

Beyond Uncomplicated vs Complicated: New Consensus Statements and Recent Clinical Trials in *Staphylococcus aureus* Bacteremia

Catherine Liu, MD

Professor

Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center

Division of Allergy and Infectious Diseases, University of Washington

Disclosures

- Research support from SNIPR Biome and AstraZeneca
- Consensus statements presented today are for adult patients

Overview

- 2026 IDSA/ESCMID Consensus Statements on *S. aureus* Bacteremia (Part 1)
- “Rapid fire” recent randomized trials in SAB

SAB Guideline Project Panel

IDSA	ESCMID	IDSA Methodologist
<u>Co-chairs</u> Henry Chambers, MD Catherine Liu, MD	<u>Co-chairs</u> Winfried Kern, MD Francois Vandenesch, MD	Lara Kahaleh, PhD
<u>Panel Members</u> Cesar Arias, MD, PhD Douglas Black, PharmD Helen Boucher, MD Vance Fowler, MD Marisa Holubar, MD, MS Chase McNeil, MD Loren Miller, MD, MPH Kyle Popovich, MD, MS Mark Rupp, MD Marc Scheetz, PharmD, MSc Bo Shopsin, MD Luke Strnad, MD	<u>Panel Members</u> Thomas Benfield, MD, DMSc Aubrey Cunnington, PhD, BMBCh Barbara Hasse, MD Achim Kaasch, MD Vincent Le Moing, MD, PhD Martin Llewelyn, MD L. Eduardo Lopez Cortes, MD Mical Paul, MD Siegbert Rieg, MD Alex Soriano, MD Steven Tong, PhD, MBBS	

SAB Guideline Project Overview

Current Scope (Part 1: 7 consensus statements for adults and children)

- Risk stratification
- Diagnostic evaluation
 - Follow-up blood cultures, echocardiography, whole-body imaging
- Duration of therapy

Future

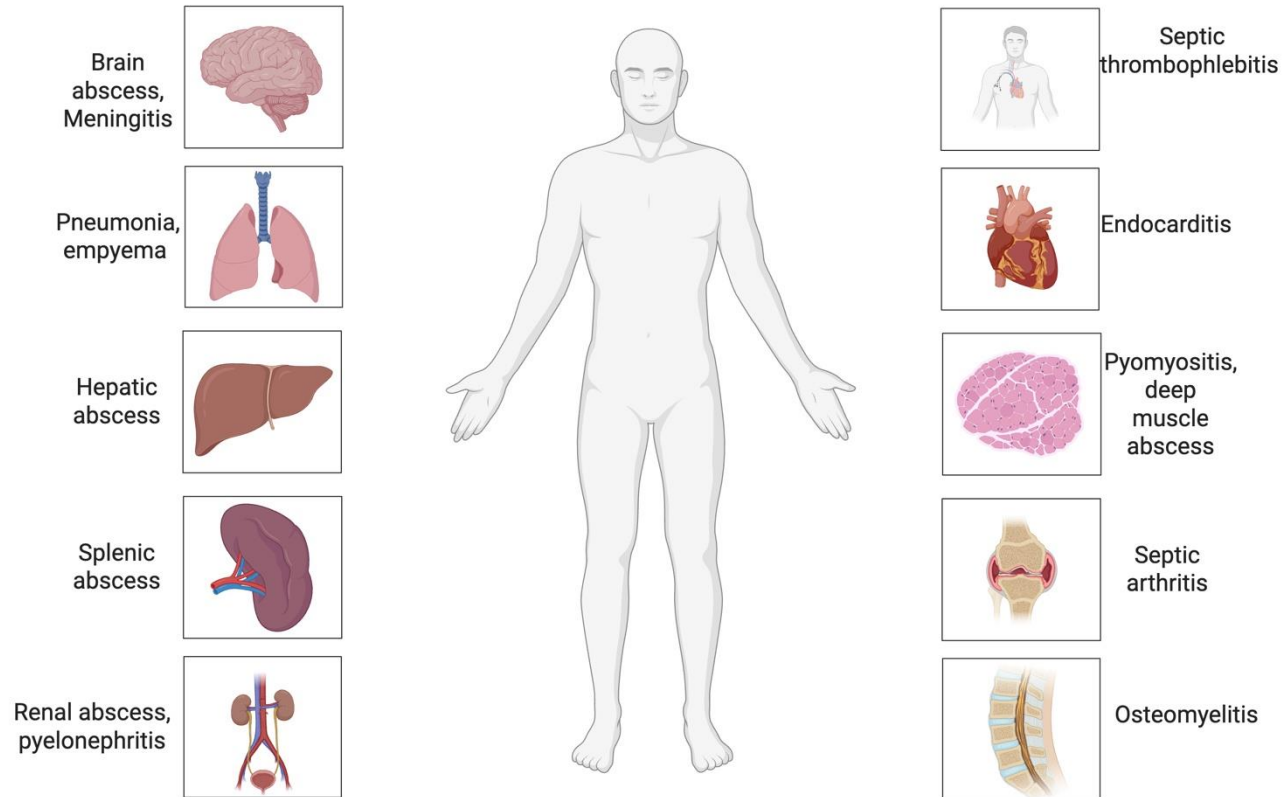
- Antibiotic selection in management of MRSA and MSSA bacteremia, oral switch, long-acting lipoglycopeptides

