2-2-2019

Identification and Treatment of Sepsis in the Field

Jamie Roney
St. Joseph Health, jroney@covhs.org

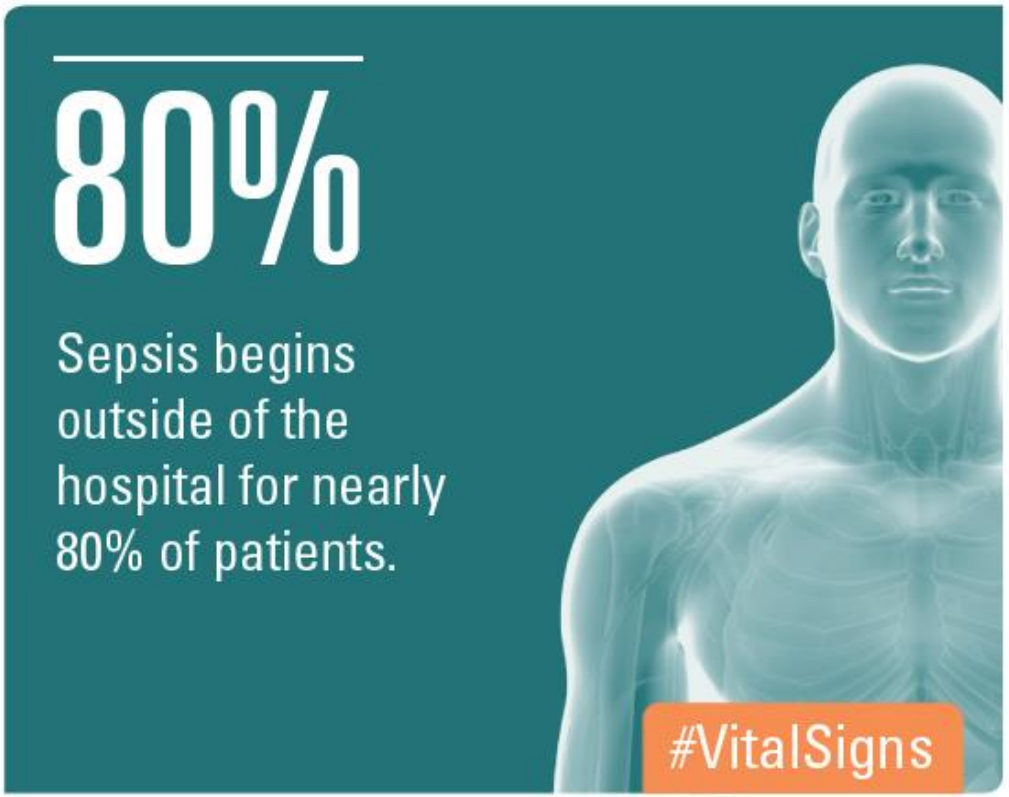
Identification and Treatment of Sepsis in the Field

Jamie K. Roney, DNP, RN-BC, CCRN-K

Purposes of Presentation

- Discuss historical versus new state of knowledge
- Identify innovative approaches to improving sepsis outcomes

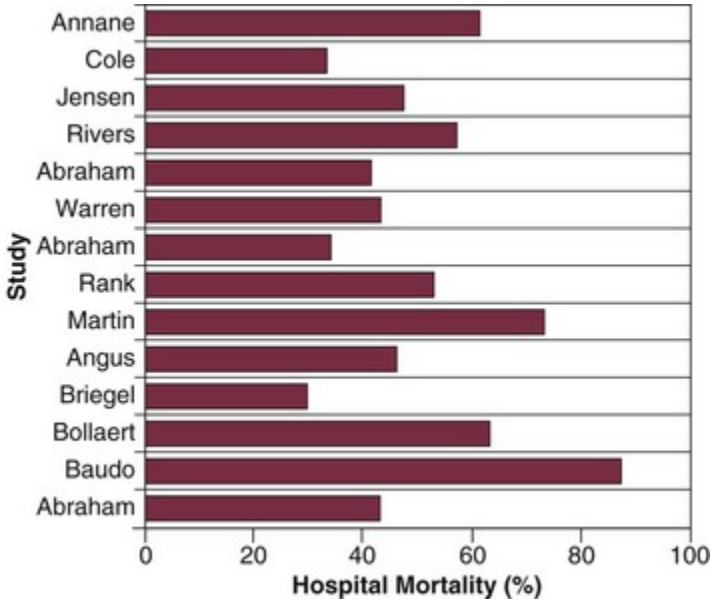
Cases More than Doubled Between 2000 & 2008



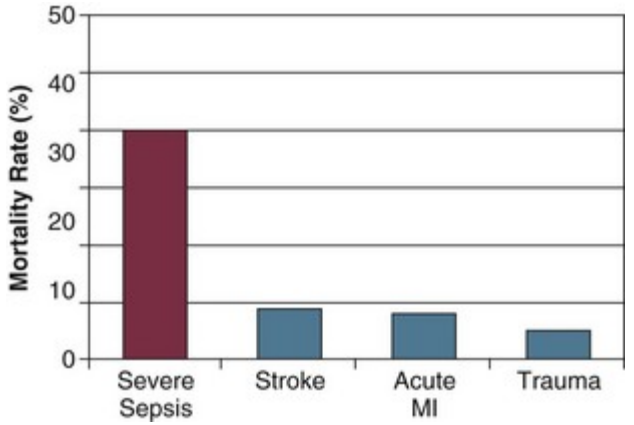
(CDC, 2017)

