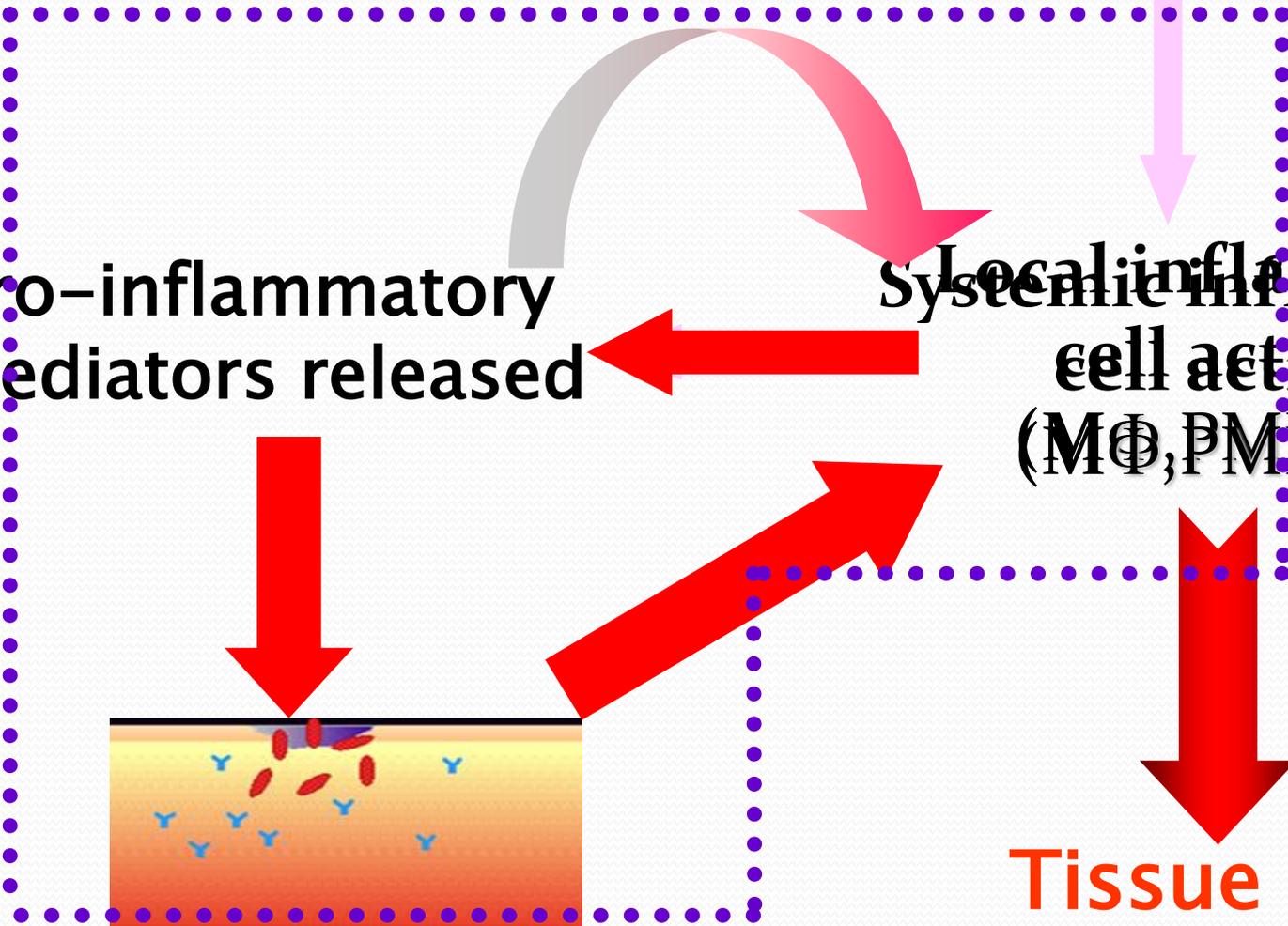
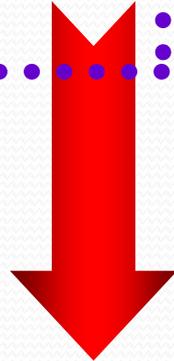
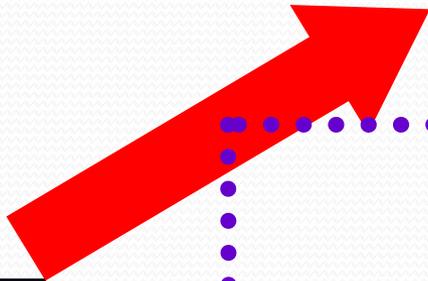
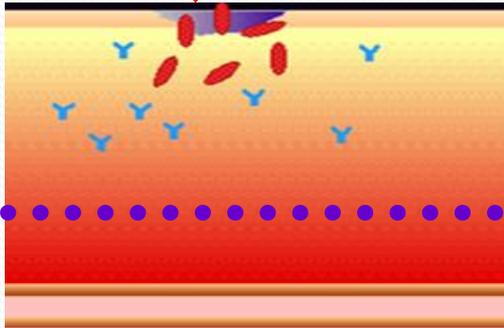


