SUPPLEMENT ARTICLE

# New Rules for Clinical Trials of Patients With Acute Bacterial Skin and Skin-Structure Infections: Do Not Let the Perfect Be the Enemy of the Good

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**Over the past decade, the United States has witnessed an epidemic of acute bacterial skin and skin-structure infections (ABSSSIs) caused primarily by community-acquired methicillin-resistant *Staphylococcus aureus*. To address this medical need as well as the ongoing threat of increasing resistance, new antibiotics are being developed. Clinical trials involving patients with complicated ABSSSI are being implemented to understand the efficacy and safety of these new antibiotic agents. Because antibiotics clearly have an effect on the resolution of the majority of these infections, placebo-controlled trials have been replaced by noninferiority studies. However, to conduct noninferiority trials a noninferiority margin must be determined on the basis of the effect size of the comparator antibiotic. The lack of modern-day placebo-controlled studies of ABSSSI makes determining effect size/noninferiority margin—and as a result, trial design—challenging. The US Food and Drug Administration (FDA) in collaboration with the Foundation for the National Institutes of Health (FNIH) have been working hard to resolve these issues and develop a new guidance to aid investigators in the conduct of these trials. In this article, we first review the 1998 guidance and its shortcomings. Next, we address the ongoing discussion of the new 2010 guidance as we understand it, along with its perceived strengths and weaknesses. Throughout this process, we wish to emphasize that the continued development of antibiotics is essential. Thus, we hope that as the FDA and FNIH move forward they will strike a balance between "The Perfect" statistical solution and "The Good" practical clinical realities.**

Acute bacterial skin and skin-structure infections (ABSSSIs; formerly cSSSIs) are among the most common infections encountered in clinical practice. During 2001–2003, there were 11.6 million outpatients visits for ABSSSI in the United States [1].The visit rate for ABSSSI was estimated to be >400 outpatient visits per 10,000 persons. More than one-half of these infections were abscesses and cellulitis, most probably caused by *Staphylococcus aureus* [1].

*S. aureus* is an evolving pathogen [2]. Rates of methicillin-resistant *S. aureus* (MRSA) related infections have been increasing at an alarming rate during the past 2 decades [3–5]. As an example, rates of MRSA isolated from intensive care units in the United States increased from 36% in 1992 to 64% in 2003 [4]. In addition, a new clone of community-associated MRSA (CA-MRSA; usually USA 300) has spread rapidly and predominates in previously healthy patients with ABSSSI [6–9]. CA-MRSA has also become a nosocomial pathogen [10], causing both noninvasive and invasive infections [11–13]. This epidemic has been complicated by the emergence of MRSA strains displaying both partial and complete resistance to vancomycin [14–18] as well as

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more gradual increases in the minimum inhibitory concentration of vancomycin in selected hospitals in the United States and abroad [19]. These changes in antibiotic resistance characteristics have been associated with poor clinical outcomes in patients with invasive diseases [20]. Despite a recent suggestion that the MRSA epidemic may be stabilizing it is likely that this evolving organism will find new ways to evade our present antibiotic armamentarium [21]. Given this background, new drugs are clearly needed to treat patients with infections due to MRSA.

## "TRADITIONAL" TRIAL CONDUCT FOR COMPLICATED ABSSSI

A well-planned and properly executed clinical trial is today a fundamentally important experimental technique that is widely accepted as the gold standard for assessing the effectiveness of a drug. The most celebrated modern clinical trial was conducted by Lind [22], who treated 12 patients with scurvy on board the ship Salisbury in the 18th century. Patients were assigned in groups of 2 to receive different interventions. The 2 patients who received 2 oranges and 1 lemon a day improved dramatically. Since that time, clinical trials have evolved in terms of science (eg, because of randomization, blinding, end points, and statistics), regulatory control (eg, guidance and oversight), and ethics (eg, use of review boards). Despite the growing layers of sophistication added over time to the design and conduct of clinical trials, a crucial component is still irreplaceable: clinical judgment.

