Erasmus MC
University Medical Center Rotterdam

EMA meeting
October 2012

Bacteraemia or severe sepsis as indication?

Yes we can (and should)!

BJ Rijnders, MD, PhD
Dep. Internal Medicine
Section of Inf Dis
Erasmus MC
Rotterdam, NL

Is it possible to include a sufficient amount of patients with clinically significant bacteremia in phase III studies?

200 YES 400 ? >500 ? >1000 ?

Most recent EMA “approval” on IV antibiotic : Ceftaroline

cSSSI (n=693):
N=29 (4%) with bacteraemia
Severe infections? 0.4% mortality (n=3, cancer, cardiac/ respiratory failure)

CAP (n=580):
N=23 (4%) with bacteremia
Severe? PORT risk class III and IV Mortality 2.4% (n=15)

Inappropriate Initial Antimicrobial Therapy and Its Effect on Survival in a Clinical Trial of Immunomodulating Therapy for Severe Sepsis

N=904 microbiologically confirmed severe sepsis/septic shock

468 patients (52%) with documented BSI !

28d mortality: **24%** (168/ 693) when adequately treated versus
39% (82/211) with inappropriate initial AB therapy (*P*<0.001)

=> 38% relative or 15% absolute mortality reduction

Am J Med. 2003;115:529 – 535

Adequacy of Early Empiric Antibiotic Treatment and Survival in Severe Sepsis: Experience from the MONARCS Trial

Table 3. Twenty-eight–day all-cause mortality rates among 2634 patients with suspected sepsis, according to receipt of adequate or inadequate antibiotic treatment.

Variable	Mortality rate, proportion (%) of patients	
	With adequate treatment (n = 2391)	With inadequate treatment (n = 243)
Overall mortality	793/2391 (33.2)	105/243 (43.2)
Treatment group		
Afelimomab	364/1174 (31.0)	57/131 (43.5)
Placebo	429/1217 (35.3)	48/112 (42.9)
Age in years		
<65	346/1328 (26.1)	42/118 (35.6)
⩾65	447/1063 (42.1)	62/124 (50.0)
Septic shock	541/1564 (34.6)	77/150 (51.3)

24% relative

10% Absolute

Mortality reduction !

MacArthur RD et al. Clin Inf Dis 2004

Adequacy of Early Empiric Antibiotic Treatment and Survival in Severe Sepsis: Experience from the MONARCS Trial.

Site of infection		
Abdomen	210/595 (35.3)	26/67 (38.8)
Lung	222/619 (35.9)	30/66 (45.5)
Blood[b]	204/568 (35.9)	33/68 (48.5)
Other or none identified	157/609 (25.8)	16/42 (38.1)
Positive blood culture results	321/935 (34.3)	48/105 (45.7)

NOTE. Data are no. of patients who died/no. of patients in group or subgroup (%).

[a] E.g., fungus.