Case

48 year old female with h/o GERD, newly diagnosed breast cancer admitted with fever after 1st cycle of chemotherapy

- ANC 480, hemodynamically stable
- No murmur, catheter site without erythema, no localizing exam findings
- **Day 1** blood cultures (port/ peripheral): **2/2 MSSA**

Is this patient at low or increased risk for deep-seated or metastatic foci of infection?

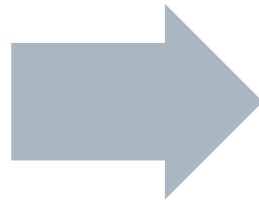


What diagnostic workup should I pursue?

A Paradigm Shift

Complicated/ Uncomplicated

- Variable definitions used
- Risk factors $\neq$ Diagnosis of deep-seated or metastatic focus of infection
- Potential misclassification → under or overtreatment



Risk Stratification

- Risk-informed diagnostic evaluation
- Establish precise clinical diagnosis
- Guide individualized management decisions

Consensus Statement 1: Risk Stratification

Key Risk Factors



Positive blood culture ≥ 48 hrs after first positive*



Community-onset*



Intracardiac device*,#

Other Important Factors

- Predisposing heart valve condition*, injection drug use*, endovascular graft, SAB in prior 90 days
- Signs or symptoms of deep-seated or metastatic foci, embolic events*, > 1 non-contiguous focus*, unknown focus

*Endocarditis increased-risk features

#Prosthetic heart valve, permanent pacemaker, automatic implantable cardioverter-defibrillator, LVAD

Initial Evaluation of SAB (Detailed H&P, follow-up blood cultures, TTE, CVC removal, ID consult)

Risk Stratification

Risk Factors for Deep-Seated/ Metastatic Foci or Relapse of Infection Present?

No (low risk)

Yes (increased risk)

Diagnostic Evaluation

Tailored Workup

*Ongoing clinical
assessment*

Deep-seated or metastatic focus identified?