During the past decade, clinical trials of patients with ABSSSI in the United States have followed a draft guidance issued by the US Food and Drug Administration (FDA) in 1998 [23]. In this guidance, "complicated" infections included infections involving deep soft tissue (eg, infective cellulitis), requiring significant surgical intervention (eg, infected ulcers, burns, and major abscesses), or having a significant underlying disease complicating the response to treatment [23]. This document, entitled "Draft Guidance," had numerous pitfalls.

First, there were no clear definitions and/or enrollment criteria for individual entities. For example, minimal lesion sizes were not defined. Words like "major" to define the appropriate abscess for enrollment left much to the discretion of the investigator. As a result of these limitations, different studies could include a wide and varying range of lesions. Second, the demonstration of severity of the infection as determined by evidence of systemic inflammation (eg, fever and leukocytosis) was not required allowing the enrollment of patients with widely varying degrees of severity. Third, the proportion of patients enrolled with a specific ABSSSI was not limited. Because of an increasing incidence of CA-MRSA-induced abscesses and the need to demonstrate microbiological evaluability, we have observed an increasing percentage of patients with abscesses in recent trials on ABSSSI [8]. This fact was particularly concerning because of the controversial role of antibiotics on this group of infections. Fourth, because ABSSSI includes several disparate entities, the length of therapy for individual patients was not preestablished but, rather, was determined through discussions between sponsors and the FDA. As a result, most recent phase 3 trials of ABSSSI used a flexible therapeutic window, usually 7–14 days [24–28]. The duration of therapy for individual patients was not dictated by protocols but determined by the assessment of the infection by investigators. Finally, in the 1998 guidance, use of previous antibiotics was acceptable for patients who still had positive culture results and were considered by investigators to have experienced treatment failure. Although not mentioned in the guidance, the FDA realized the difficulty of enrolling treatment-naive patients and allowed limited antibiotic exposure (eg, duration $<$24 h) in several ABSSSI trials [25, 29, 30].

However, the most important factor impacting trial design is the fact that, for numerous reasons, all phase 3 trials involving patients with cABSSSI conducted in the past 2 decades have used a noninferiority design. With use of this design, a study intends to demonstrate that the difference in response between the active control and the test drug is less than some prespecified noninferiority margin. To determine the noninferiority margin, the historical evidence of sensitivity to drug effects (HESDE) must be calculated. HESDE is the historical evidence that a new treatment is superior to placebo, as demonstrated repeatedly by appropriately designed clinical trials.. The quantitation of the superiority margin allows the calculation of a reliable estimate of the effect size from which a noninferiority margin can be determined [31]. This noninferiority margin should be smaller than a fraction (eg, 50%) of the effect size/HESDE. Because a reduction in mortality was noted with the introduction of sulfonamides and penicillins [32], modern placebo-controlled studies are not available in patients with cABSSSI. As a result, the most important challenge for noninferiority trials has been justifying the noninferiority margin [32].

All the problems described above have led the FDA, in collaboration with the Foundation for the National Institutes of Health (FNIH), to reconsider trial design and elaborate a new guidance for patients with cABSSSI [33].

## NEW TRIAL DESIGN IN cABSSSI: PROS AND CONS

To more precisely categorize patients with cutaneous infections into a group requiring systemic antibiotics necessitated changing several previous FDA "rules" in the new design of trials of patients with cABSSSI [33]. Most relevant changes are summarized in Table 1.

### Minimal Skin Involvement

A minimum area of skin involvement (eg, erythema, edema, or induration size $\geq$75 $cm^2$) was recently recommended by the

**Table 1. Changes in the 2010 US Food and Drug Administration Guidance in Trials of Patients With Complicated Acute Bacterial Skin and Skin Structure Infections (cABSSIs)**