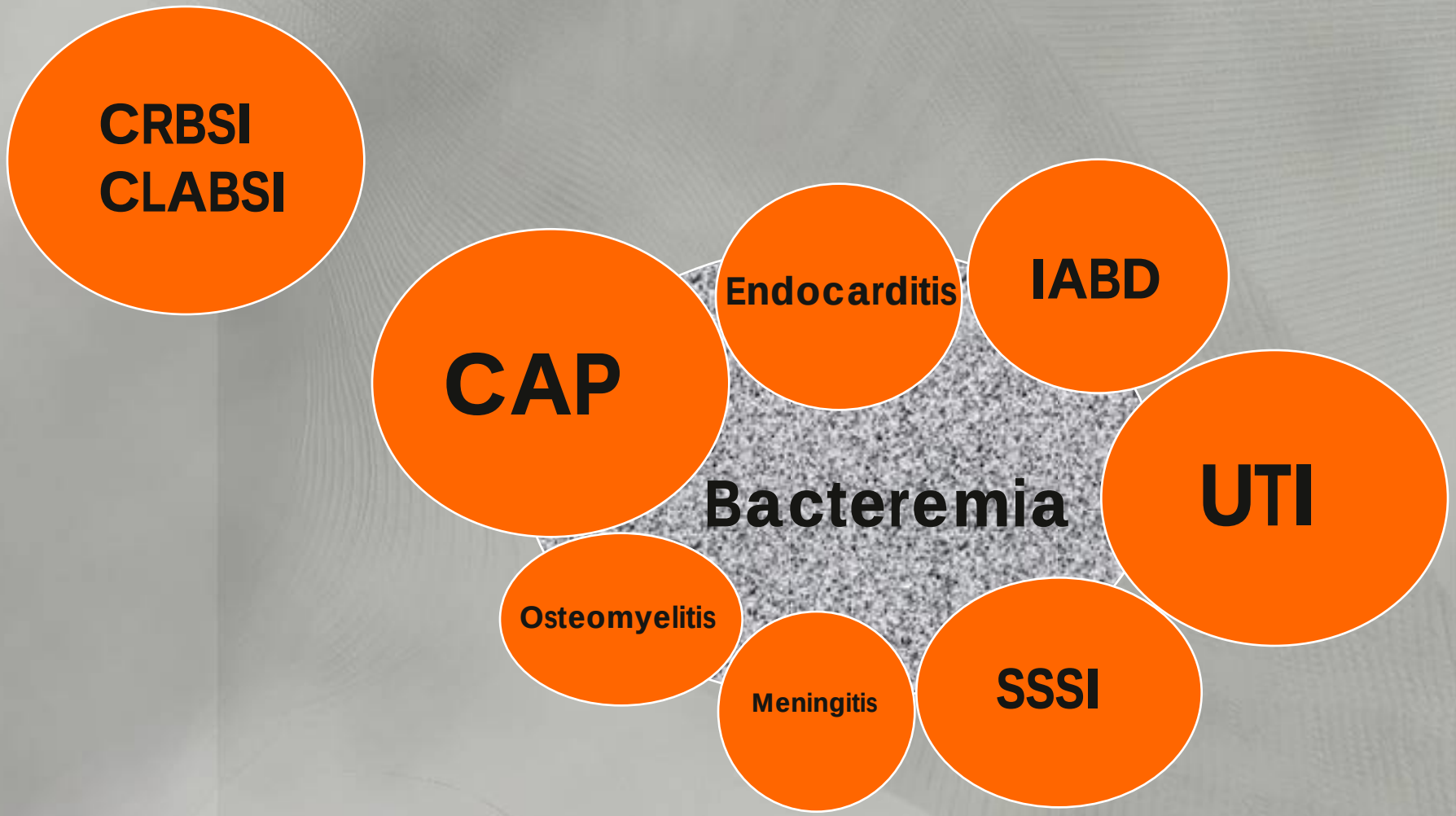
[b] Primary bacteremia, in which blood was the only identified site of infection.

= 1040 patients with BSI: **568** primary !

MacArthur RD et al. Clin Inf Dis 2004

Despite heterogeneity of the cause/source of the sepsis/bacteremia:

Treatment effect of appropriate versus inappropriate therapy = clear


CRBSI
CLABSI
CAP
Endocarditis
IABD
Bacteremia
UTI
Osteomyelitis
Meningitis
SSSI

3.5.1 Bacteraemia

Non-pathogen-specific

It may be possible to accumulate sufficient clinical data to support an indication for use of an antibacterial agent in the treatment of bacteraemia that is associated with specific types of infection, with or without restriction to certain pathogens. For example, in the case of agents that have been in use for many years and are indicated for use in a broad range of infections the total evidence may be considered sufficient for an indication that reads *Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above* (i.e. referring to the list of indications approved).

It is likely that at the time of first approval there will be very little clinical experience with an antibacterial agent in the treatment of bacteraemic patients. If no concern arises from review of the subset with accompanying bacteraemia then no statement is made about use in such patients in the SmPC except to mention the limited experience. If the antibacterial agent has been evaluated in several indications and the total number of bacteraemic patients treated across these indications is deemed sufficient (e.g. ~50 or more) to support a conclusion that efficacy is comparable to that in other patients or, at least, comparable to that of other treatments, then the addition of the sentence above could be considered appropriate.

Pathogen-specific

Studies that enroll patients with bacteraemia due to a specific pathogen but regardless of the underlying infection are not usually considered sufficient to support a pathogen-specific indication without additional qualification because this would imply that the test agent could be used to treat such cases regardless of the location of the primary focus/foci of infection (which will anyway be unknown in a proportion of cases).