Epidemiology

Compilation of Septic Shock Mortality

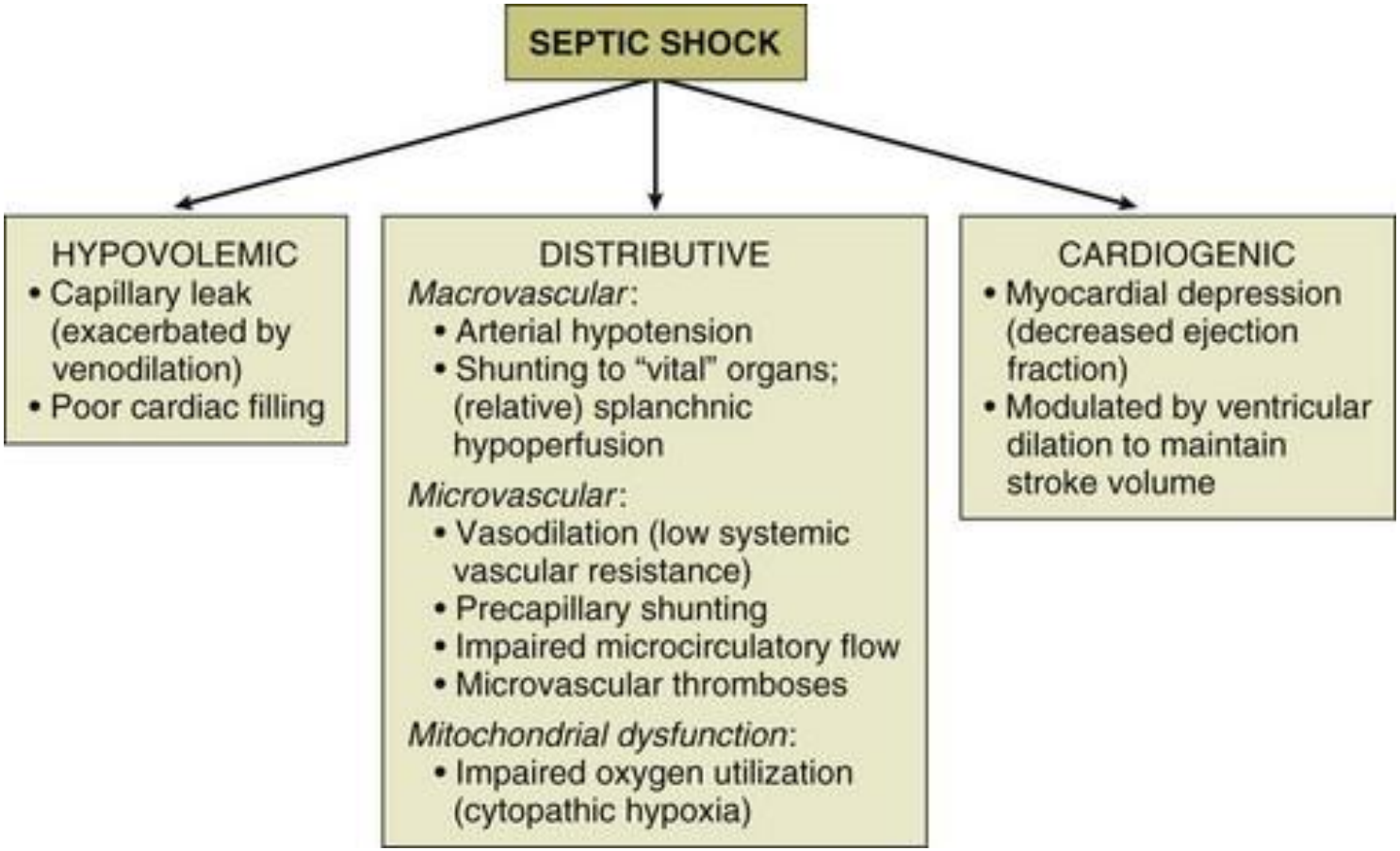


Incidence (cases per 100,000 population)



(Trzeciak, Dellinger, & Parrillo, 2016)

Hemodynamic Profile in Septic Shock



(Trzeciak, Dellinger, & Parrillo, 2016)

In the United States…

- More than 1.5 million people develop sepsis
- At least 250,000 Americans die as a result
- Sepsis develops outside the hospital
- Accounts for 1 in 3 hospital deaths
- "Detecting sepsis early and starting immediate treatment is often the difference between life and death" CDC Director Brenda Fitzgerald, M.D.

(CDC, 2017)

Early Goal Directed Therapy (EGDT)

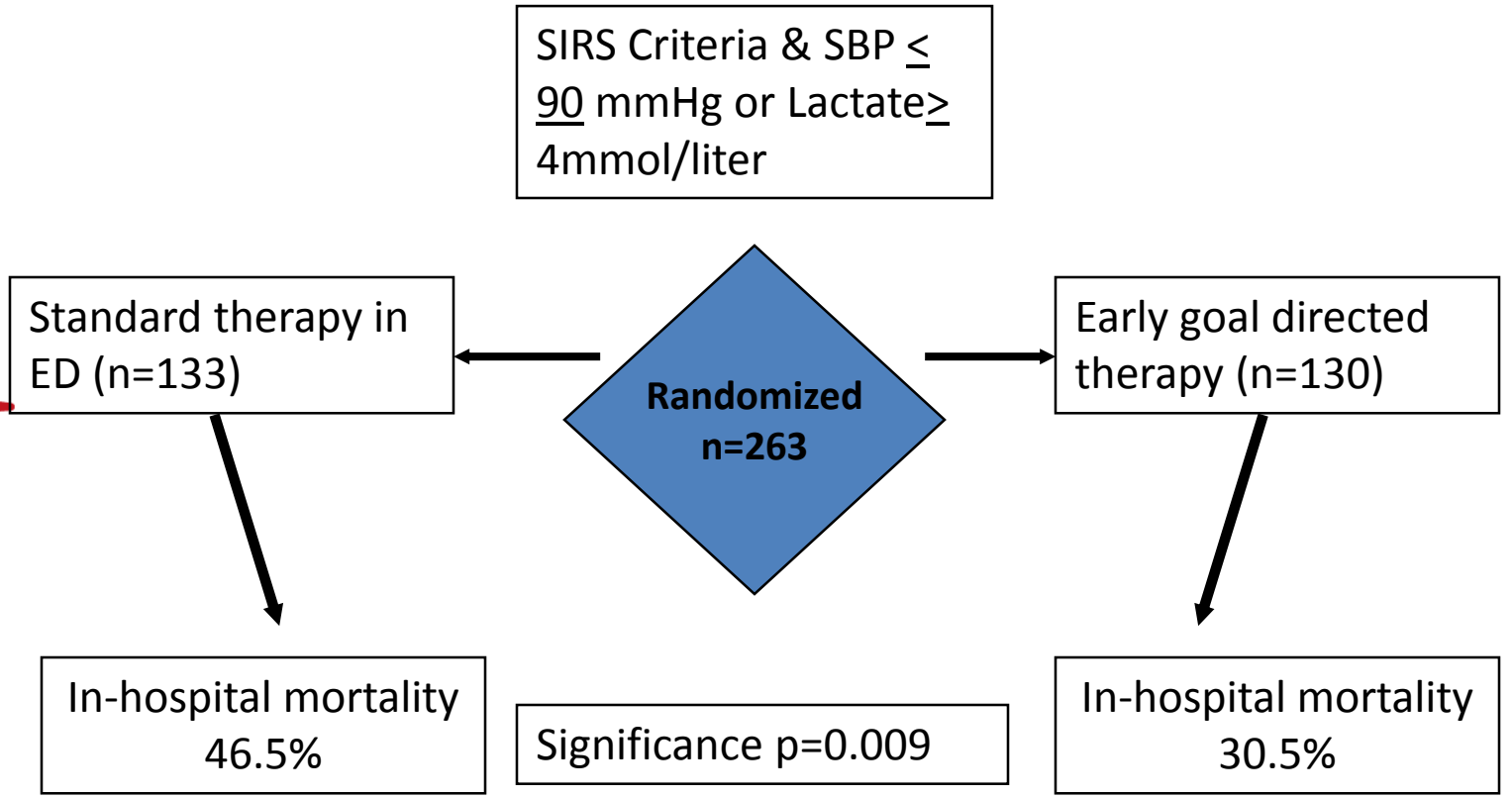
History of EGDT

- Prior to 2001, no standard for early management of severe sepsis and septic shock
- The prevailing mortality was over 40-50%
- Early goal-directed therapy (EGDT) was compared to standard care in a landmark clinical trial

Rivers, E. Nguyen, B., Havstad, M.A., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., Tomlanovich, M.. for the early goal directed therapy group. (2001). *New England Journal of Medicine, 345,*(19)1368-1377.

