Early antibiotics in UNDIFFERENTIATED sepsis- a friend or foe?

Gabor Xantus

Acknowledgement

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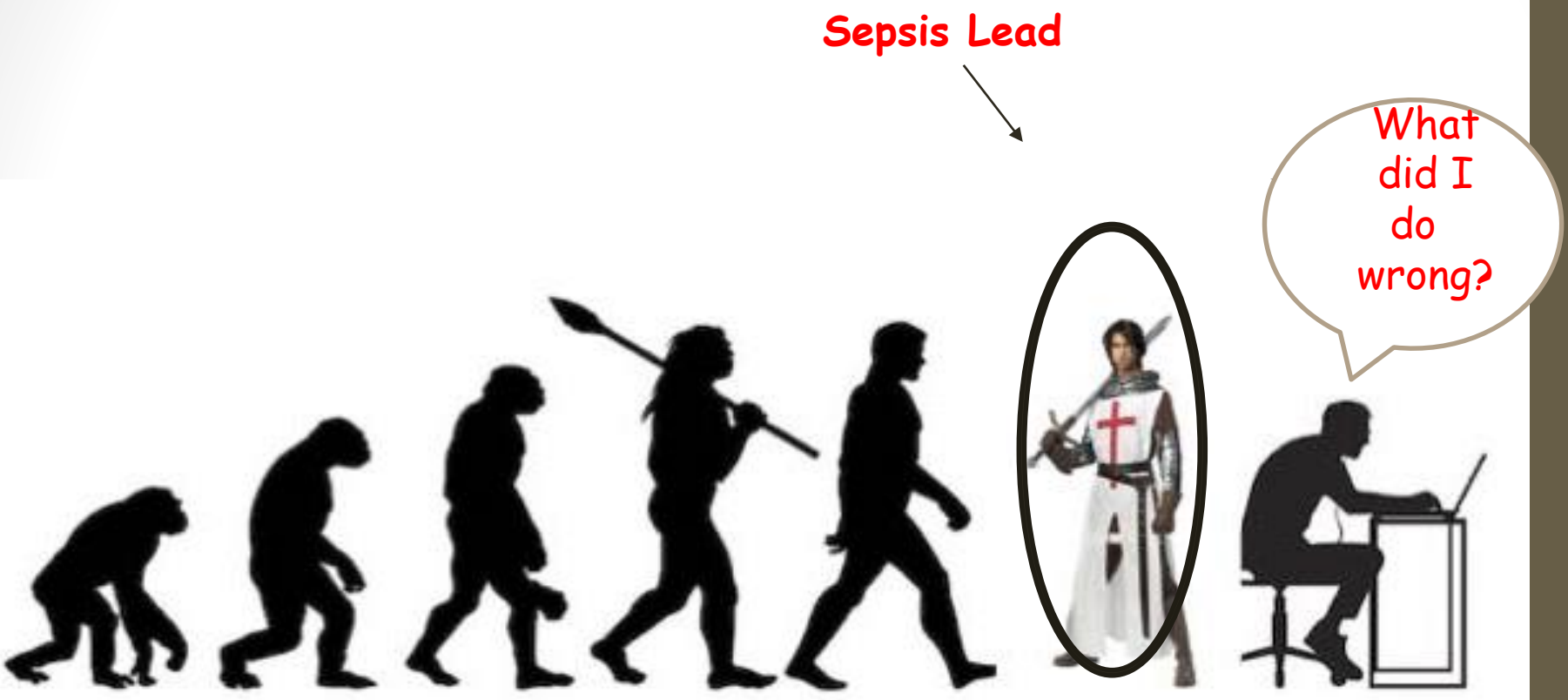
- And my family who tolerated quite well that I was not around in the last year or so…

Audits in 3 hospitals

No improvement in 7 and 30 days mortality with increased adherence to SEPSIS-6 (number of patients receiving antibiotics and fluids < 1 hour)

Where I came from



Sepsis 6 targets within 1 hour and improve outcome receive more funding

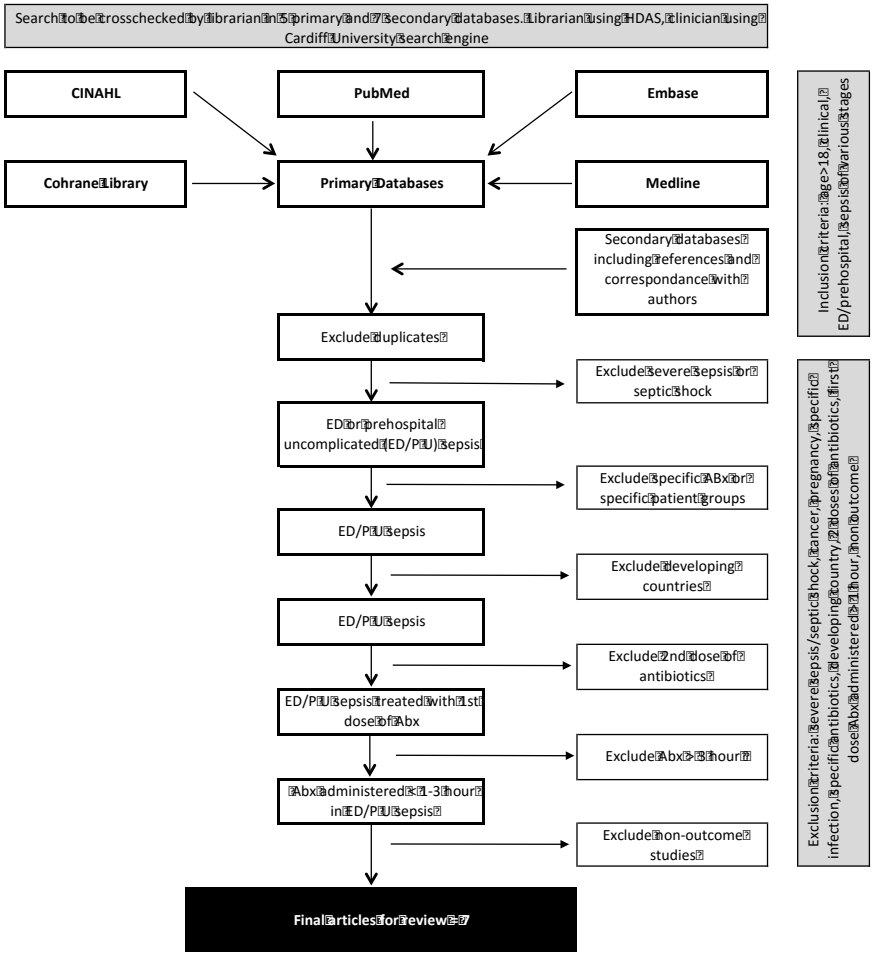
What does the literature say?