What's the problem if new AB is used for bacteremia/sepsis of unknown source as long as this agent was well-studied in this patient population?

=> Clinicians do this all the time as 1/3th or more of cases of sepsis at the ER are initially of unknown origin

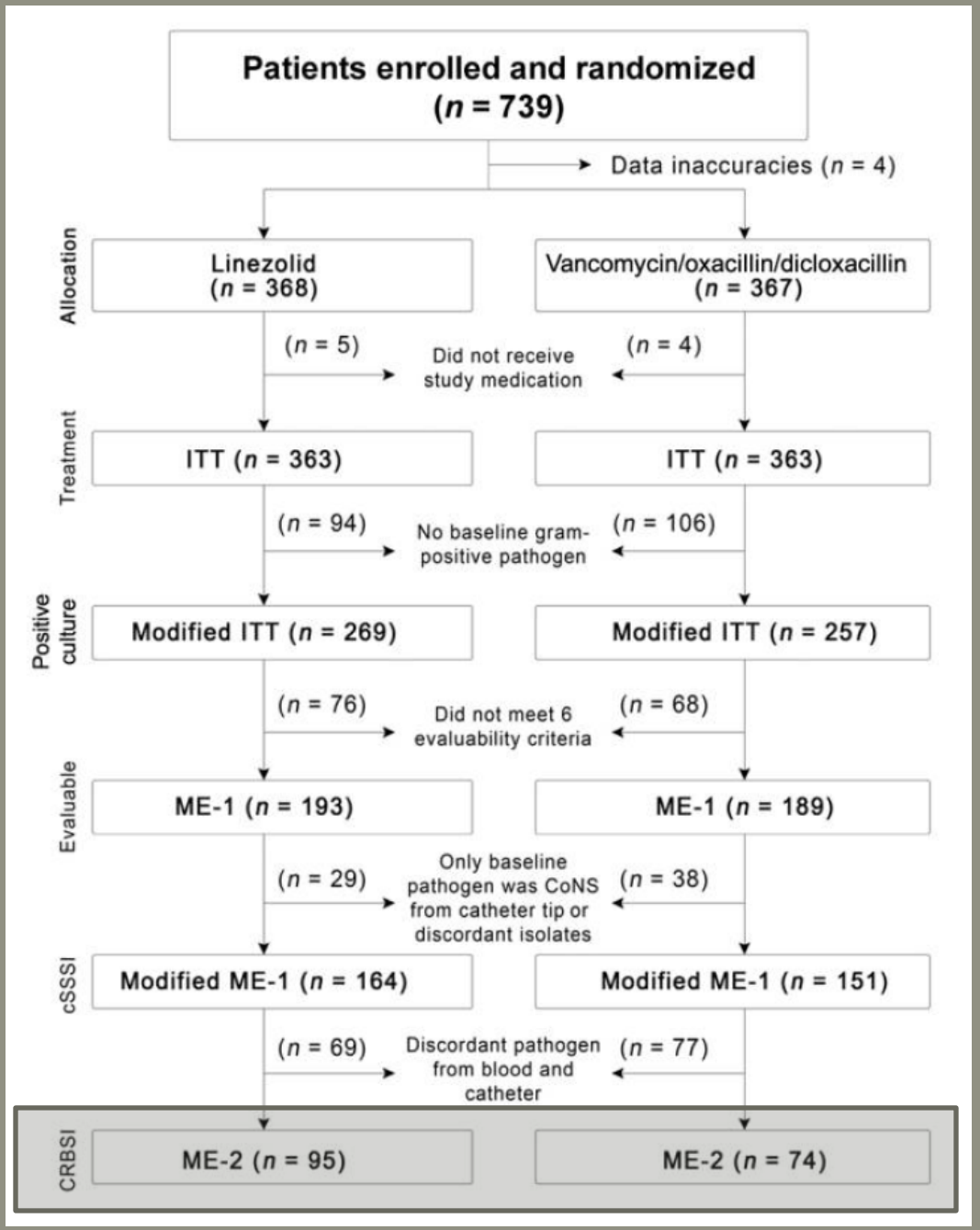
=> Ofcourse human PK and the best available animal PK PD data at least for the most frequent causes of sepsis are a conditio sine qua non

=> Study protocol could mandate switch to approved drug when source of bacteremia becomes clear during follow-up

With regards to S. aureus BSI: infection site remains unknown in substantial proportion of pts, with primary bacteraemia in up tot 33% of cases which means that a significant part of these serious infections are not covered by site-specific indications.