Stop the Clock on Septic Shock

The NEW ENGLAND JOURNAL of MEDICINE



Rivers, E. Nguyen, B., Havstad, M.A., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., Tomlanovich, M.. for the early goal directed therapy group. (2001). *New England Journal of Medicine, 345,*(19)1368-1377.

EGDT Validation & Adoption

- Similar outcomes reported in over 70 observational and randomized controlled studies comprising over 70,000 patients
- EGDT was largely incorporated into the first 6 hours of sepsis management (resuscitation bundle)

De Backer, D., & Dorman, T. (2017). Surviving Sepsis Guidelines: A continuous move toward better care of patients with sepsis. *Jama*, *317*(8), 807-808. doi:10.1001/jama.2017.0059

“Early interventions in severe sepsis and septic shock: A review of the evidence one decade later”

Meta-analysis of over 50 publications looked at only the past decade of evidence

- Relative risk reduction (RRR) of 0.37
- Absolute risk reduction (ARR) of 18.3%
- Number needed to treat (NNT) of 5.45
- Crude mortality reduction of 17.7%

Rivers, E.P., Katranji, M., Jaehne, K.A., Brown, S., Abou Dagher, G., Cannon, C. & Coba, V. (2012). Early interventions in severe sepsis and septic shock: A review of the evidence one decade later. *Minerva Anestesiologica,78(6),* 712-24.

Comparison of Sepsis Intervention Studies Using the Resuscitation Bundle Compared to the Original EGDT Study

	Summary of implementation study		Rivers et al.	
	Before or Control	After	Control	EGDT
Number of patients	9527	9884	133	130
APACHE II score	24.2	24.2	20.4	21.4
Sex, % Males	58.15	57.3	50.4	50.8
Age (years)	63.8	62.9	64.4	67.1
Mortality before (SD)**	46.8 (26)%	29.1 (12)%	46.5%	30.5%
Relative risk reduction	0.37		0.34	
Absolute risk reduction	18.3%		16.0%	
NNT	5.45		6.25	

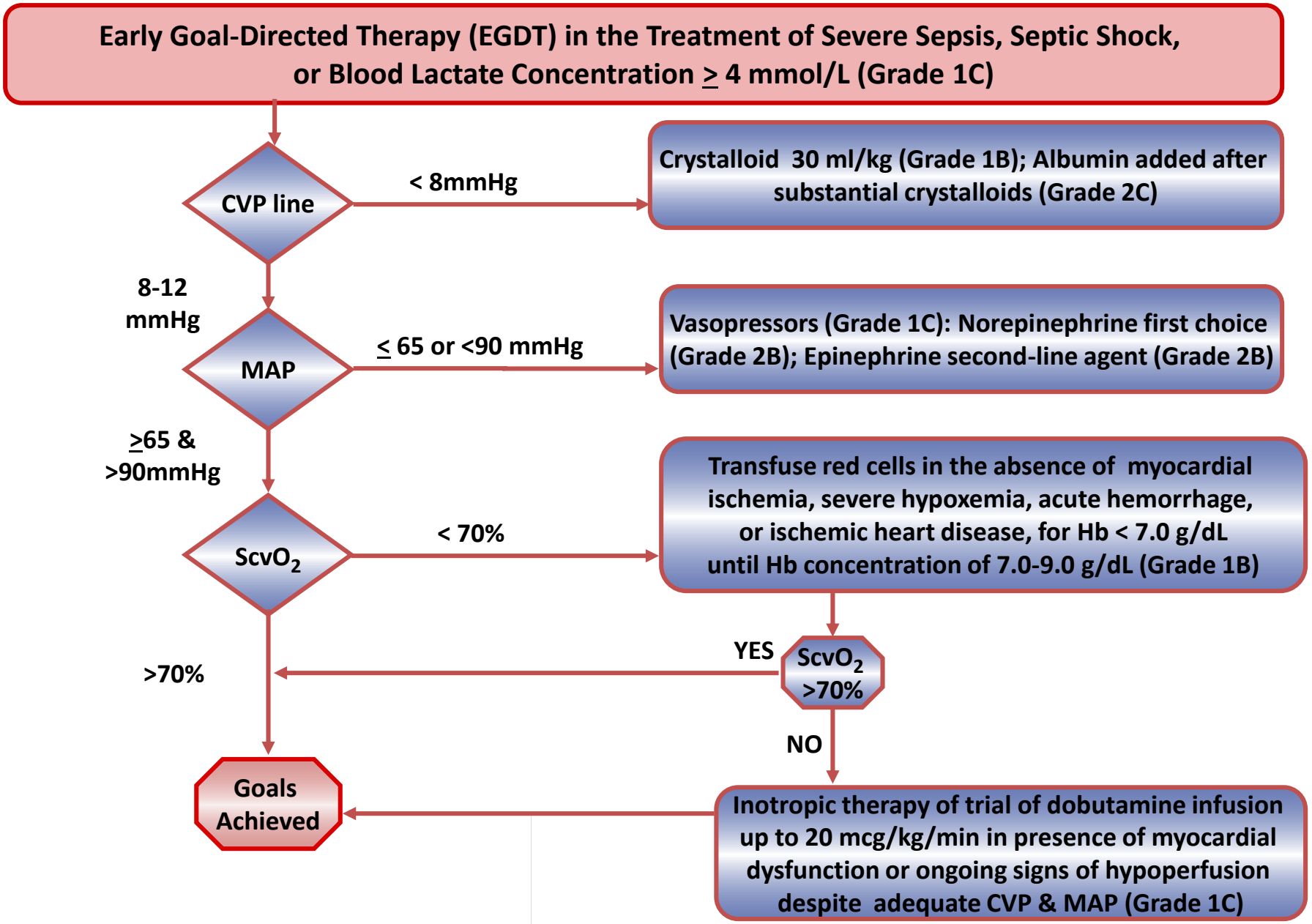
Note. Includes before and after concurrent implementation studies. **The average mortality of each study. NNT=number needed to treat. Adapted from "Early Interventions in Severe Sepsis and Septic Shock: A Review of the Evidence One Decade Later", by E.P. Rivers, M. Katranji, K.A. Jaehne, S. Brown, G. Abou Dagher, C. Cannon, and V. Coba, 2012, *Mirnerva Anestesiologica 78(6),* 712-24.