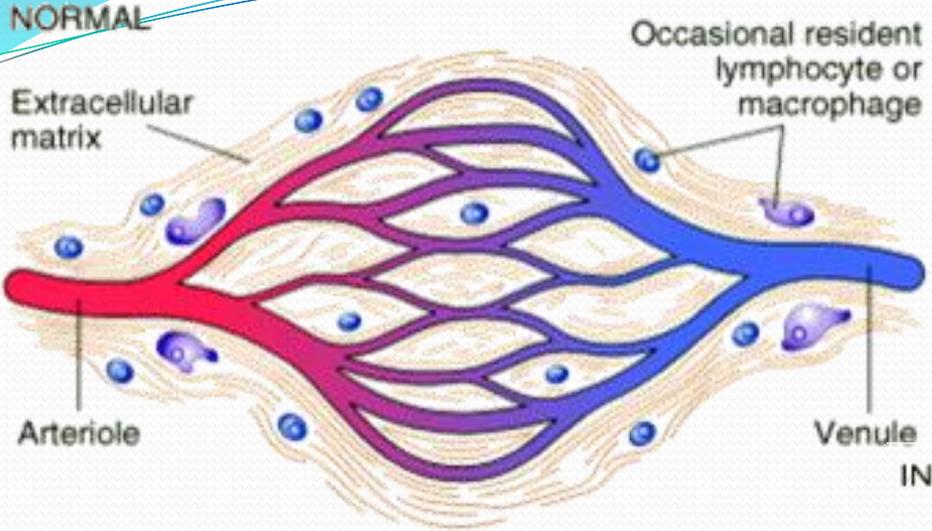
Inflammatory stimulator

Pro-inflammatory mediators released

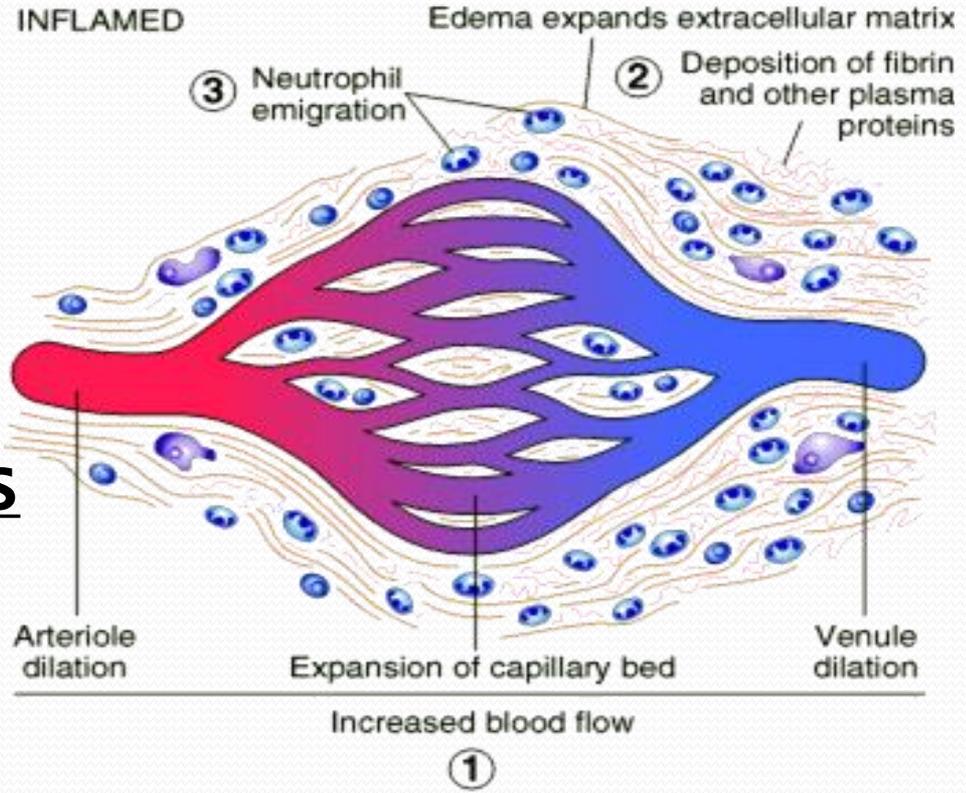
Systemic inflammatory cell activated
(MO, PMN, VEC,)