Study of linezolid for CRBSI can be seen as “a sepsis/bacteremia without a known source study” as only 23% of the 735 included pts turned out to have CRBSI

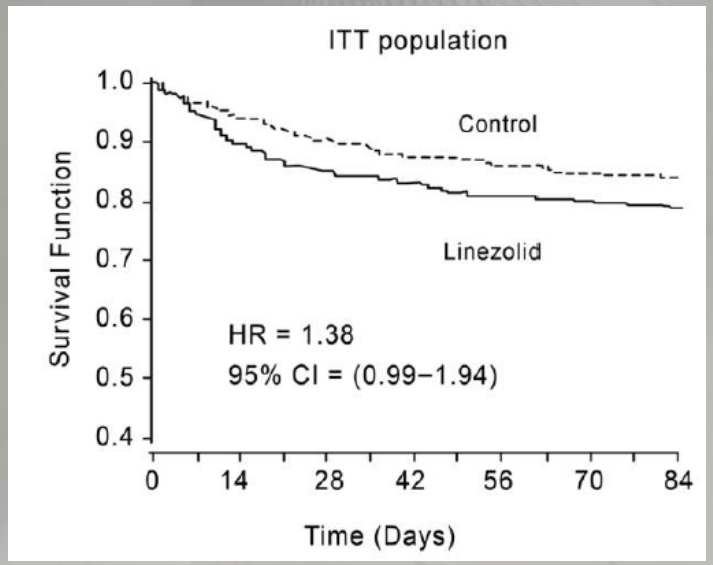
=>

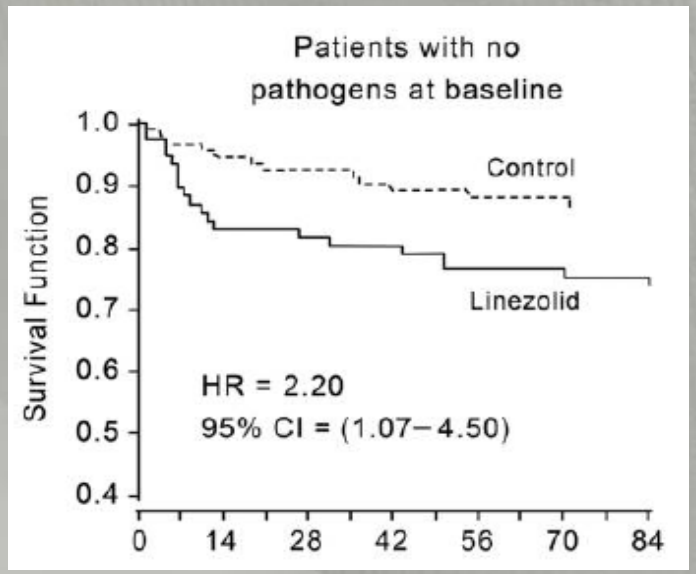

Patients enrolled and randomized (n = 739)
Data inaccuracies (n = 4)
Allocation
Linezolid (n = 368)
Vancomycin/oxacillin/dicloxacillin (n = 367)
(n = 5)
Did not receive study medication
(n = 4)
Treatment
ITT (n = 363)
ITT (n = 363)
(n = 94)
No baseline gram-positive pathogen
(n = 106)
Positive culture
Modified ITT (n = 269)
Modified ITT (n = 257)
(n = 76)
Did not meet 6 evaluability criteria
(n = 68)
Evaluable
ME-1 (n = 193)
ME-1 (n = 189)
(n = 29)
Only baseline pathogen was CoNS from catheter tip or discordant isolates
(n = 38)
cSSSI
Modified ME-1 (n = 164)
Modified ME-1 (n = 151)
(n = 69)
Discordant pathogen from blood and catheter
(n = 77)
CRBSI
ME-2 (n = 95)
ME-2 (n = 74)

23%

Study of linezolid for CRBSI can be seen as "a sepsis/bacteremia without a known source study" as only 23% of the 735 included pts turned out to have CRBSI

=> We learnt that linezolid +- azthreonam/amikacin should not be used in this setting





Study of linezolid for CRBSI can be seen as "a sepsis/bacteremia without a known source study" as only 23% of the 735 included pts turned out to have CRBSI

=> We learnt that linezolid +- azthreonam/amikacin should not be used in this setting

=> Possibly other AB used for empiric therapy of sepsis are inferior to others.