| 1998 Guidance | 2010 Guidance | Pros | Cons |
|---|---|---|---|
| No minimal size requirements | Minimal size of cABSSSI lesion $\geqslant$75 $cm^2$ | Patients comparable across trials; small infections excluded | Measurement technique remains undefined; definition of $\geqslant$75 $cm^2$ is arbitrary |
| ''Major abscess'' and wound infection were not defined | Erythema/induration extending $\geqslant$5 cm from the peripheral margin of abscess/wound (in addition to minimal size $\geqslant$75 $cm^2$) | Improve patient comparability across trials; surrounding erythema correlates with minimal size of cellulitis | No evidence in adults that such a margin defines infections which will benefit from antibiotics |
| Systemic signs of infection not formally required | Systemic signs of infection (eg, fever) and/or proximal lymphadenopathy required | Improve patient comparability across trials | Requirement of fever for enrollment will result in under representation of important groups (eg, diabetic and/or elderly persons) |
| Proportion of infection types enrolled (eg, abscesses) not limited | Proportion of patients enrolled with abscesses limited to $\leqslant$30% | Diminishing noise in treatment effect (assuming the unproven hypothesis that major abscesses do not benefit from antibiotic therapy) | More time and resources required to complete c ABSSSI trials in the CA-MRSA era |
| Primary end point: clinical cure at test of cure visit (usually within 7–14 days after end of therapy) | Primary end point: cessation of spread of primary lesion and resolution of fever 48–72 h after enrollment | HESDE available | HESDE only available from 1930s; cessation of spread does not constitute or replace clinical cure; measurement technique and definition of cessation of spread debatable |
| Prior antibacterial therapy allowed for those with positive cultures. | Prior antibacterial therapy only allowed for clinical failures, single dose of short acting antibiotics $\geqslant$3days before enrollment or treatment for an indication other than cABSSSI using an antibiotics inactive against pathogens associated with cABSSSI | Prevents non-study drug effect on primary end point | Significantly increases in difficulty of enrollment |

**NOTE.** cABSSSI denotes complicated acute bacterial skin and skin structure infections; CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* HESDE, historical sensitivity to drug effect.

FDA [33]. Although this change will allow enrolling patients with more comparably size lesions, it is unclear whether larger areas of inflammation define complicated skin infections. For example, a severity score for skin infections developed from the linezolid trials showed that a lesion size $<$150 $cm^2$ (compared with $>$150 $cm^2$) and surgical wounds were both independently associated with clinical failure [34]. These observations suggest that depth may be more important than extension. Unfortunately, precisely defining the depth of infection is challenging. On a similar note, small lesion size does not guarantee an uncomplicated course of infection. In 1941, Skinner and Keefer [35] reported 122 cases of *S. aureus* bacteremia, 25% of which originated from boils or carbuncles. Finally, the challenges of accurately measuring the area of 3-dimensional irregular cutaneous infections cannot be over-emphasized. Proposed solutions, such as planimetry and digital photography [36], are both untested in patients with cABSSSI and require significant increases in time and expense. Presently, the Dermatology Division of FDA recommends live observer evaluations for the primary end point assessment.

### Systemic Signs of Infection

The FDA is also recommending that all patients with cABSSSI demonstrate evidence of inflammation extending beyond the primary lesion (eg, a tender enlarged lymph node proximal to the infection) or systemic inflammation such as fever (temperature, $\geqslant$38°C) at the time of enrollment [33]. Although an increase in the white blood cell (WBC) count (eg, to $>$10,000 cells/$mm^3$) or bands (eg, to $>$10%) are not specifically mentioned in either the old or new guidances, they are expected to be accepted components of systemic inflammation. Indeed, most recent trials in cABSSSI have required at least 1 systemic sign as part of

their inclusion criteria [27, 29, 37–39]. Unfortunately, the association of these signs with severity of disease or response to antibiotics is still awaiting investigation.

The present debate focuses on the requirement that all patients be febrile at the time of enrollment. Recent large trials have enrolled 14%–33% febrile patients [25, 28], and a retrospective study from Australia showed that only 43% of patients admitted with infective cellulitis, patients who by definition required intravenous therapy for their infection, had fever or hypothermia [40]. These data suggest that the requirement for fever would result in a significant increase in money, time, and the number of sites. More importantly, excluding afebrile patients may lead to underrepresentation of important populations, such as diabetic persons, immunocompromised persons, and/or elderly persons, whose ability to mount a febrile response to infection is often impaired [41].

Although the presence of fever and the WBC count are easy to determine, the systemic response goes far beyond these clinical/laboratory signs. For instance, nonspecific markers, such as erythrocyte sedimentation rate, C-reactive protein level, and procalcitonin level may be useful not only in defining a more difficult-to-treat cohort but also as future surrogate markers for response to therapy [42]. It is also clear that further investigation is required before using any of these surrogate markers to define severity of infection and although resolution of fever [41] and/or WBC count may help indicate that the patient is responding to therapy they have not yet been shown to be equivalent to and thus replace clinical cure.