Tissue injury





Inflammation



Inflammatory cells

Inflammatory cytokines

The surviving sepsis campaign

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

- 1) Measure lactate level
- 2) Obtain blood cultures prior to administration of antibiotics
- 3) Administer broad spectrum antibiotics
- 4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

- 5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
- 6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
 - Measure central venous pressure (CVP)*
 - Measure central venous oxygen saturation (Scvo₂)*
- 7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥ 8 mm Hg, Scvo₂ of $\geq 70\%$, and normalization of lactate.



ANESTHESIA for the UNINTERESTED

by ALEXANDER A. BIRCH
and JOHN D. TOLMIE

University Park Press Baltimore · London · Tokyo



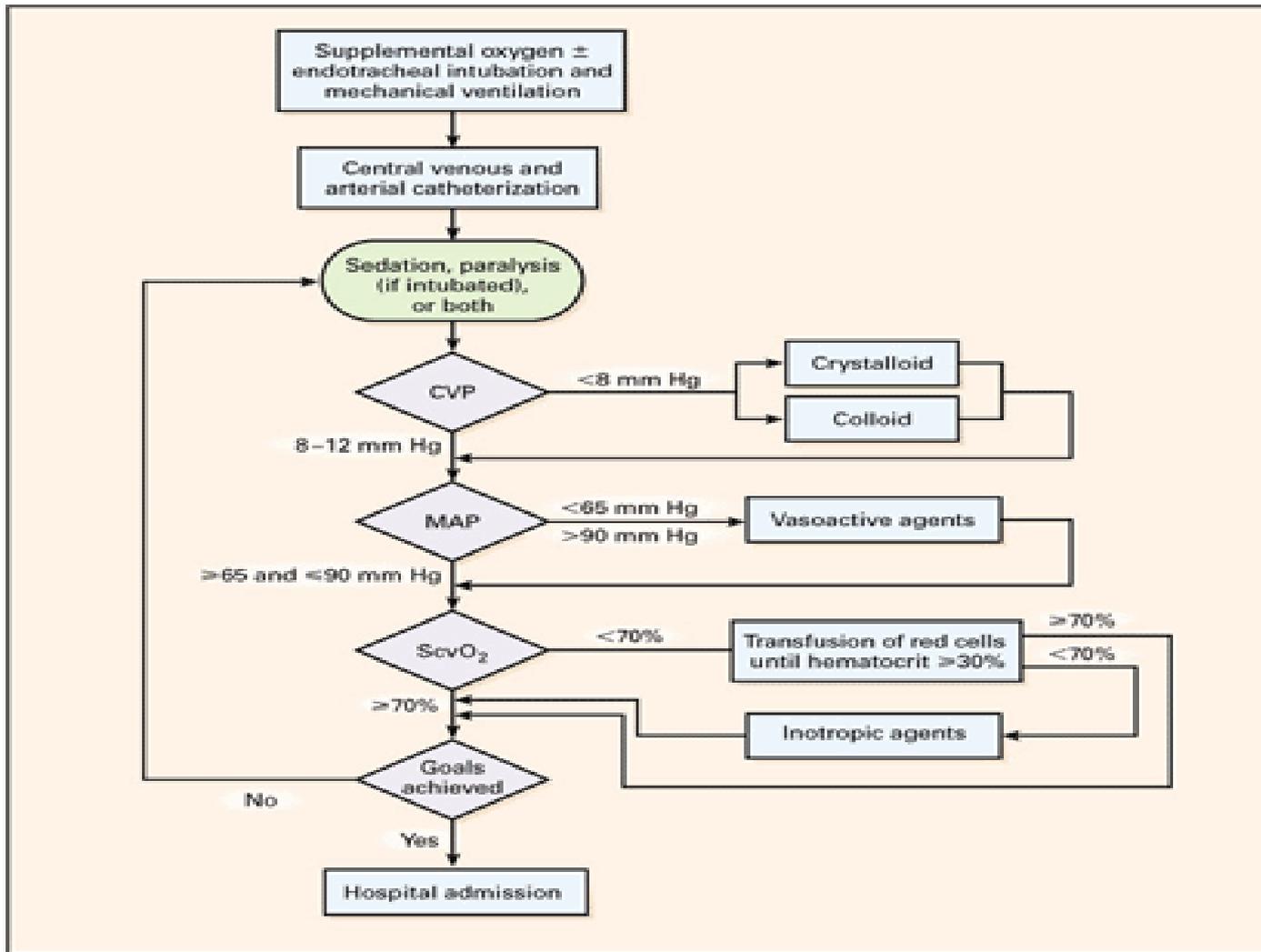
METHYLENE BLUE

- The discovery of nitric oxide as a mediator in the systemic inflammatory response rose the idea of preventing it by inhibiting nitric oxide. This was based on the knowledge of the role played by nitric oxide in guanylate cyclase enzyme activation, cyclic guanosine monophosphate production, and smooth vascular muscle relaxation