- Trials that study the efficacy of a drug for sepsis/bacteremia without a source could become "game changers" and improve care of this life-threatening clinical syndrome.

Clin Infect Dis. 2009 Jan 15;48(2):203-12

Pathogen-specific

Studies that enroll patients with bacteraemia due to a specific pathogen but regardless of the underlying infection are not usually considered sufficient to support a pathogen-specific indication without additional qualification because this would imply that the test agent could be used to treat such cases regardless of the location of the primary focus/foci of infection (which will anyway be unknown in a proportion of cases).

E.g. documentation of efficacy for severe sepsis/bacteremia of ceftaroline +- aztreonam/aminoglycoside would be very wellcome.

The drug is already approved for CAP and cSSI:

=> Pts could continue the drug as diagnosis of cSSI or CAP becomes clear

=> Pts responding to therapy without diagnosis of source continue as well

=> Pts with diagnosis of non-approved indication during therapy can switch to approved R/

612 **3.5.2 Treatment of acute bacterial infections in neutropenic patients**

....

629 The most objective basis for the assessment of efficacy would be the comparison of bacterial
630 eradication rates in the subset of patients with a positive blood culture pre-treatment between the
631 test and comparative regimens. Patients with an obvious primary focus should also have a
632 resolution of infection.

....

633 Due to the complex nature of these patients, difficulties in ascertaining the range of co-existing
634 pathogens and lack of clear distinction between the treatment and prophylactic role of antibacterial
635 agents (even in the subset with a documented bacterial pathogen) the resulting indication would
636 likely reflect the utility of the agent in the overall management of such patients rather than
637 specifying use in the treatment of bacterial infections.

⇒ The management of neutropenic patients with fever can be a labeled indication

⇒ Why should the treatment of (severe) sepsis/bacteremia of unknown source not become a labeled indication as well?

Not a good indication to study:

Suspected CRBSI: As low as 10% are confirmed to have CRBSI at the end

CRBSI in general: Coag neg staph = self-limiting if CVC is removed. Non-inferiority does not prove efficacy

Good indication:

CRBSI or CLABSI with S. aureus, but CVC removal should be obligatory

Primary S. aureus BSI

Other possible future indications that should be strongly considered:

- ***Severe sepsis of unknown origin or primary BSI in general***

  To start on the safe site: drug of which efficacy for some of the causes of sepsis and bacteraemia is already documented (SSSI, UTI, CAP)

  If later source is identified: appropriate/specific "for indication approved" therapy can be given (e.g. FQ for UTI)

- ***Empiric therapy for sepsis / bacteraemia in chronic hemodialysis patients***

  + Morbidity mortality is high and S. aureus BSI frequent in these patients

  + Study population / centers are well-defined

  Control: IV vancomycine (or cefazole if MRSA<5%) +- aztreonam

Pathogen-specific

Studies that enroll patients with bacteraemia due to a specific pathogen but regardless of the underlying infection are not usually considered sufficient to support a pathogen-specific indication without additional qualification because this would imply that the test agent could be used to treat such cases regardless of the location of the primary focus/foci of infection (which will anyway be unknown in a proportion of cases).

An exception to this approach could apply to agents that are expected to be clinically active against uncommon or rare pathogens and/or multi-resistant pathogens for which there are few treatment options. In such cases, depending on the level of evidence that can be provided, an indication that includes bacteraemic patients regardless of the focus of infection might be considered possible with an adequate qualification of the circumstances of use.

For VRE/MRSA and possible also gram-negative MO:

Molecular techniques will enable prompt inclusion up to 48hrs earlier!

I hope I have convinced you that:

1. Sufficiently large studies should be possible

2. There is a urgent medical need for these studies as the current management of these patients is not evidence based

3. A well thought-out design can avoid most of the hurdles.