Table 3. Change in achievement of bundle targets

	Initial Quarter Achieved, %	Final Quarter Achieved, %[a]	*p* Value Compared With Initial
Initial care bundle (first 6 hrs of presentation)			
Measure lactate	61.0	78.7	≤.0001
Blood cultures before antibiotics	64.5	78.3	≤.0001
Broad-spectrum antibiotics	60.4	67.9	.0002
Fluids and vasopressors	59.8	77.0	≤.0001
CVP >8 mm Hg	26.3	38.0	≤.0001
$Scvo_2$ >70%	13.3	24.3	≤.0001
All resuscitative measures	10.9	21.5	≤.0001
Management bundle (first 24 hrs after presentation)			
Steroid policy	58.5	73.9	≤.0001
Administration of drotrecogin alfa policy	47.4	53.5	.003
Glucose control	51.4	56.8	.0009
Plateau pressure control	80.8	83.8	.24
All management measures	18.4	25.5	≤.0001

CVP, central venous pressure; $Scvo_2$, central venous oxygen saturation.

[a]Represents the last quarter of data submission from each institution during the 2-yr data analysis pe
institution participation.



Rhodes, A., Evans, L. E., Alhazzani, W., Levy, M. M., Antonelli, M., Ferrer, R., … De Backer, D. P. (2017). Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Critical Care Medicine*, *45*(3), 486–552. https://doi.org/10.1097/CCM.0000000000002255

New Evidence Arises from 2013 & 2014 Clinical Trials

Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE

H. Bryant Nguyen, Anja Kathrin Jaehne, Namita Jayaprakash, Matthew W. Semler, Sara Hegab, Angel Coz Yataco, Geneva Tatem, Dhafer Salem, Steven Moore, Kamran Boka, Jasreen Kaur Gill, Jayna Gardner-Gray, Jacqueline Pflaum, Juan Pablo Domecq, Gina Hurst, Justin B. Belsky, Raymond Fowkes, Ronald B. Elkin, Steven Q. Simpson, Jay L. Falk, Daniel J. Singer and Emanuel P. Rivers

Critical Care 2016 **20**:160 | **DOI:** 10.1186/s13054-016-1288-3 | © Nguyen et al. 2016

Published: 1 July 2016

EGDT Challenges Arise

- A trio of trials (ProCESS, ARISE, and ProMISe question need for elements of EGDT or the need for protocolized care
- Comparing trial conduction methodology and sepsis mortality trends are essential for an appropriate interpretation of these trials' conclusions
- Challenges are reflected in the CMS Sepsis Core Measure provider assessment options

Nguyen, H. B., Jaehne, A. K., Jayaprakash, N., Semler, M. W., Hegab, S., Yataco, A. C., … Falk, J. L. (2016). Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. *Critical Care*, *20*, 1–16. https://doi.org/10.1186/s13054-016-1288-3

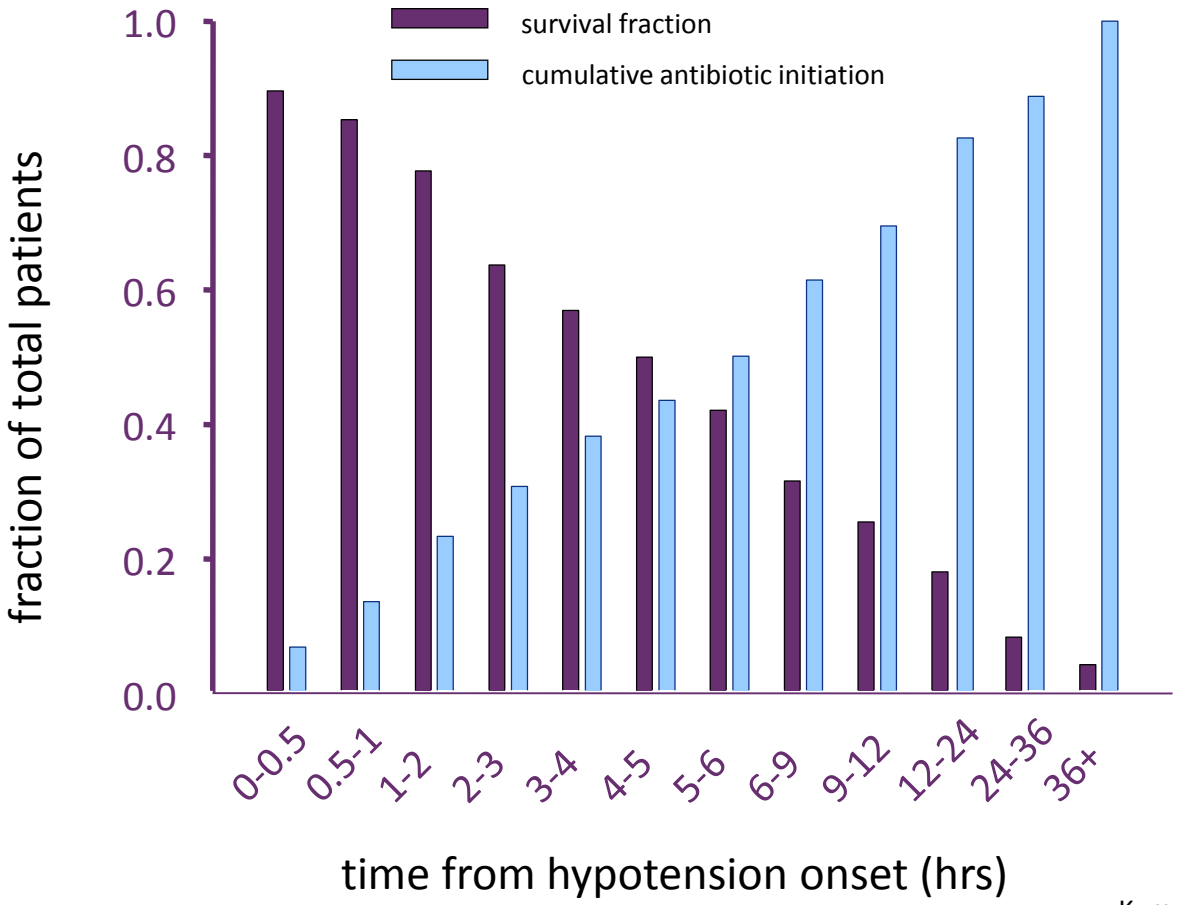
Conclusion of EGDT vs Alternative Strategies

- EGDT has been shown to have internal & external validity in reducing mortality
- The trio of trials suggest alternative strategies can provide an equal reduction in mortality
- Due to multiple methodological differences when compared to the original EGDT trial (including undefined usual care), there is no external validity of these alternative strategies

Nguyen, H. B., Jaehne, A. K., Jayaprakash, N., Semler, M. W., Hegab, S., Yataco, A. C., … Falk, J. L. (2016). Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. *Critical Care*, *20*, 1–16. https://doi.org/10.1186/s13054-016-1288-3

Stop the Clock on Septic Shock

Cumulative Initiation of Effective Antimicrobial Therapy and Survival in Septic Shock



Kumar et al. *CCM*. 2006:34:1589-96.