METHYLENE BLUE

- Methylene blue is believed to act through competition with nitric oxide, in binding to the iron heme-moiety of soluble guanylate cyclase resulting in enzyme activation. This inhibits the increases in the levels of cGMP, and thereby precludes its vasorelaxant effect in vascular smooth muscle .

GOAL DIRECTED THERAPY



PATIENTS AND METHODS

- Patients were eligible for the study if they fulfilled the criteria for severe sepsis diagnosed <72 hrs, and septic shock diagnosed <24 hrs before randomization, starting from norepinephrine dose $\geq 0.2 \mu\text{g}/\text{Kg}/\text{min}$ required to maintain mean arterial pressure (MAP) between 70 and 90 mmHg.
- The fluid resuscitation was considered adequate when additional infusion caused no further increase in cardiac index (CI), and pulmonary artery occlusion pressure remained between 8 and 18 mm Hg. Dobutamine was infused when required to maintain CI $>3.5 \text{ L}/\text{min}/\text{m}^2$.

PATIENTS AND METHODS

- **Study group (1)**: received methylene blue bolus in dose 1 mg/Kg followed after 2 hours by infusion 0.5 mg/Kg/hr for 4 hours.
- **Study group (2)**: included 20 patients received the same volume of normal saline by infusion.

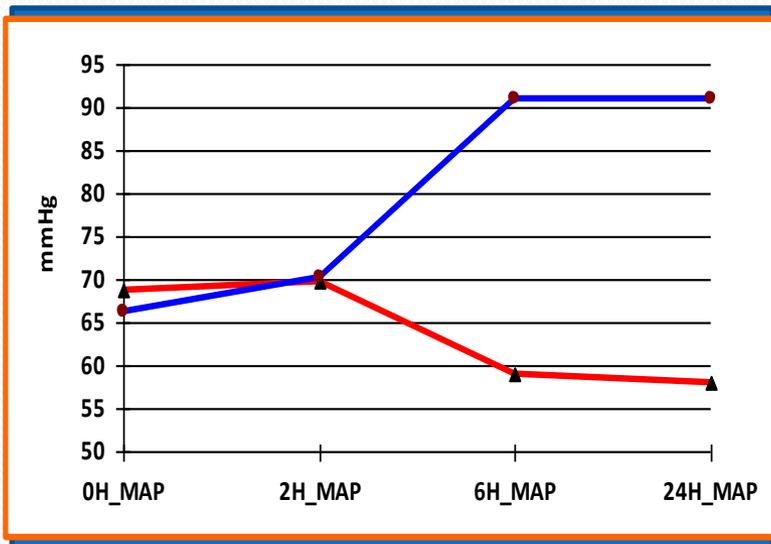
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Exclusions criteria

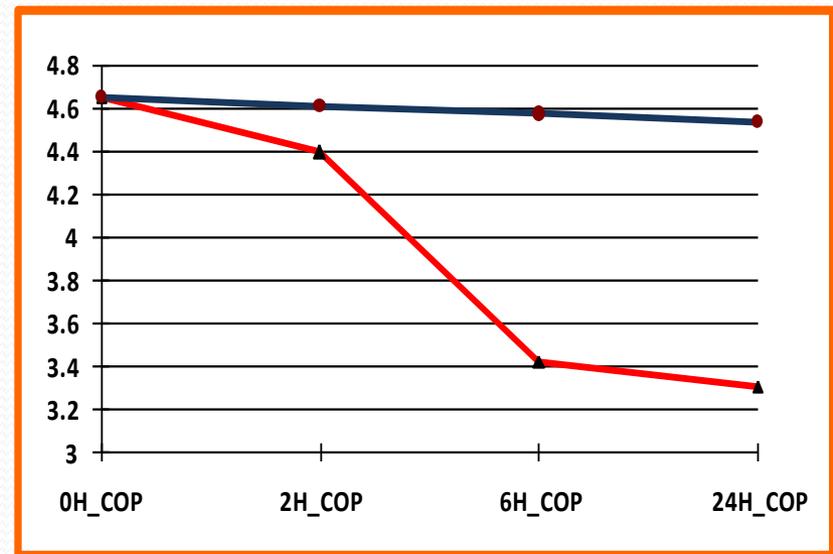
- Pregnant females.
- Patients sensitive to methylene blue.
- Patients with known G6PD deficiency
- Age less than 18 years old.
- Significant valvular heart disease.
- Present or suspected coronary artery disease.
- Present or suspected acute mesenteric ischemia.
- Vasospastic diathesis (e.g Raynaud's syndrome)