No

Yes

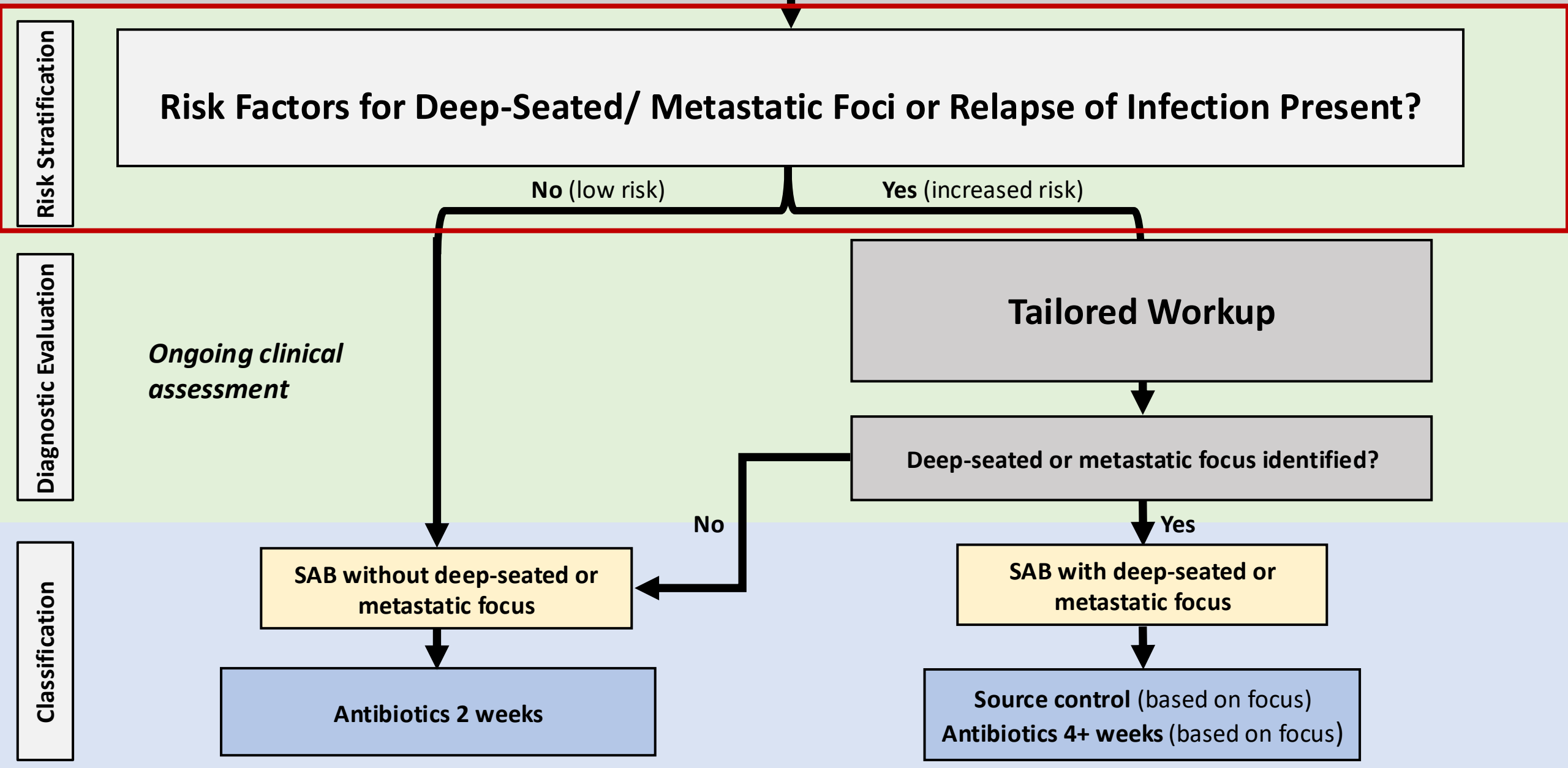
**SAB without deep-seated or
metastatic focus**

**SAB with deep-seated or
metastatic focus**

Classification

Antibiotics 2 weeks

**Source control (based on focus)
Antibiotics 4+ weeks (based on focus)**



Case (cont'd)

Day 1 port & peripheral blood: **2/2 MSSA**

Day 2 port & peripheral blood: **2/2 MSSA**

Day 3 port is removed

What is your approach to follow-up blood cultures (FUBC)?

Consensus Statement 2

Obtain 2 sets of FUBC at 48 hrs after first positive

Repeat as 1 or 2 sets every 24-48 hrs until negative



Day 1
+ Bcx



+ FUBC at ≥ 48 hours



- Further diagnostic evaluation
- Source control reassessment

Individualize FUBC strategy

Intensify monitoring (eg, negative FUBC on 2 consecutive days if + FUBC ≥ 48 hrs, endocarditis/ endovascular focus, ongoing signs/ sx)

Positive FUBC $\geq$ 48 hrs is a Key Predictor of Deep-Seated or Metastatic Foci of Infection

17 studies (N $\geq$ 100 pts) found significant association (aOR range 1.3-45.6) regardless of timing of active antibiotic therapy

Measured from first positive	Measured from start of active abx	Measured from start of abx
Finkelstein 2012	Chang 2003	Grillo 2022 (active treatment not specified)
Gow 2015	Gallego Rodriguez 2024	
Longobardo 2019	Hill 2007	
Palraj 2015	Gasch 2014	
Papadimitriou-Olivgeris 2022	Kinamon 2023	
Tubiana 2016	Perez 2018	
Kim 2024		
Wang 2023		
Albertson 2015		

Case (cont'd)

Day 3 blood cultures (collected after port removal) are negative and she is afebrile.