#### Limiting the Proportion of Patients With Abscesses

Previous studies suggested that a majority of patients with abscesses can be cured with incision and drainage [43, 44]. More recent studies conducted during the CA-MRSA epidemic "confirmed" that abscesses are highly likely to be cured with drainage alone [45, 46]. Unfortunately, these studies usually included outpatients with small abscesses (eg, median of 15 mL of pus and median surrounding cellulitis of $\leq$25 $cm^2$). Furthermore, inactive antibiotic therapy was shown to be an independent risk factor for failure in patients with skin infection due to CA-MRSA [47], and a pediatric study found that drainage frequently failed for patients with abscesses $>$5 cm in diameter when appropriate antibiotic regimens were not given [48]. The fact that recurrences can be seen in $\sim$10% of patients with abscesses has also been well described before CA-MRSA era [43].

As a result of these conflicting study results, the FDA has recommended that abscesses be limited to $\leq$30% of the enrolled population [33]. In addition enrollment of major abscesses will require that the abscess have surrounding cellulitis and/or erythema extending at least 5 cm from the peripheral margin of the abscess diameter. These proposed changes will assist in the enrollment of more comparable patients and may also help include in trials patients whose abscesses are more likely to benefit from antibiotics. However, this 30% limit in the percentage of patients with abscesses enrolled in cABSSSI trials may result in eliminating $>$10% of trial population [2525]. The impact on enrollment difficulty and resulting trial cost of this new limitation remains to be determined.

#### Changing the Primary End Point

The most controversial discussion to date has focused on moving the primary end point of all ABSSSI trials from the test-of-cure time point (usually 14–28 days after enrollment) to cessation of spread and resolution of fever at 48–72 h after enrollment [33]. In addition, the determination of cure versus failure, previously made by the investigator, will now be a result of lesion size measurements (ie, no progression of lesion size versus size at the time of enrollment) and temperature readings (ie, afebrile patients being those with a temperature $\leq$ 37.6°C) at a time point long before the completion of antibiotic treatment.

Where do these radical new changes come from? As we mentioned above, there are no contemporary data from placebo-controlled studies providing HESDE for clinical cure at the test-of-cure timepoint. However, HESDE for a much earlier and different end point was available from old studies. During the 1930s, Snodgrass and Anderson [49, 50] conducted 2 clinical trials involving patients with erysipelas comparing sulphamides (prontosil, a prodrug for sulphanilamide, and sulphanilamide) with no antibiotics (ultraviolet light or antitoxin). The end points were duration of spread of the local lesion after enrollment, duration of fever, and time to resolve "toxic symptoms." In both studies, cessation of spread after 48 h of therapy was higher in the antibiotic group (99% vs 73% and 98% vs 77%, respectively). Tables 2 and 3 display the main results from these studies. Because these "placebo"-controlled studies constitute HESDE, the FDA believed that a switch in the primary efficacy endpoint to cessation of spread and absence of fever at 48–72 h was required. Importantly, however, the cessation of spread and absence of fever must be sustained at 10–14 days after randomization by investigator determination of clinical cure or failure (now a secondary efficacy end point) [33].

The use of a cessation of spread as the primary end point outcome deserves several comments. First, very much like resolution of fever, cessation of spread only indicates that the patient is on the path to recovery, albeit not far along the path. It does not indicate cure; it must be coupled with subsequent evaluations to constitute a cure. From a clinician's standpoint, failing this early endpoint does not translate into clinical failure. Second, nearly half the patients in the Snodgrass and Anderson studies had cessation of spread at enrollment (suggesting enrollment late in the course of the infection), making the timing of treatment effect questionable. Despite these caveats, contemporary trials involving patients with infective cellulitis