RESULTS

- Haemodynamic monitoring (at 0,2,6 and 24 hrs)
- (1) *Mean arterial blood pressure* (2) *Cardiac output*

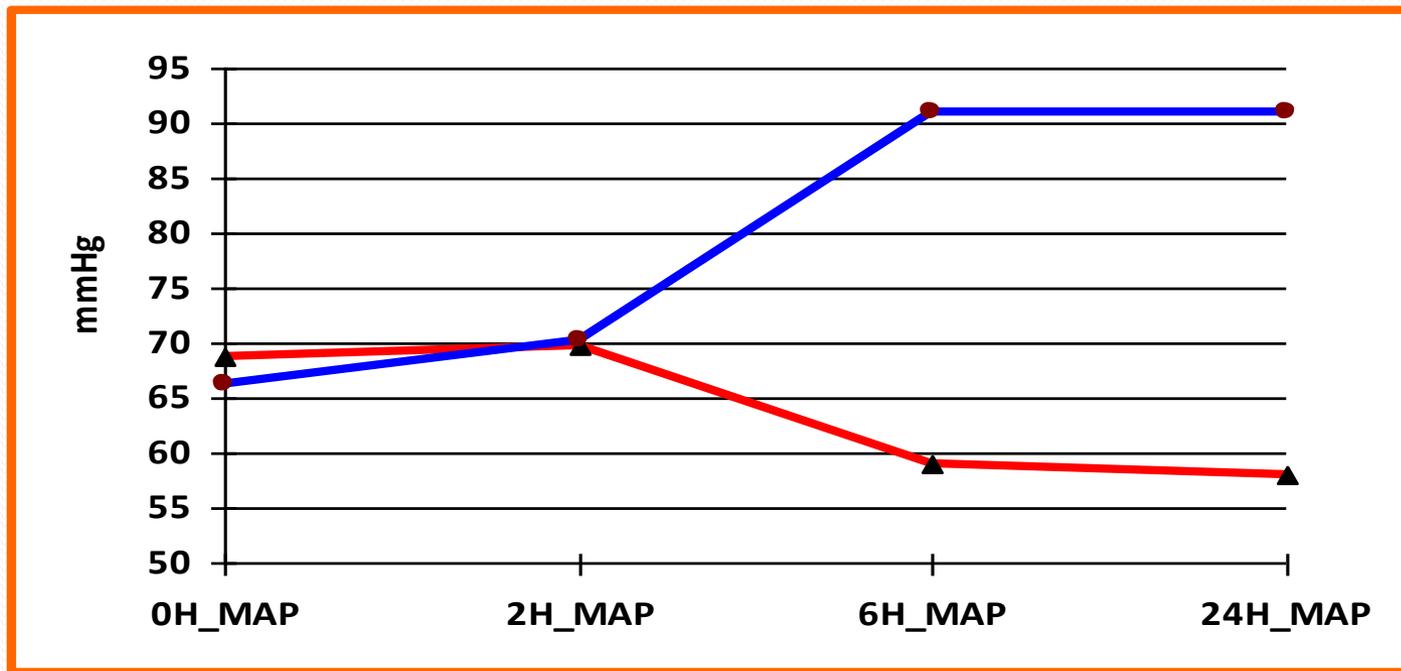


Graph (1): Showing marked difference between the methylene blue group and the control group.



Graph(2): Follow-up chart showing CO follow-up among both control and cases comparing the cardiac output between the methylene blue group and the control group.