Do you recommend a TTE?

Consensus Statement 3

Routinely perform TTE in all adults with SAB

- Although there may exist a group of adult patients with SAB at very low risk of endocarditis for whom TTE may be unnecessary, criteria to define such a population have not been consistently established.

Evidence Summary: Performance Characteristics of SAB Prediction Scores for Endocarditis

Prediction Score	Studies	Sensitivity (%)	Specificity (%)	PPV(%)	NPV (%)
VIRSTA	8 studies	97% (92%-100%)	43% (36%-53%)	20% (9%- 20%)	99% (97%-100%)
VIRSTA+	1 study	100%	33%	23%	100%
PREDICT D1	7 studies	15% (0%-30%)	96% (93%-99%)	33% (0%-67%)	89% (84%-95%)
PREDICT D5	9 studies	94% (52%-100%)	46% (26%-69%)	19% (9%-31%)	96% (95%-100%)
POSITIVE *Medians (range) are reported if > 1 study	5 studies	78% (76%-93%)	69% (63%-74%)	27% (14%-38%)	95% (93%-100%)
LAUSTAPHEN	1 study	97%	58%	26%	99%

- Primarily designed to identify **low risk** patients for whom **TEE** could be deferred
- Only 1 study assessed if scores could safely exclude IE without TTE with <1% risk, NLR <.05
 - No score met predefined threshold to r/o IE without TTE**

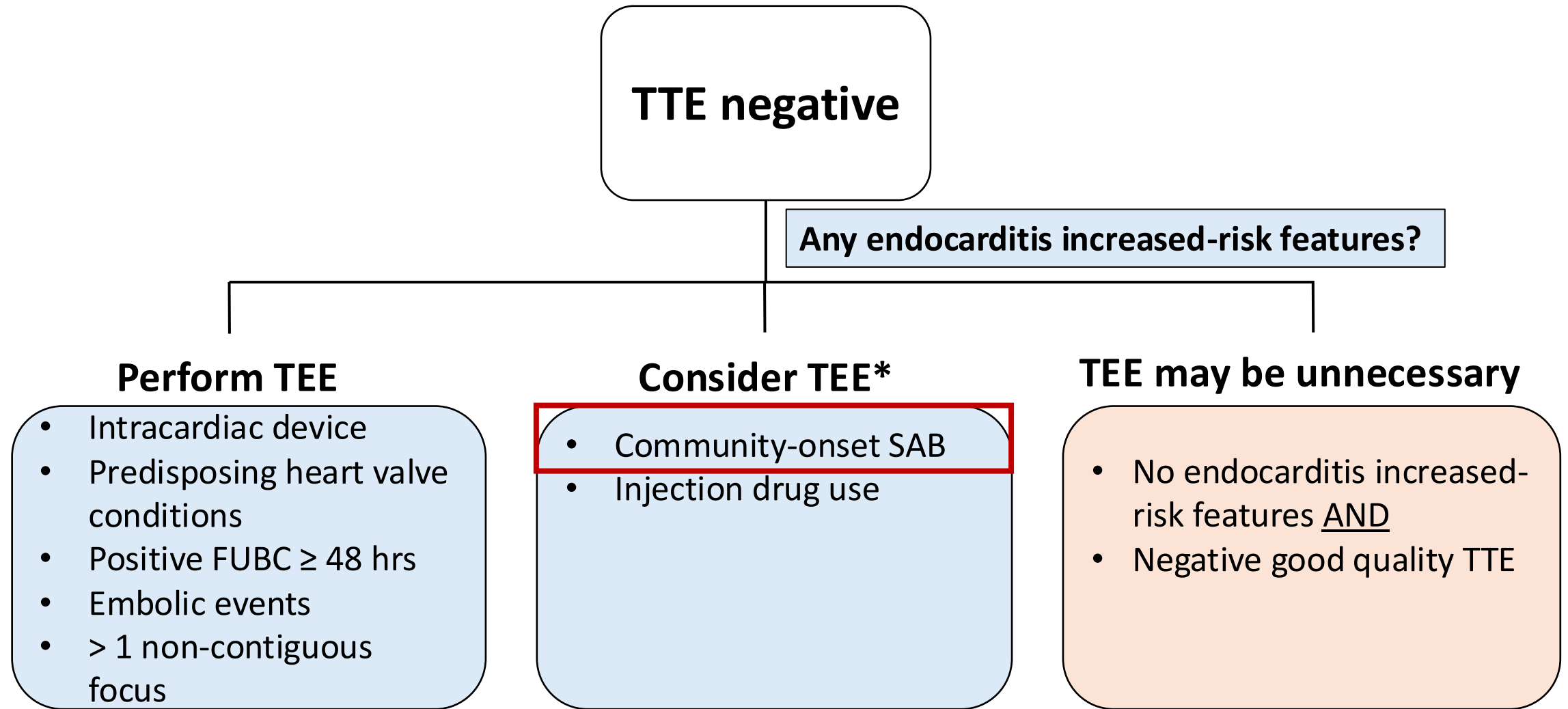
Case (cont'd)