**Table 2. Spread of Lesion in the Study by Snodgrass and Anderson [50] Comparing Sulphonilamide With Ultraviolet Light in Patients with Erysipelas**

| Method of treatment | Duration of spread, days | | | | | | Total no. of cases |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | ⩾5 | |
| Sulphanilamide | 78 (60.0) | 48 (36.9) | 3 (2.3) | 1 (.77) | … | … | 130 |
| Ultra-violet Light | 48 (39.3) | 24 (19.7) | 17 (14) | 12 (9.9) | 14 (11.5) | 7 (5.7) | 122 |

**NOTE.** Data are no. (%) of patients.

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demonstrated that the median time for cessation of spread was 20–36 h [51, 52] (Figure 1). Review of recent phase 2 data for the torezolid trial demonstrated that the overwhelming majority of infections had stopped spreading at 72 h [53]. Therefore, a 72-h end point may well be a reasonable first attempt at defining a nonclinical end point. However, much more work needs to be done to define the parameters and repercussions of this change.

### The Consequences of These Changes?

As a result of the early primary end point, prior antibiotic therapy (the standard has been <24 h of effective treatment within the previous 7 days) will be more limited (Table 1). The decision requiring enrolled patients to be treatment naive is essential to determine the true effect of the intervention now that the primary end point is only 48–72 h after enrollment. However, the exclusion of recently treated patients (eg, those treated within the past 24 h) will make enrollment considerably more difficult, because a significant proportion of patients in cABSSSI trials received prior antibiotic therapy before enrollment [25].

Another important consideration is the effect anti-inflammatory drugs on spread of lesion. A randomized, placebo-controlled trial showed that prednisolone may hasten median time of healing by 1 day in patients with erysipelas [54]. Similarly, nonsteroidal anti-inflammatory drugs may shortened the time to regression of lesions in patients with cellulitis [55]. In addition, both of these medications significantly impair the demonstration and quicken the resolution of fever. As a result the new guidance allows the use of only short-acting antipyretic medications for fever and analgesic drugs without antipyretic activity for pain [33] . Although it will be difficult to control pain without the use of anti-pyretic/anti-inflammatory agents, it will be important to avoid these medications for the first 72 h to get an accurate assessment of antibiotic effect.

### Noninferiority Margin

For noninferiority trials, the FDA requires noninferiority margins to preserve a fraction of treatment effect (estimated from the HESDE). Traditionally, this fraction was arbitrarily set at 50% (''take half''), and the noninferiority margin in cABSSSI trials was commonly requested to be at 10%.

However, the new guidance uses HESDE to choose a margin on the basis of the assumption that the current clinical trials are sufficiently similar to the historical studies (constancy assumption) [56]. Compared with the 1930s, the standard of care (including antibiotics) for ABSSSI has evolved, comorbidities have changed, and pathogens have shifted (from group A *Streptococcus* to CA-MRSA) [6, 7]. In addition, the margin preserving at least 50% of the effect of an active control by the new drug has been questioned [57]. If we take into consideration all of these drawbacks and uncertainties, the FDA has provided a conservative estimate of 12% in treatment effect for stop of spread and resolution of fever between 48-72 h in patients receiving antibiotics [33]. Clearly stated, the new noninferiority margin should be <12%, although such margin has not been defined.

A recent investigation using data from 1900–1950 (before widespread use of penicillin) has determined noninferiority margins preserving at least 50% of the treatment effect in patients with cABSSI [32]. Such noninferiority margins were as

**Table 3. Spread of Lesion in the Study by Snodgrass and Anderson [49] Comparing Prontosil (Sulphamide Drug) With Other Therapies in Patients With Erysipelas**

| Method of treatment | Duration of spread, days | | | | | | Total no. of cases |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | ⩾5 | |
| Ultraviolet light | 32 (32.65) | 26 (26.53) | 17 (17.34) | 11 (11.22) | 5 (5.1) | 7 (7.14) | 98 |
| Prontosil | 48 (47.06) | 36 (35.29) | 16 (15.69) | 1 (.98) | 1 (.98) | 0 | 102 |
| Ultraviolet light plus prontosil | 19 (35.85) | 26 (49.06) | 7 (13.21) | 0 | 1 (1.89) | 0 | 53 |
| Antitoxin | 14 (31.81) | 7 (15.91) | 10 (22.23) | 9 (20.45) | 4 (9.09) | 0 | 44 |

