Solving the Antibiotic Crisis: A Top Down Strategic Re-Think

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Imperfect Information

- We've been talking about statistics and scientific data for years, with inadequate progress in solving the antibiotic crisis—it's time to change the dialogue

- Regulatory science (like clinical medicine) requires making life or death decisions based on imperfect information

Scientific Limitations

- "Scientists should be on tap, not on top." Winston Churchill

Scientific Limitations

- Antibiotics became available 20 years before the regular use of randomized, placebo-controlled trials
- Thus, we have an imperfect understanding of the precise magnitude of effect of antibiotics vs. placebo for life-threatening infections
- This complicates justification of endpoints and non-inferiority margins

Scientific Limitations

- Science will not be able to give us the definitive answers we want, because the definitive scientific studies (randomized, placebo-controlled trials) cannot be done
- Any data to estimate antibiotic effect vs. placebo for modern endpoints is going to be imperfect and subject to critique
- There will be no silver bullet

Scientific Limitations

- Since science cannot solve this problem, we need a Winston Churchill-esque solution that balances pros vs. cons based on:
  - ALL available data (not selected)
  - An understanding of how serious the problem is (what are the stakes)
  - An understanding of how likely harm is to occur from either acting or not acting

The Risk

- If we don’t consider all available data, the stakes, and balance risks of acting or not, we can inadvertently get led astray

Skin Example

- Multiple types of suboptimal but available data show that antibiotics are effective for skin infections (e.g., historical data;[1] dose escalation modern data on dalbavancin;[2] pharmacometric modern data on exposure-response[3])

- The FDA draft guidance on ABSSSI focuses exclusively on the historical, unverifiable data of sulfa vs. UV lamp therapy from 1937[4]

[1]Spellberg et al '09 CID 49:383-91; [2]Seltzer et al '03 CID 37:1298-303; [3]Ambrose et al '12; [4]Snodgrass and Anderson '37 BMJ 2(3933):101-4 & 2(4014):1156-9

Skin Example

As a result:

1. Patients are defined as a treatment success if they have “cessation of lesion spread” after 3 days of antibiotic therapy —does not distinguish treatment success from failure

- No patient or provider would consider a patient with a lesion unchanged in size after 3 days of antibiotic therapy to be a treatment success

Skin Example

2.The endpoint has no assay sensitivity

- By the FDA's analysis,[1] oral sulfa was 99% effective in 1937 using this endpoint, but we know sulfa was much less effective than penicillin (mortality 2.2% vs. 0.3%)[2]
- If much less effective therapy is 99% effective, how can this endpoint distinguish more from less effective therapy?

[1]FDA ABSSSI Guidance, Table 2 pg 29; [2]Spellberg et al. CID 49:383-91

Skin Example

3. We have a constancy paradox

   either modern antibiotics like ceftaroline are LESS effective than oral prontosil rubrum was in 1937 (success rates 74% for ceftaroline[1] vs. 99% for oral sulfa)

   OR

   the endpoint has no constancy in the modern era and cannot be justified

[1]FDA Briefing Document for 9/7/10 AdCom, Ceftaroline, Table 6B.11

HABP/VABP Example

- Antibiotics have a treatment effect for mortality in HABP/VABP
- But, mortality is also confounded and often driven by factors aside from antibiotic therapy in HABP/VABP
- When an endpoint is used that is confounded by non-treatment factors, it makes it EASIER to show non-inferiority

HABP/VABP Example

- The fact that most of the historical data available for HABP/VABP is with a mortality endpoint should not handcuff our options to consider other endpoints (a solution will be forthcoming)

Other Examples

- A post-hoc analysis suggested that prior, long-acting antibiotic therapy may affect clinical cure in CABP

- As a result, no prior antibiotics are allowed in CAP, HABP/VABP, ABSSSI, cUTI, and ? cIAI, even though no similar post-hoc (or other) data are available in these other settings

Other Examples

- Eliminating prior antibiotics makes trials of CAP, HABP/VABP, cUTI, and cIAI unenrollable, particularly in the US
- Whatever enrollment occurs will enrich for less severely ill patients, & outside the US
- What are the ethics of encouraging substandard medical practice overseas?
- Where is the consideration of the harm of not allowing a single dose of prior Tx?

Other Examples: NI Margins

- Estimated antibiotic effect vs. placebo for ABSSSI, CABP, HABP/VABP, and cUTI are all different, but the math is manipulated to justify a 10% NI margin for all

- Wider margins: pro = more feasible trials, con = less precision of treatment effects

- The NI margin should balance pros and cons based on risk:benefits of the drug

Other Examples: NI Margins

- Does a 15% NI margin mean we are willing to accept a drug that is 15% less effective than the comparator?
- No--the NI margin compares the lower bound of the confidence interval, NOT the true difference in efficacy
- There is only a 1 in 400 chance that a drug truly 15% worse than the comparator would be found to be NI with a -15% margin in 2 NI studies (Spellberg et al. Clin Investigation ’11 1:19-32)

The Solutions

1. For acute, serious/life-threatening bacterial infections, the only acceptable endpoint is clinical cure (alive with resolution of all baseline signs or symptoms attributable to infection)

- Patients and providers expect that we eradicate bacterial infections and restore baseline physiological function—this is what is required to show success

The Solutions

2. Accept that the antibiotic effect vs. placebo for clinical cure must be at least as large as the mortality effect (i.e., if 30% less patients are dead with antibiotic therapy than placebo, at least 30% more patients are clinically improved)

- Thus, if you are confident in the mortality benefit of the antibiotic, this can be used to justify clinical response endpoints

The Solutions

3. The NI margin should allow for greater uncertainty about treatment effect for agents with specific advantages over available drugs, and should also be based on how badly new therapy is needed

- To balance uncertainty with unmet need, drugs with minimal, moderate, or substantial advantages over existing therapy should have 10%, 12.5%, and 15% NI margins in their trials

The Solutions

4. Allow pre-study antibiotic therapy

- Failure to allow pre-study therapy causes harm (see below) that greatly outweighs the theoretical risk to NI interpretation

Harm from Banning Pre-Study Antibiotics

- The trials cannot be completed;
- Whatever enrollment occurs will be enriched for less severely ill patients;
- Enrollment will be >90% outside the US;
- Patient harm will be caused by encouraging substandard medical practice, including overseas

The Solutions

5. Harmonization--these solutions may seem familiar, because the Europeans are already doing them

Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003417.pdf