Blood cultures collected on Day 3 remain negative to date. She has been afebrile for 24 hrs.

TTE: negative for valvular vegetations, but fair quality study due to motion artifact

Do you recommend a TEE?

Consensus Statement 4: Risk Stratified Approach to TEE



***Based on TTE quality, other IE-risk factors, clinical response, impact on management**

Case (cont'd)

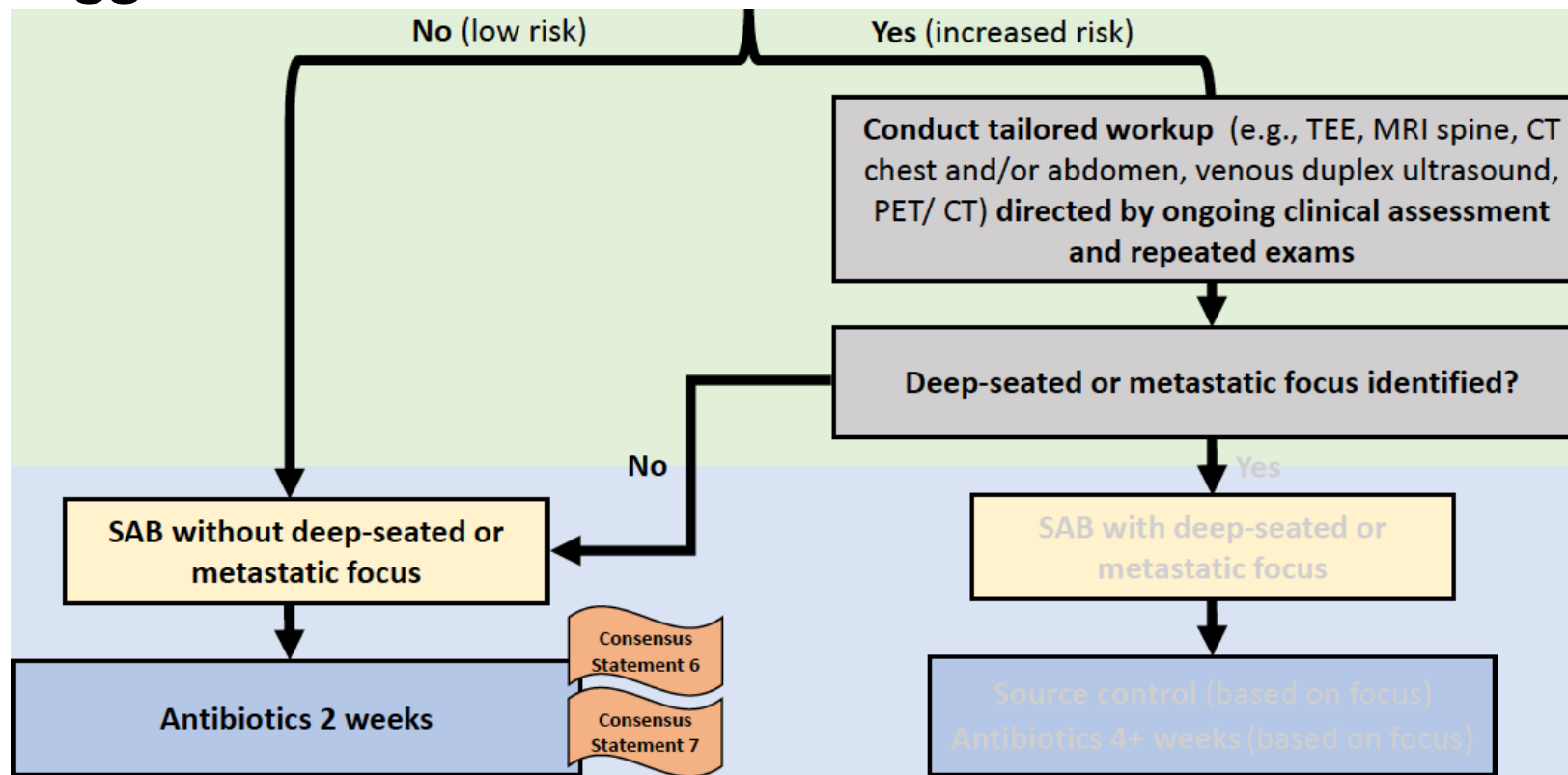
- TEE deemed high risk due to h/o esophageal stricture
- Repeat TTE performed, good quality study (motion artifact resolved): no vegetations, no valve stenosis/ sclerosis, no significant regurgitation
- Afebrile x 48 hours, no new signs or symptoms of infection, ANC 1380
- **Day 3** blood cultures: negative x 48 hrs