**NOTE.** Data are no. (%) of patients.

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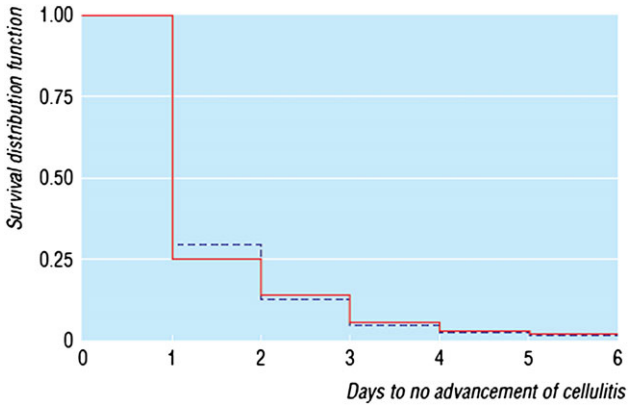


**Figure 1.** Stop of spread in patients with infective cellulitis treated with antibiotics.
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follows: 14% for cellulitis and erysipelas, 21% for wound infections, and 7% for major abscesses [32]. Unfortunately, the true margins for individual types of infections are still unclear. Retrospective analyses of phase 2 trials suggest that using cessation of spread at 48-72 h may result in cure rates exceeding 90%. If this is verified, a noninferiority margin of considerably less than 10% may be required.

## WHERE TO NOW?

Given the pervasive changes in clinical trial design of cABSSSI, several issues require further discussion.

1. **Test the changes before implementing.** Most recent changes in trials on cABSSSI in the United States have been done based on theory. Unfortunately, no strong clinical evidence accompanies such modifications. The "new rules" may result in major changes in the number of sites, the length of trials, and the resulting costs of antibiotic development. At the time this is taking place, the Infectious Diseases Society of America is pleading for new antibiotics. We strongly suggest testing new theoretic trial designs before requiring their implementation.
2. **Develop new approaches to studying cABSSSI.** Algorithms to develop antibiotics in patients with cABSSSI should be rediscussed—for example, requiring 1 large registrational phase 3 trial instead of 2 phase 3 trials for drug approval. Allowing antibiotic development to leapfrog over cABSSSI to study more invasive infections (eg, bacteremia) initially rather than waiting 2-4 years for the completion of a skin and skin-structure infection trial is another consideration.
3. **Consider placebo-controlled trials using a 48-h end point.** A small (eg, 50 patients) placebo-controlled ABSSSI study could ideally be conducted in low-risk patients who are observed closely as inpatients during the initial 3-day study period. This approach would allow determining the true effect of new antibiotics and pose little risk to a healthy, nontoxic population.
4. **Test short therapies in ABSSSI.** There is some evidence suggesting that antibiotic therapy for 5 days is comparable to 10 days in patients with uncomplicated cellulitis [58]. To our knowledge, there have been no randomized trials comparing the length of therapy in patients with complicated ABSSSI. Trials incorporating new treatment algorithms such as this should be a priority in our attempts to preserve antibiotic potency.
5. **Preserve rules for already approved studies.** This is in contrast to the present FDA opinion, in which changes in regulatory science mandate immediate modifications in trial design, including ongoing and recently completed trials. Maintaining consistent guidelines during studies would greatly assist obtaining external financial support for future trials in the anti-infective field.
6. **Promote collaboration.** Increase academic government partnerships in the antibacterial section, much like has been done in other sections and divisions, such as cardiology. Collaboration with the FNIH is a good first step forward. Other steps, such as establishing collaboration with the European Medicine Agency and other regulatory agencies, would be significant milestones in simplifying new antibiotic development.
7. In their 1937 article, Snodgrass and Anderson stated, "Clinical judgment, however, is not statistically assessable…" [50, p. 1157]. When statistical issues are difficult to resolve clinical judgment must prevail. Creation of a stable set of guidelines under which to conduct clinical trials for antibiotic approval is essential for the continuation of active research efforts by the pharmaceutical industry. If the rules are changed between the initiation of the trial and the approval of a new antibiotic, then reasons to invest in new antibiotics will be deeply undermined. We believe that is time to be practical, innovative, and collaborative. Otherwise, all we have is perfection but no new antibiotics.

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