- Kumar et al. (2007) 7% increase in mortality with the elapsed hour in the ICU (single-center observational)
- Siddiqui and Razzak (2010) no evidence of benefit in the ED in severe sepsis/septic shock (Cochrane Review)
- Seymour et al. (2015) no no evidence of benefit in the ED in severe sepsis/septic shock (systematic review/meta-analysis)
- NO DATA REGARDING UNDIFFERENTIATED SEPSIS

I do not want to touch upon

- No set definition
- No uniform screening method (SIRS, ATS, Manchester Triage, etc.)
- No standardised identification (ICD codes was physiology)
- No uniform stratification tool (PIRO, MEDS, SOFA, APACHE)
- No standardized mortality reporting (7,28,30,60,90, 360 day)

Review of evidence



Review of evidence

	Design	Location	Sample size	Obs period	Mortality Expressed	Grading (CEBM)
Jalili et al. 2013	Retrospective observational	Asia	145	03.07-06.06	**Improved (%)**	**4**
Wisdom et al. 2014	Retrospective observational	Australia	220	01.12-12.12	**Not improved HR**	**2C**
De Groot et al. 2015	Prospective observational	Europe	1,137		**Not improved HR**	**2B**
Burrell et al. 2016	Pre-post observational	Australia	26,792	08.09-12.13	**Improved (%)**	**4**
Liu et al. 2017	Retrospective observational	USA	35,000	06.10-12.13	**Improved OR**	**2C**
Johnston et al. 2017✚	System review Meta-analysis	Australia	209✚	N/A	**Improved OR**	**1C**
Alam et al. 2018	RCT	Europe	2,672	06.14-06.16	**Not improved HR**	**1C**

TOTAL OBSERVATIONS > 66,500 more then a quarter received IVAB<1 hour

Review of evidence - 2

	Uncomplicated	Severe sepsis	Septic shock
Jalili et al. 2013	No mortality benefit	No mortality benefit	Trending towards benefit
Wisdom et al. 2014	No mortality benefit	No mortality benefit	N/A
De Groot et al. 2015	No mortality benefit	No mortality benefit	No mortality benefit
Burrell et al. 2016	No mortality benefit	Improved mortality	N/A
Liu et al. 2017	No mortality benefit	Trending towards benefit	Significantly improved mortality
Johnston et al. 2017✚	N/A	N/A	N/A
Alam et al. 2018	N/A	N/A	N/A

Step back and take a cold hard look

Noise or signal?

- Jalili et al. (2013) potential selection bias, descriptive statistics, inadequate power, did not adjust for fluids/vasopressors
- Wisdom et al. (2014) potential selection bias, inadequate power, did not adjust for fluids/vasopressors
- De Groot et al. (2015) sound methodology but did not recruite to power in septic shock
- Burrell et al. (2016) unreliable database, scant demographics, did not adjust for fluids/vasopressors
- Liu et al. (2017) did not adjust for fluids/vasopressors
- Alam et al. (2018) >30% intentional protocol violations resulting control arm 1/10th of the interventional arm, did not adjust for fluids/vasopressors, not adjusted to severity

Unexpected finding

Unexpected findings

- De Groot et al. (2017) longer hospitalization in the low acuity cohort if antibiotics started < 3 hours. No subgroup analysis for adverse events N= 412No analysis on departmental impact: crowding, LOS in ED, length on trolleys, etc.

- Burrell et al. (2017) significant increase in mortality in the low acuity cohort from 3.2% to 6.2% (p=0.047) if antibiotics and 2nd liter of iv fluid was commenced < 1 hour. No analysis for adverse events. No analysis on departmental impact: crowding, LOS in ED, length on trolleys, etc.

False positive result?

Spurious conclusions?

But my main concern is this

Opportunity cost

Opportunity cost represents the benefits an individual misses out on when choosing one alternative over another

Prioritizing the 1 hour target

- May deplete the shop floor (2x nurse to administer IVAB and fluids, 1x senior clinician to overlook the compliance, etc.)
- May increase the use of resuscitation beds and resources
- May slow down patient flow and increase of total LOS on ED, time spent on ED stretchers, etc. for the non-septic patients
- May increase the the chance for human errors, drug errors etc. due to increased pressure on staff

Conclusions

- Antibiotics, fluids and vasopressors are the cornerstone of management – no doubt
- The optimal timing/importance of timing of antibiotics in the undifferentiated sepsis cohort is yet unknown
- The uncomplicated sepsis group needs further research to customize care and ensure optimal patient management in departmental level

Any questions?

Thx for staying here on Thursday afternoon ☺