What duration of therapy do you recommend?

Consensus Statement 7

Patients stratified as increased-risk SAB and classified as **without deep-seated or metastatic foci of infection** after diagnostic evaluation:

- Suggest antibiotic treatment duration of **2 weeks**



Some Caveats and Potential Barriers...

- **Diagnostic limitations** may restrict ability to exclude deep-seated infection and >14 days of therapy should be considered in select pts:
 - **Retained intracardiac device, recent endovascular graft, DVT at central venous catheter site**, particularly when high suspicion for deep-seated infection (e.g. + FUBC ≥ 48 hrs)
- **Prospective studies** needed to validate risk-stratified approaches to treatment duration
- **Educate patients** about signs/ symptoms that should prompt re-evaluation, including those suggestive of previously undetected deep-seated or metastatic infection

Conduct initial evaluation

History of illness, past medical & surgical history, physical exam, follow-up blood cultures, TTE, CVC removal, ID consult

Consensus
Statement 2

Consensus
Statement 3

Risk Stratification

Assess whether at least one risk factor exists

Key risk factors: community-onset¹, positive FUBC obtained ≥ 48 hours after first positive¹, intracardiac device^{1,2}

Other important factors: predisposing heart valve conditions^{1,3}, injection drug use¹, endovascular graft⁴, SAB in prior 90 days, signs or symptoms of deep-seated/ metastatic foci, embolic events¹, >1 focus of infection¹, unknown focus of infection

Consensus
Statement 1

No (low risk)

Yes (increased risk)

Diagnostic Evaluation

Conduct tailored workup (e.g., TEE, MRI spine, CT chest and/or abdomen, venous duplex ultrasound, PET/ CT) **directed by ongoing clinical assessment and repeated exams**

Consensus
Statement 4

Consensus
Statement 5

Deep-seated or metastatic focus identified?

No

Yes

SAB without deep-seated or metastatic focus

SAB with deep-seated or metastatic focus

Classification

Antibiotics 2 weeks⁵

Consensus
Statement 6

Consensus
Statement 7

Source control (based on focus)
Antibiotics 4+ weeks⁵ (based on focus)

Summary

Uncomlicated/
Complicated SAB



Initial evaluation

- Careful history and physical exam, follow-up blood cultures, TTE

Risk stratification

- **STRATIFY** patients as “**low risk**” or “**increased risk**” for deep-seated/ metastatic foci or relapse of infection

Diagnostic evaluation

- **IDENTIFY**: Intensity of diagnostic evaluation guided by risk factors, clinical findings, and ongoing assessment

Classification

- **CLASSIFY** as “**SAB with or without deep-seated or metastatic focus of infection**”
- Individualize treatment decisions based on final diagnosis

Validation of the risk stratification framework is needed

Cefazolin vs Antistaphylococcal Penicillin (ASP) as Initial Therapy for MSSA Bacteremia



Efficacy

Cefazolin $\approx$ ASP

CloCeBa: Cefazolin **noninferior** composite 90-day outcome: micro success w/o relapse, clinical success, mortality

SNAP: Cefazolin **noninferior** 90-day mortality



Safety

Cefazolin $>$ ASP

CloCeBa and SNAP: Cefazolin $\downarrow$ **serious adverse events**, AKI, Rx discontinuation due to adverse events



Questions/ Caveats

Cefazolin Inoculum Effect?