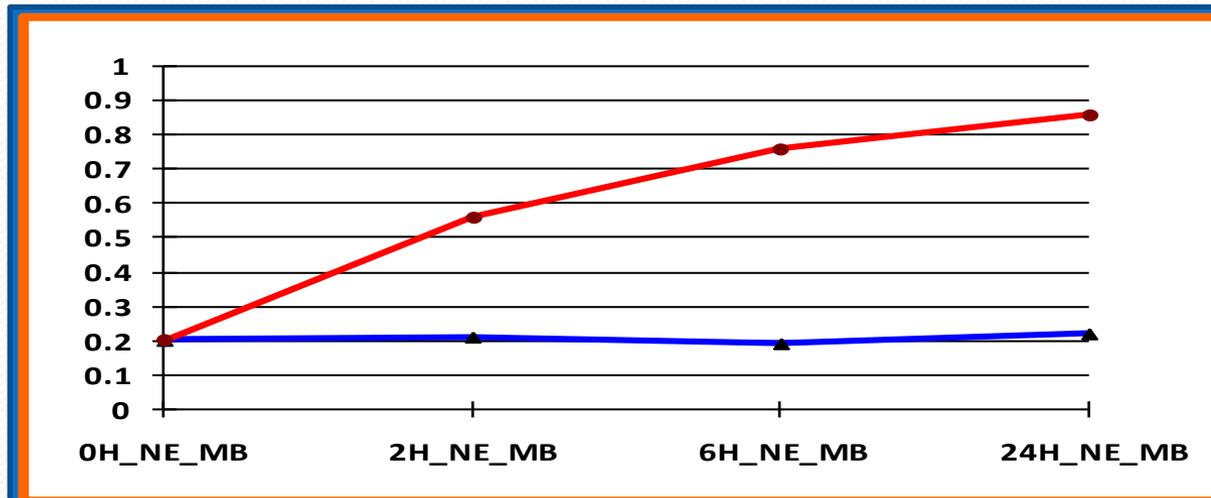
RESULTS



Graph (3): Follow-up chart showing SVR follow-up among both control and cases comparing the systemic vascular resistance between the methylene blue group and the control group.

RESULTS

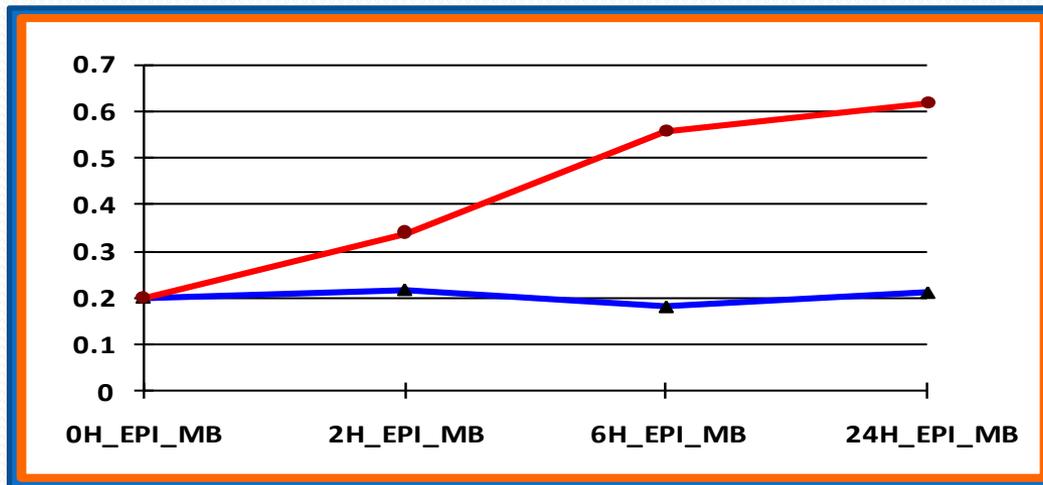
- (B) Vasopressor requirement:
- 1) Norepinephrine requirement:



Graph (4): Follow-up chart showing NE requirement follow-up among both control and cases comparing norepinephrine requirement between the methylene blue and the control group.

RESULTS

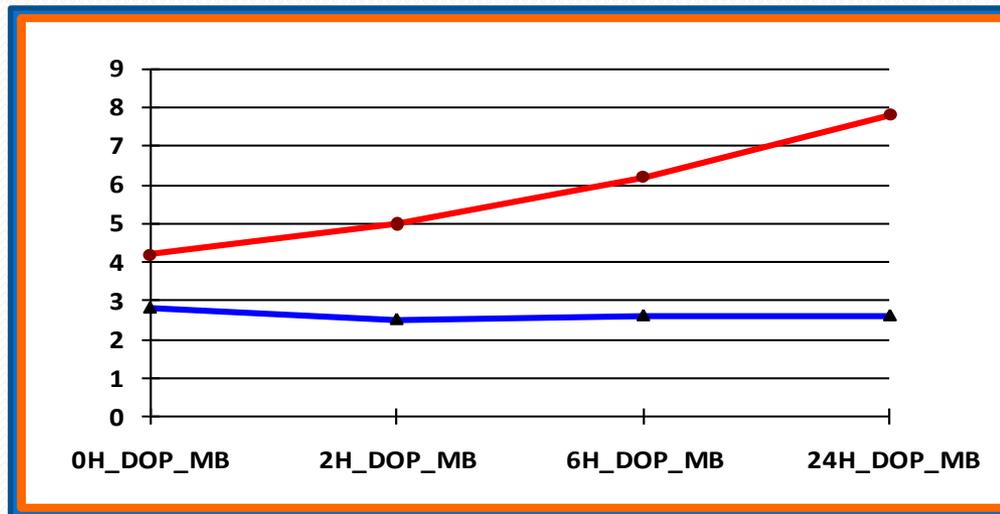
- (2) Epinephrine requirement:



Graph (5): Follow-up chart showing epinephrine (EPI) follow-up among both control and cases, comparing epinephrine requirement between the methylene blue and the control group.

RESULTS

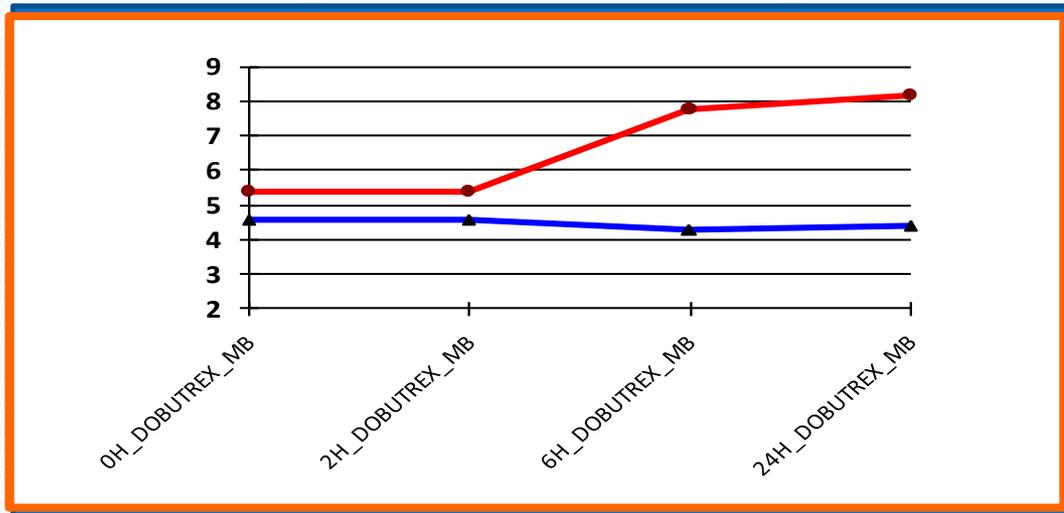
- (3) Dopamine requirement:



Graph (6): Follow-up chart showing dopamine requirement follow-up among both control (red lines) and cases (blue lines), Comparing dopamine requirement between the methylene blue and the control group.

RESULTS

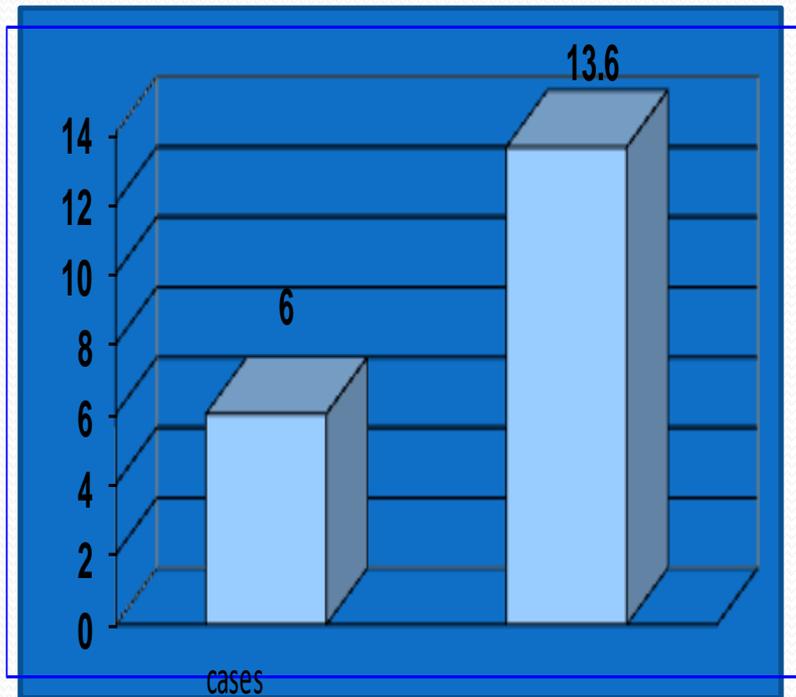
- (4) Dobutamine requirement:



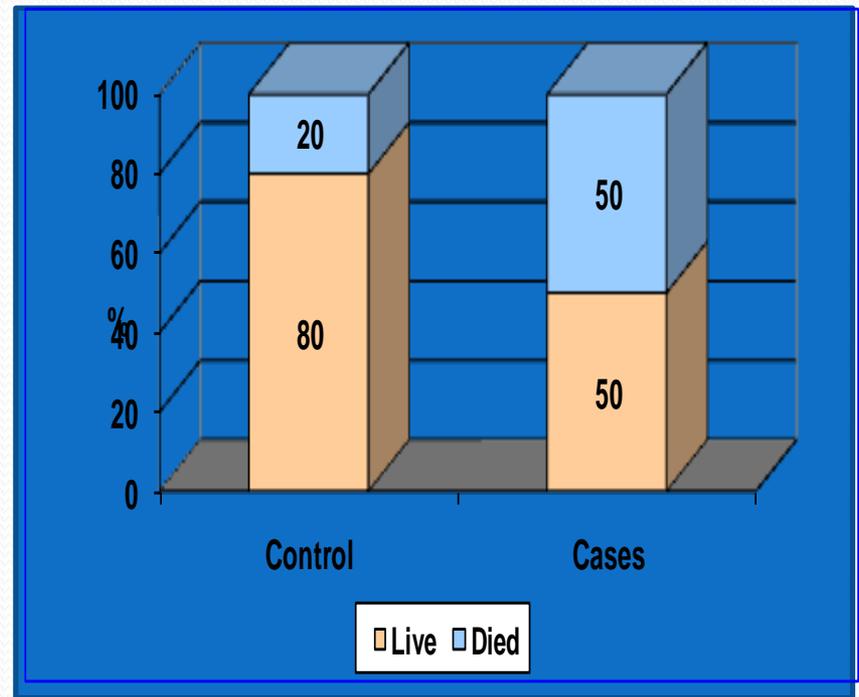
Graph (7): Follow-up chart showing dobutamine requirement follow-up among both control (red lines) and cases (blue lines), Comparing dobutamine requirement between the methylene blue and the control group.

RESULTS

D) Intensive care length of stay:



Graph (8): Comparison between control and cases as regards ICU Stay. Marked difference is shown regarding the intensive care length of stay being much lower in the methylene blue group b



Graph (9): Comparison between control and cases as regards frequency of living and died cases.

- There was no significant statistical differences regarding the central venous pressure, pulmonary artery pressure, pulmonary artery occlusion pressure, also there was no statistical difference regarding arterial blood gases, oxygen extraction ratio. Except for increased oxygen consumption index that increased after 24 hours in the methylene blue group that may represent improved mitochondrial function and respiratory enzymatic process or may be the decreased arterial venous shunting giving more time to tissue to improve their uptake coupled with improved cardiac output.

- 
- There was also no significant statistical differences regarding the liver function tests (ALT or AST), also no effect on renal function represented by serum creatinine
 - The decision if the use of this drug routinely to all patients or when to use it and if it should be the drug of first choice for the septic induced hypotension needs further investigation.

CONCLUSION

- The incidence of sepsis has increased steadily over the last three decades.
- Aggressive fluid challenge and administration of catecholamines still play a vital role in the current treatment regimen of patients with septic shock.
- The mechanism of widespread vasodilation involves the activation of the soluble intracellular enzyme guanylate cyclase (GC) by nitric oxide (NO), resulting in the production of cyclic guanosine monophosphate (cGMP).

CONCLUSION

- Methylene blue is believed to act through competition with nitric oxide in binding to the iron heme moiety of soluble guanylate cyclase resulting in enzyme activation. This inhibits the increase in the levels of c GMP, and thereby precludes the vasorelaxant effect of nitric oxide.
- It can be concluded that the early application of methylene blue (defined by the need for norepinephrine in a dose of $\geq 0.2 \mu\text{g}/\text{Kg}/\text{min}$ required to maintain mean arterial pressure (MAP) between 70 and 90 mmHg) with a dose of 1mg/kg bolus followed by 0.5mg/kg /hr for 4 hrs showed favourable effects on haemodynamics of cardiac output and decreasing the length of hospital stay. Inflammatory response, as in other situations, encourages the use of methylene blue (MB) as a therapeutic option .

CONCLUSION

- The decision of the credibility, efficacy and timing of this drug application, and if to use this drug routinely early to all patients or not to needs further investigation.



Who's Watching the Patient?



Pierson, IN: Tobin, Principles and Practice of Critical Care Monitoring

1973 October war



THANK YOU!

Any
questions

