Challenges in building a diagnostic for 'sepsis'

Tim Sweeney, MD, PhD CEO, Inflammatix, Inc.

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Disclosures

Employee of and stockholder in Inflammatix, Inc.

Sepsis has two 'axes'

Sepsis-3 (*Singer et al. JAMA 2016*): Sepsis is defined as <u>life-threatening</u> organ dysfunction caused by a dysregulated <u>host response to infection</u>.

"Is there an infection?"

Acute infection:

Antibiotics, maybe discharge?

Non-infectious Illness:

Other dx, maybe discharge?

SEPSIS:

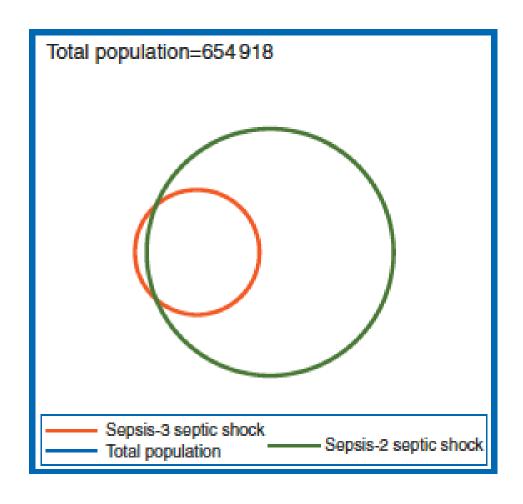
Broad-spectrum abx, Maybe ICU?

Other critical illness:

Other dx, maybe ICU?

"Is the patient really sick?"

Who has 'organ dysfunction'?

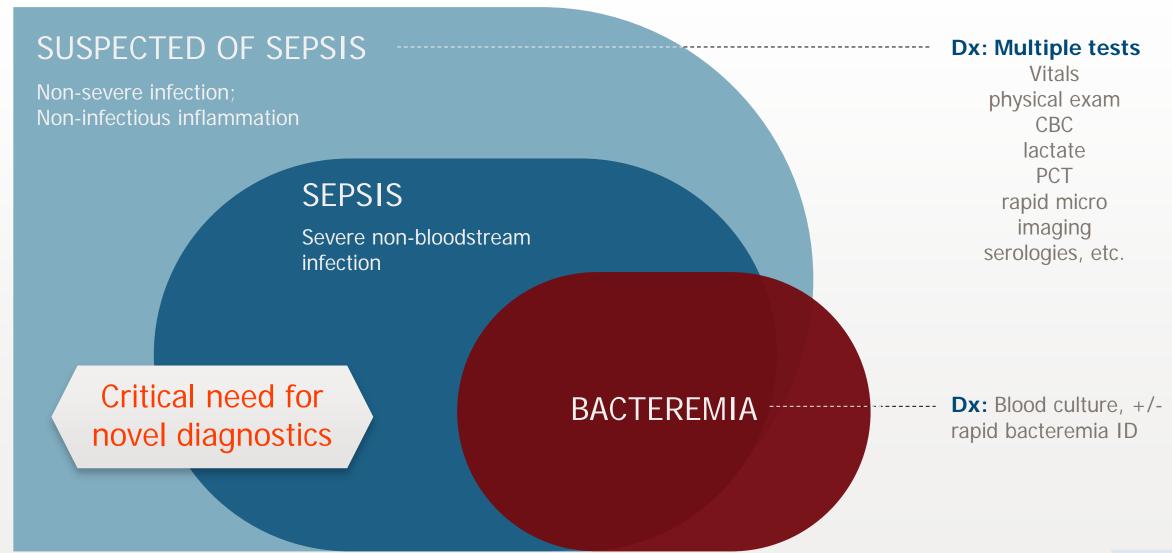


In a cohort of 654k ICU patients:

Green = sepsis-2 + shock Orange = sepsis-3 + shock

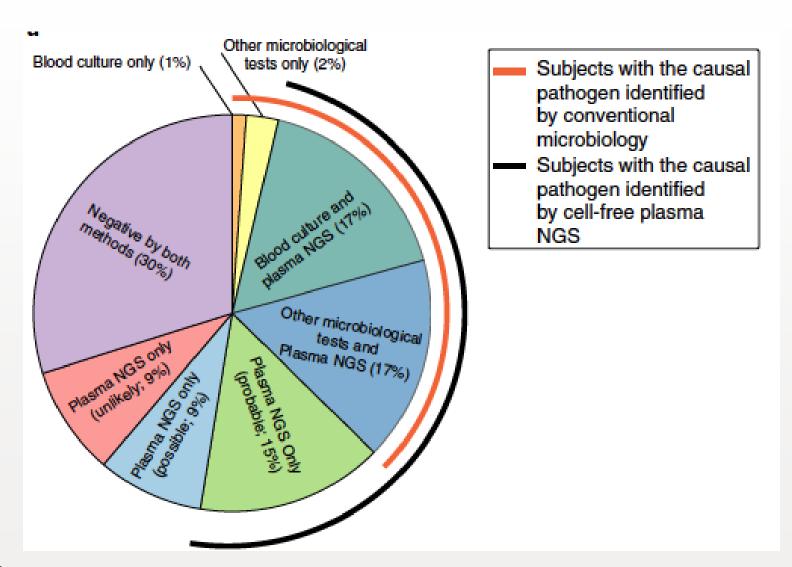
Which one is 'right'?

Bacteremia diagnostics are not necessarily sepsis diagnostics



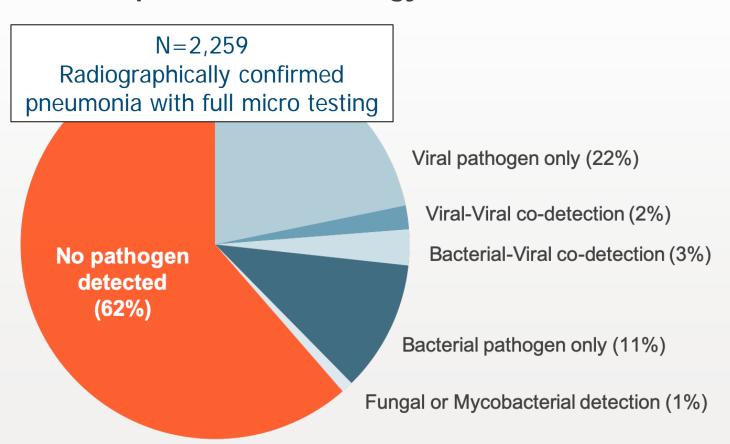
Is a microorganism a pathogen?

Pushing the bounds with NGS is only a marginal benefit



Who has a non-bloodstream infection?

Most patients with infections don't have positive microbiology



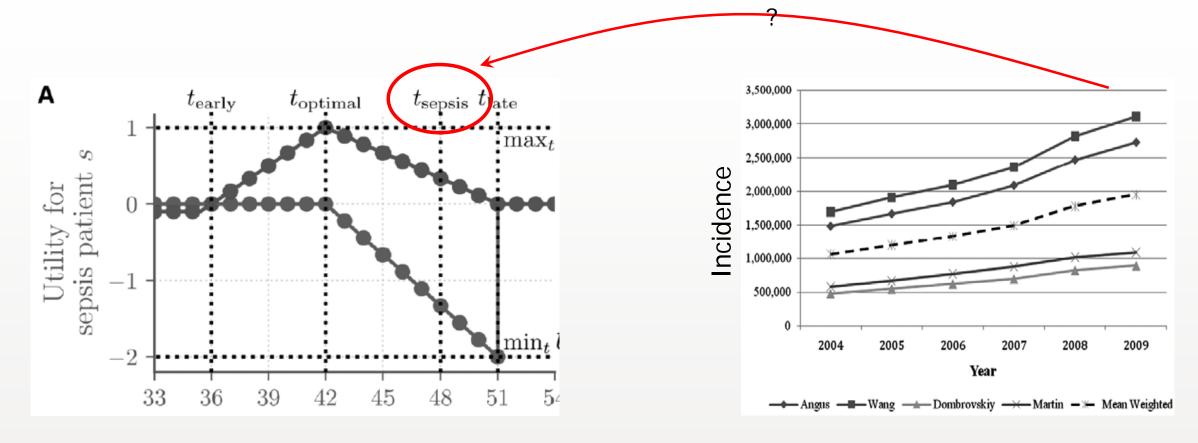
Physicians can't agree on the rest:

Free kappa 0.24(!) – 0.7 in adjudicating who has a bacterial infection

Lopansri, J Intens Care, 2019

Jain et al, NEJM 2015 Inflammatix 7

EHR 'sniffers': what is 'sepsis' in the record?

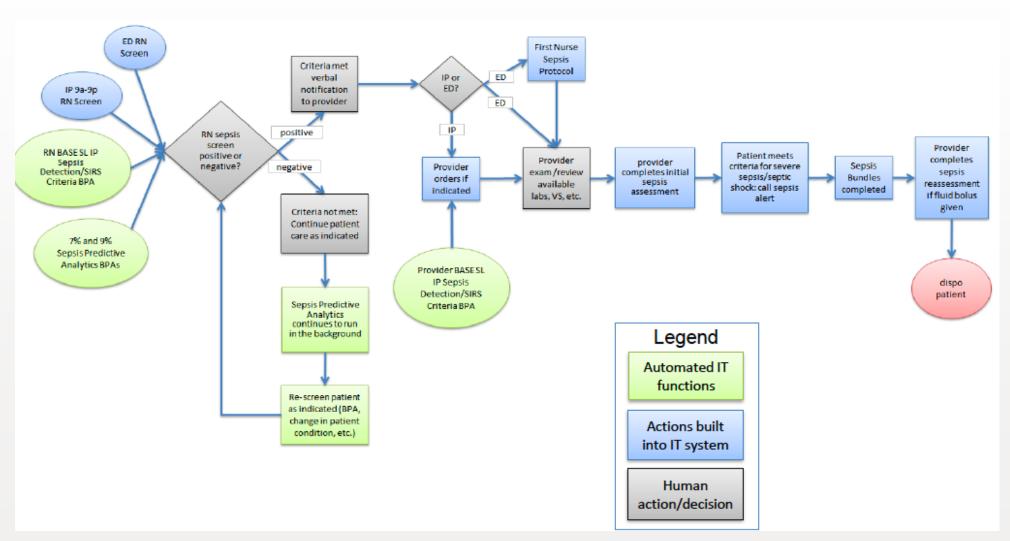


All EHR models rely on 'time of sepsis'...

...but 'sepsis' has a ~5-fold range using different criteria!

Workflow: Early - POC? Late - clinical lab?

The right answer doesn't help if given at the wrong time



Prior 'sepsis' diagnostics have been major market failures

Must make an economic difference / must cause physician practice change

Sepsis: the LightCycler SeptiFast Test MGRADE®, SepsiTest™ and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi – a systematic review and economic evaluation

Stevenson M, Pandor A, Martyn-St James M, Rafia R, Uttley L, Stevens J, et al. Sepsis: the LightCycler SeptiFast Test MGRADE®, SepsiTest™ and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi – a systematic review and economic evaluation. *Health Technol Assess* 2016;**20**(46).

What does the future hold?

EHR 'sniffers'

- Instant (but not in ED)
- Risk stratification / prognostication
- What does a clinician do with the data?

Biomarker panels

- 5-30 min
- Infection and prognostication separately and purposefully
- Is the marker generalizable?

Rapid ID + AST

- 4-6 hrs
- AST routinely actionable
- 'Negatives' decreased if downstream of good biomarkers
- Still lots of 'negatives'; genotypic vs. phenotypic AST

Someday:

Therapy-response prediction? 'Endotypes'?