CloCeBa: Noninferiority in blaZ type A subgroup not met

SNAP: Similar treatment effect in endocarditis group; results of testing for inoculum effect pending

Oral Switch vs Continued IV Therapy for Low Risk SAB



Efficacy

PO switch $\approx$ IV

SABATO (low-risk SAB): No difference in composite primary outcome of SAB-related complication in 90d

POET (stable, L-sided IE): No difference treatment failure MSSA subgroup at 6 mths & 5 year follow-up



Safety

PO switch $\approx$ IV

SABATO: Adverse events RR 1.28; 95% CI (0.84-1.95)

POET: Adverse events RR 0.83; 95% CI (0.36-1.87)



Questions/ Caveats

When to switch?

SABATO: 5-7 days IV

POET: median 17 days IV

Does this apply to MRSA?

SABATO: 8% MRSA

POET: 0% MRSA

Dalbavancin vs SoC IV as Consolidation Therapy for SAB



Efficacy

Dalbavancin $\approx$ IV

DOTS:

Not superior to IV by
DOOR outcome

Non-inferior to IV clinical
efficacy outcome



Safety

Dalbavancin $\approx$ IV

DOTS:

Similar rates of SAEs and
treatment-related AEs

More AE leading to
treatment
discontinuation in IV arm



Questions/ Caveats

Which population?

**When to switch? DOTS
(median 7d IV)**

Optimal dosing? TDM?

Risk of resistance?



Thank you!

catherine.liu@fredhutch.org

Consensus Statement 5

- In patients with increased-risk SAB and with an **unknown focus** after initial evaluation, perform either:
 - **Whole-body imaging (e.g. [18F]FDG-PET/CT) OR**
 - **Combinations of imaging modalities** (e.g. chest/ abd CT, duplex venous U/S, etc) that evaluate most likely sites of infectious foci

Remarks

- Assumes initial diagnostic evaluation including follow-up blood cultures, echocardiography, and symptom/exam-directed imaging has been performed based on risk stratification and as clinically indicated.
- Decisions regarding imaging approach should be guided by the patient's clinical condition and availability of each imaging modality.

What is the Effect of PET/CT vs no PET/CT on Clinical Outcomes Among Patients with Increased-Risk SAB?



Mortality

3 studies: benefit
(range aHR 0.20-0.45)

1 study: no benefit
(confounder & immortal
time bias aHR 1.07,
95%CI 0.63-1.83)



Relapse

2 studies: no difference
in relapse 3 or 6 mths

1 study: ↑ relapse in
PET/CT group (7.6% vs
2.2%, $p < .0001$)

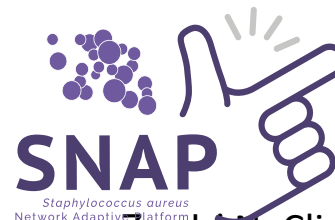


Treatment Modification

**3 studies: ↑ duration of
Rx** (42-47 vs 16-23d)

**2 studies: ↑ source
control** interventions

RCTs needed!



Consensus Statement 6

Patients **stratified as low-risk SAB** and **classified as without deep-seated or metastatic foci of infection:**

- Suggest antibiotic treatment duration of **2 weeks** rather than longer or shorter courses

Evidence Summary: Duration of Therapy Low-Risk SAB without Deep-Seated or Metastatic Foci

15 retrospective studies

(None met all prespecified criteria for low-risk SAB)

- **14 days vs > 14 days:** No difference in Rx failure, relapse, or death at 90 days
- **< 14 days vs $\geq$ 14 days:** 1 study $\uparrow$ risk of relapse; 1 study no difference in relapse; 3 studies no difference in mortality

3 systematic reviews

(Only 1 included studies with adjusted effect estimates)

- No significant difference in relapse, 30-day or 90-day mortality
- **All 3 concluded well-designed RCTs needed**