Running average survival in septic shock based on antibiotic delay (n=2154)

For each hour's delay in administering antibiotics in septic shock, mortality increases by 7.6%

Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, … Feinstein. (2006). Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Critical Care Medicine*, *34*(6), 1589–1596.

Sepsis Antibiotic Recommendations

- Give all antimicrobials simultaneously
- Broad spectrum coverage targeted for suspected type of infection
- Keep available on units to avoid pharmacy delays

(Rhodes et al., 2017)

Choice of Vasopressors to Correct Hypotension in Septic Shock

- Norepinephrine is the recommended first-line agent (Grade 2B)
- Epinephrine (added to or substituted for norepinephrine)
  - Administer through a central catheter (Grade 1C)
  - Arterial line placed for monitoring (ug)
- Vasopressin or Dopamine may be considered as second-line agents
  - Vasopressin 0.03 units/min can be added to norepinephrine, but not recommended as sole vasopressor or at higher doses (ug)
  - Dopamine alternative only in highly selected patients (eg. Patients with low risk of tachyarrhythmias & and absolute relative bradycardia (Grade 2C)
  - Phenylephrine not recommended (Grade 1C)

(Rhodes et al., 2017)

CMS Sepsis Core Measure

Stop the Clock on Septic Shock

SSC Sepsis Initial Treatment Bundle

Must be Completed in the First 3 Hours for Severe Sepsis or Septic Shock!

1. Serum Lactate Measured
2. Blood Cultures Prior to Antibiotic Administration
3. Broad-Spectrum Antibiotics Goal of One Hour
4. Treat Hypotension and/or Elevated Lactate ($\geq$2mmol/L) with Crystalloid Fluids of 30 ml/kg

(Rhodes et al., 2017)

Stop the Clock on Septic Shock

SSC Sepsis Bundle Elements

Must be Completed in the First 6 Hours for Severe Sepsis or Septic Shock:

1. Apply Vasopressors for Ongoing Hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) $\geq$ 65 mmHg
2. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate $\geq$ 4 mmol/L (36 mg/dL):
   - Maintain central venous pressure (CVP) $\geq$ 8 mmHg
   - Maintain central venous oxygen saturation ($ScVO_2$) $\geq$ 70%
3. Remeasure lactate if initial lactate was elevated ($\geq$2mmol/L)

(Rhodes et al., 2017)

Stop the Clock on Septic Shock

SSC Sepsis Management Considerations

1. Administer Low-Dose Steroids by a Standard Policy
2. Maintain Adequate Glycemic Control
3. Prevent Excessive Inspiratory Plateau Pressures

(Rhodes et al., 2017)

CMS Sepsis Core Measure Inclusions & Exclusions

- Includes
  - Inpatients age 18 and over with an ICD-10-CM principal or other diagnosis code of Sepsis, Severe Sepsis, or Septic Shock
- Excludes
  - Patients under the age of 18 years
  - Patients with a LOS of greater than 120 days
  - **Patients with a directive for comfort measures documented by the provider within 3 hours of presentation of severe sepsis**
  - **Patients with a directive for comfort measures documented by the provider within 6 hours of presentation**
  - Patients receiving intravenous antibiotics for more than 24 hours prior to presentation with severe sepsis

CMS Sepsis Core Measure Inclusions & Exclusions

- Excludes
  - Patient is a transfer from another hospital or ambulatory surgery center
  - **Patients or surrogate refuses care**
    - **i.e. blood draw, fluid administration, or antibiotics**
    - **Must be documented by provider or have a witnessed consent form stating the refusal of care present in the medical record**
    - **Consent form can be witnessed by nurse or provider**

Challenges & Opportunities

Surviving Sepsis Campaign Definition of Time Zero

- Will always be when the chart annotation suggests signs & symptoms are all present
- May be from nursing charting, laboratory flow sheets, physician documentation, anything with a time stamp
- Will equal triage time if all signs and symptoms are present at triage

(Rhodes et al., 2017)

ACCP/SCCM Redefining Sepsis

Sepsis versus Septic Shock

Seymour, C. W., Liu, V. X., Iwashyna, T. J., Brunkhorst, F. M., Rea, T. D., Scherag, A., … Angus, D. C. (2016). Assessment of clinical criteria for sepsis: For the Third International Consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA: Journal of the American Medical Association*, *315*(8), 762–774.

New definition of sepsis

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection

(Seymour et al., 2016)

New definition of septic shock

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone

(Seymour et al., 2016)

New Sepsis Definitions

- Advantages
  - Incorporates most up-to-date thinking on sepsis pathobiology
  - Provides closest approximation possible to describing "what sepsis is"
- Concerns
  - Of limited practical utility as they contain elements that cannot be clinically identified
  - "organ dysfunction"
  - "dysregulated host response"

Issues with the 1991 & 2001 Definitions

- SIRS based
- “Severe Sepsis” is problematic
  - Different assessment criteria yield different results
- SIRS sensitivity
  - SIRS is an appropriate response to infection or any other stimulus that activates inflammation
- Sepsis versus Severe Sepsis is confusing
  - Most people say “sepsis” when they mean “severe sepsis”
  - What the initial two task forces called “sepsis” is what most people call “infection”

Diagnosing Sepsis

SIRS versus SOFA

Systemic Inflammatory Response Syndrome (SIRS)

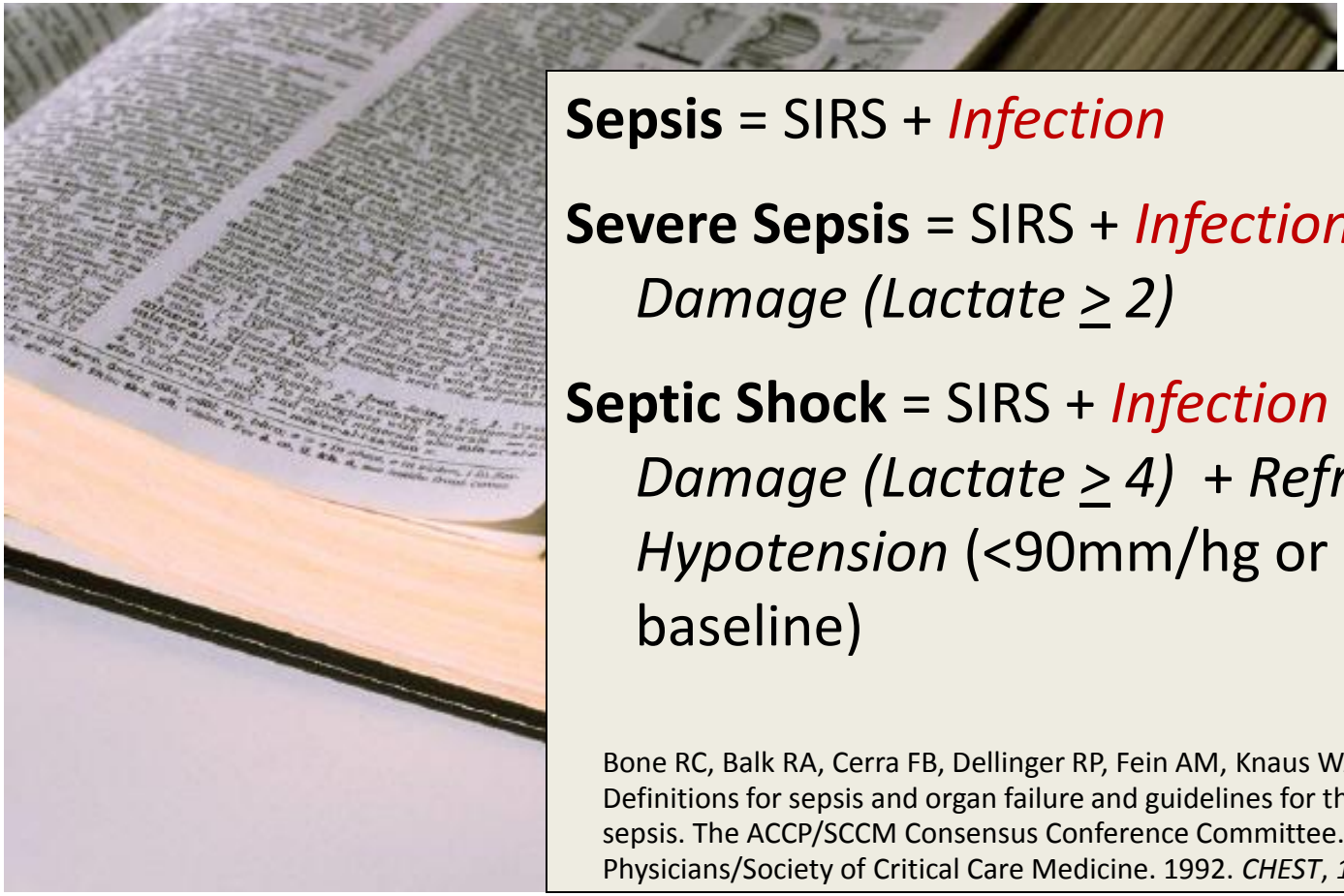
- ❑ Temperature ≥ 38°C (100.4°F) or ≤ 36°C (96.8°F)
- ❑ Heart Rate ≥ 90 beats/min
- ❑ Respiratory Rate > 20 breaths/min or $PaCO_2$ ≤ 32 mmHg or use of a ventilator
- ❑ WBC ≥ 12,000 or ≤ 4,000/m^3 or ≥ 10% immature neutrophils (bands)

If at least **TWO** of the above are present, **&**
Current or Recent Infection…You have SEPSIS

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, … Sibbald WJ. (2009). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. *CHEST*, *136*(5), e28.

Stop the Clock on Septic Shock

ACCP/SCCM Consensus Sepsis Definitions



Sepsis = SIRS + *Infection*

Severe Sepsis = SIRS + *Infection* + *End Organ Damage (Lactate ≥ 2)*

Septic Shock = SIRS + *Infection* + *End Organ Damage (Lactate ≥ 4)* + *Refractory Hypotension* (<90mm/hg or <40% below baseline)

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, … Sibbald WJ. (2009). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. *CHEST*, *136*(5), e28.

New Recommendations Aim to Redefine Definition & Enhance Diagnosis of Sepsis, Septic Shock

- New method to assess for organ dysfunction is Sequential (Sepsis-Related) Organ Failure Assessment (SOFA)
- The new diagnostic tool is named quickSOFA or qSOFA
- If a patient has two or three components of qSOFA, the patient should be examined for organ failure.
- The qSOFA assessment:
  - An alteration in mental status
  - A decrease in systolic blood pressure of less than 100 mm Hg
  - A respiration rate greater than 22 breaths/min

(Seymour et al., 2016)

SIRS versus qSOFA Screening by Clinicians

New Recommendations Aim to Redefine Definition & Enhance Diagnosis of Sepsis, Septic Shock

- The task force recommends that its report be designated “Sepsis-3” recognizing the two earlier iterations to define sepsis
- 1991 “Sepsis-1”
- 2001 “Sepsis-2”

(Seymour et al., 2016)

“Neutropenic sepsis: Prevention and management in people with cancer” NICE Clinical Guidelines

Bate, J., Gibson, F., Johnson, E., Selwood, K., Skinner, R., & Chisholm, J. (2013). Neutropenic sepsis: Prevention and management of neutropenic sepsis in cancer patients (NICE Clinical Guideline CG151). *Archives of Disease in Childhood -- Education & Practice Edition*, *98*(2), 73–75. https://doi.org/10.1136/archdischild-2013-303634

Defines Neutropenia & Fever

Diagnose neutropenic sepsis in patients having anticancer treatment whose neutrophil count is 0.5 x 10^9 per liter or lower and who have either:

- a temperature higher than 38°C

or

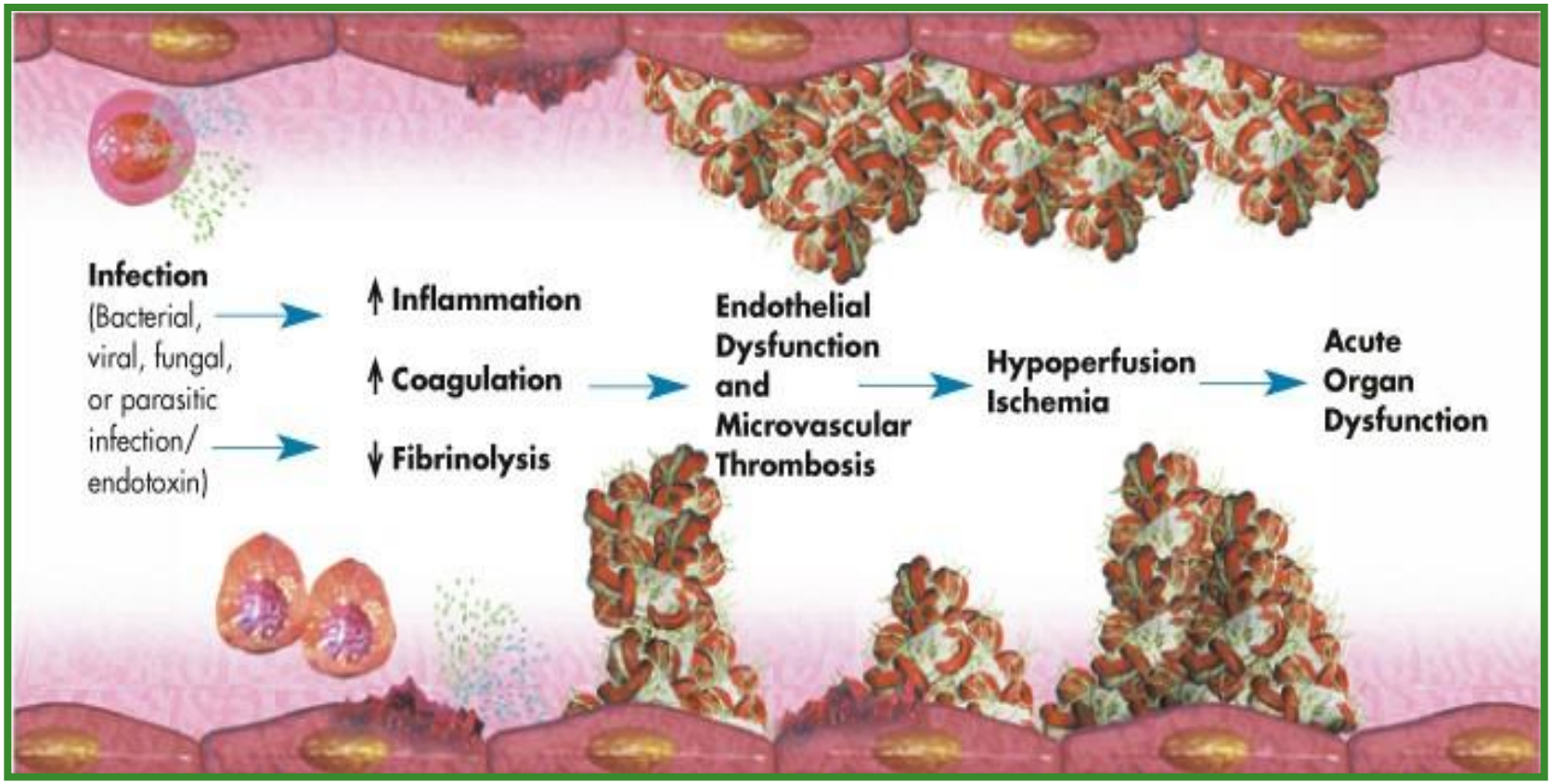
- other signs or symptoms consistent with clinically significant sepsis

(Bate et al., 2013)

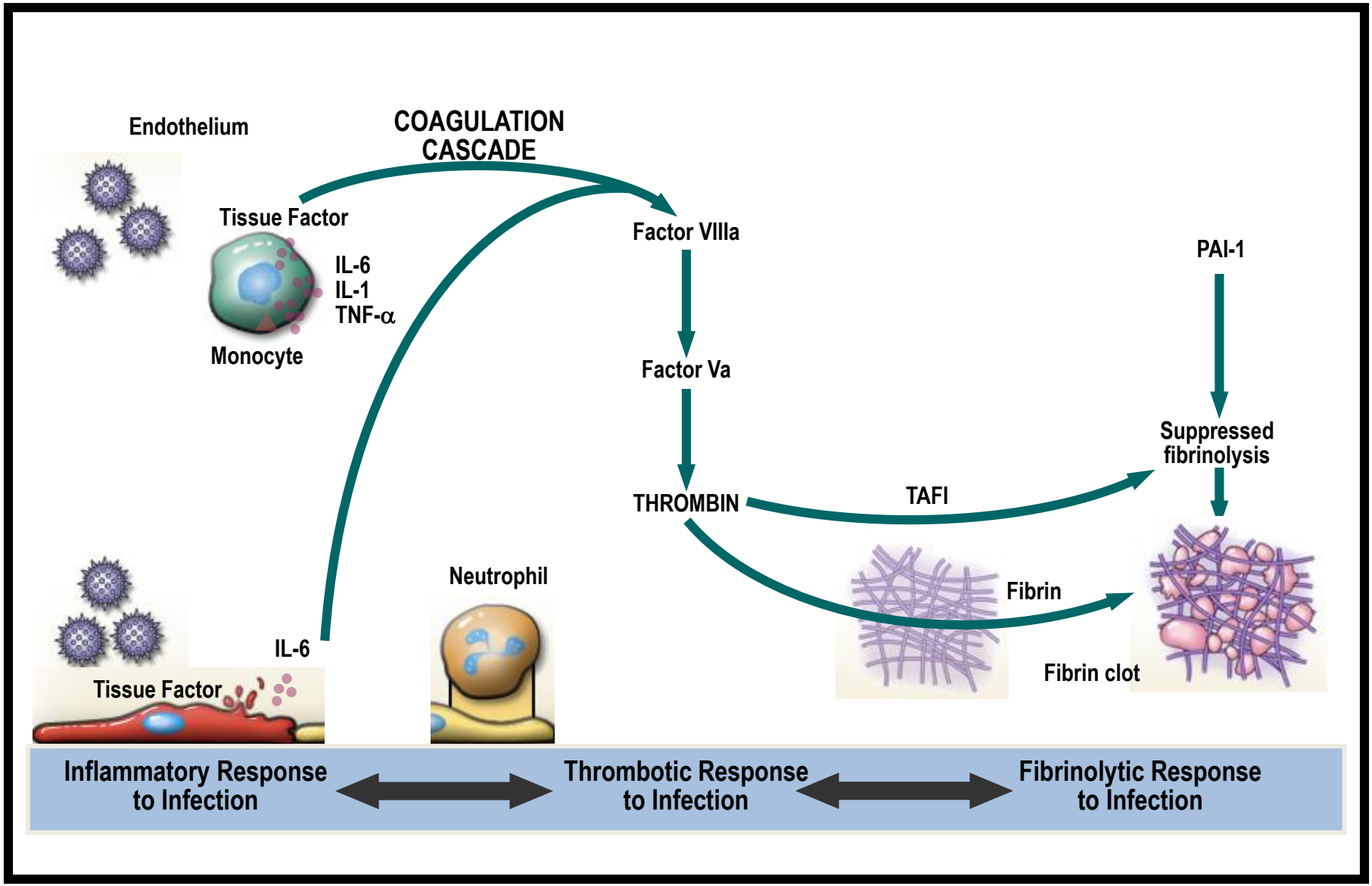
Educate Caregivers & Peers

- The usual signs of infection are fever, pus, pain, swelling, and redness may not show up as the ANC gets lower
- These signs are caused by neutrophils fighting off germs
- Monocytes can still cause fever in the person who has neutropenia
- In severe neutropenia, a fever may be the only sign of an infection

Diagnostic Recommendations



Pathobiology of Sepsis



Microcirculatory Failure in Sepsis

(Trzeciak, Dellinger, & Parrillo, 2016)

Innovations to Improve Outcomes

- Recognition
  - Lactic acid
  - Physiologic change detection
  - Biomarkers
  - Data analytics
- Treatment
  - Communication
  - Escalation
  - Challenge scopes of practice
- Monitoring
  - Special units
- Challenge barriers
  - Attitudes
  - Assumptions
  - Knowledge
- Caregiver Competency
  - Simulation
  - Gaming

Conclusion

References

- Agulnik, A., Mora Robles, L. N., Forbes, P. W., Soberanis Vasquez, D. J., Mack, R., Antillon-Klussmann, F., & ... Rodriguez-Galindo, C. (2017). Improved outcomes after successful implementation of a pediatric early warning system (PEWS) in a resource-limited pediatric oncology hospital. *Cancer*, *123*(15), 2965-2974. doi:10.1002/cncr.30664
- Bate, J., Gibson, F., Johnson, E., Selwood, K., Skinner, R., & Chisholm, J. (2013). Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients (NICE Clinical Guideline CG151). *Archives of Disease in Childhood -- Education & Practice Edition*, *98*(2), 73–75. https://doi.org/10.1136/archdischild-2013-303634
- Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, … Sibbald WJ. (2009). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. *CHEST*, *136*(5), e28.

References

- Centers for Disease Control and Prevention (2017). *Cost of cancer-related neutropenia or fever hospitalizations.* Retrieved from https://www.cdc.gov/cancer/dcpc/research/articles/neutropenia.htm
- Dellinger, R. P., Schorr, C. A., & Levy, M. M. (2017). A users' guide to the 2016 Surviving Sepsis Guidelines. *Intensive Care Medicine*, *43*(3), 299-303. doi:10.1007/s00134-017-4681-8
- De Backer, D., & Dorman, T. (2017). Surviving Sepsis Guidelines: A continuous move toward better care of patients with sepsis. *Jama*, *317*(8), 807-808. doi:10.1001/jama.2017.0059
- Knight, T., Ahn, S., Rice, T. W., & Cooksley, T. (2017). Special Article: Acute Oncology Care: A narrative review of the acute management of neutropenic sepsis and immune-related toxicities of checkpoint inhibitors. *European Journal of Internal Medicine*, *45*(Special Issue: Acutely Ill Patients), 59-65. doi:10.1016/j.ejim.2017.09.025

References

- Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, … Feinstein. (2006). Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Critical Care Medicine*, *34*(6), 1589–1596.
- Lee-Hwa, T., Abhirami A., A., Rashmi, S., Almohanad, A., Jiqing, Z., Christiano Tanese de, S., & ... Rebecca C., A. (2018). Sepsis increases perioperative metastases in a murine model. *BMC Cancer, Vol 18, Iss 1, Pp 1-9 (2018)*, (1), 1. doi:10.1186/s12885-018-4173-4
- Nguyen, H. B., Jaehne, A. K., Jayaprakash, N., Semler, M. W., Hegab, S., Yataco, A. C., … Falk, J. L. (2016). Early goal-directed therapy in severe sepsis and septic shock: insights and comparisons to ProCESS, ProMISe, and ARISE. *Critical Care*, *20*, 1–16. https://doi.org/10.1186/s13054-016-1288-3
- PAN, D., PONDAIAH, S., SANTIBANEZ, V., VAZQUEZ DE LARA, F., SABHARWAL, B., & MATHEW, J. (2018). Trends in morbidity, mortality, and survivor outcomes in septic shock: A decade after the publication of the Surviving Sepsis Guidelines. *CHEST*, *154*, 371A. https://doi.org/10.1016/j.chest.2018.08.339

References

- Penack, O., Becker, C., Buchheidt, D., Christopeit, M., Kiehl, M., von Lilienfeld-Toal, M., & ... Ostermann, H. (2014). Management of sepsis in neutropenic patients: 2014 updated guidelines from the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO). *Annals of Hematology*, *93*(7), 1083-1095. doi:10.1007/s00277-014-2086-0
- Rhodes, A., Evans, L. E., Alhazzani, W., Levy, M. M., Antonelli, M., Ferrer, R., … De Backer, D. P. (2017). Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Critical Care Medicine*, *45*(3), 486–552. https://doi.org/10.1097/CCM.0000000000002255 Rivers, E. Nguyen, B., Havstad, M.A., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., Tomlanovich, M.. for the early goal directed therapy group. (2001). New *England Journal of Medicine, 345,*(19)1368-1377.
- Rivers, E. Nguyen, B., Havstad, M.A., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., Tomlanovich, M.. for the early goal directed therapy group. (2001). *New England Journal of Medicine, 345,*(19)1368-1377.

References

- Rivers, E.P., Katranji, M., Jaehne, K.A., Brown, S., Abou Dagher, G., Cannon, C. & Coba, V. (2012). Early interventions in severe sepsis and septic shock: A review of the evidence one decade later. *Minerva Anestesiologica,78(6),* 712-24.
- Seymour, C. W., Liu, V. X., Iwashyna, T. J., Brunkhorst, F. M., Rea, T. D., Scherag, A., … Angus, D. C. (2016). Assessment of clinical criteria for sepsis: For the Third International Consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA: Journal of the American Medical Association*, *315*(8), 762–774.
- Trzeciak, S., Dellinger, R.P., & Parrillo, J.E. (2016). Chapter 23, septic shock. *Critical Care Anesthesia Key: Fastest Anesthesia & Intensive Care & Emergency Medicine Insight Engine*. Retrieved from https://aneskey.com/septic-shock/

Contact Information

jroney@covhs.org