Sepsis and the Receding Grail
Introduction

Sepsis is a life-threatening illness culminating in multi-organ dysfunction paired with a systemic inflammatory response. The disease burden is considerable: it is the single most expensive condition treated in hospitals, with annual costs in the US projected at nearly $24bn. It is the leading cause of death in intensive care units (ICUs) worldwide, and has an annual mortality rate of 250,000 in the US alone. Incidence of sepsis is also on the rise nationally, with estimates pegging an increase of 13% over a five-year period beginning in 2004, and the global impact of sepsis will only worsen with time due to a rising elderly population and increasing incidence of infection from antibiotic-resistant pathogens. Despite this, the only therapies available to septic patients are antimicrobials and supportive care.

Although there has been an increase in prognosis over the last two decades from mortality highs of 50%, positive outcomes have been ascribed almost exclusively to advances in supportive care, rather than goal-directed therapy, and there is a pressing need for a viable therapeutic agent. Following a single-center ICU trial in 2001, standard of care for sepsis moved to protocolized resuscitation in the form of Early Goal-Directed Therapy (EGDT). Recently discredited by three large multicentered government-funded trials (ProMISe, ARISE, and ProCESS), which showed no benefit in hospital or 90-day mortality between EGDT and usual resuscitation arms, this has underscored that the need for a pharmacological therapy remains unmet despite half a century of continuous clinical research. This white paper will profile the historical and ongoing clinical landscape of sepsis research, with a focus on industry activity.

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8. As sepsis is a downstream indication, to reduce noise, all data in this white paper correlates to trials in which sepsis is the exclusive target disease.
Current landscape

The landscape of sepsis clinical research is pockmarked by disappointing results and only a single proprietary compound to ever successfully complete a Phase III trial: human recombinant activated protein C, which was clinically demonstrated to modulate severe inflammatory response but was taken off the market after a follow-on placebo-controlled trial (PROWESS SHOCK) failed to replicate the results of the earlier pivotal study. However, ongoing development continues unabated, and a view of the historical space sees a healthy distribution of candidates across all phases of research. Of note, is that although industry-sponsored trials are eclipsed in volume by all other sponsor types (eg, academic, government, co-operative group), most activity in novel therapeutics is concentrated within the industry. Across 54 ongoing Phase II, II/III, and III trials ex-industry, all are either in already-approved drugs or are evaluating candidates with industry originators.

Figure 1. Sepsis trials by trial and drug status, industry versus all other sponsor types

Note: For historical (completed and terminated) trials, data for those completing in the last three years were used. For these trials the regulatory status of the drug reflects current data as of writing, rather than the status of the drug at time of trial implementation.

Source: Trialtrove®, November 2017
Turning a wide-angle lens to clinical activity by phase and sponsor, we see a heavy slant among ex-industry sponsors toward Phase IV studies, as would be expected, with these comprising 50% of all trials (Figure 2). Industry-sponsored trials have a more orthodox spread but slightly taper off after Phase II, which is likely indicative of lack of efficacy, even in smaller cohorts, being a common bar to further progression.

Figure 2. Sepsis trials by phase, industry versus all other sponsor types

Note: Phase II and I/II; Phase III and II/III; Phase IV and Other are grouped.

Source: Trialtrove®, November 2017
Looking at a similar spectrum of trials now ordered by status, we find a relatively high number of terminated trials within industry versus all other sponsor types, at 19% versus 10% of overall trials, respectively (Figure 3). A likely culprit is a knock-on effect from the preponderance of novel therapeutics within industry-sponsored trials, which leads to a higher rate of failure – a theme that we revisit later in this report.

Figure 3. Proportion of sepsis trials by status, industry versus all other sponsor types

Note: Two Temporarily Closed trials have been incorporated into the Closed totals for all other sponsor types.

Source: Trialtrove®, November 2017
Despite the failure of several high-profile candidates such as eritoran, Trialtrove data show that the number of industry-sponsored trials in sepsis has never been higher. Following a slight decline in 2009/10, 2015/16 saw the launch of 30 trials by industry sponsors (Figure 4). There is also ongoing interest in non-bacterial sepsis as an indication, with 11 industry-sponsored trials initiated over the same time period (data not shown). Year-to-date data for 2017 continue the trend, with 14 trials coming online or expected to.

**Figure 4. Industry trials initiated by year**

![Figure 4](source: trialtrove, november 2017)
**Geographic distribution**

As would be expected for a condition with an infectious etiology, most of the disease burden of sepsis is localized to developing countries which lack the resources for implementation of many of the therapies associated with improved prognosis, such as source control measures and fluid resuscitation. However, most research remains concentrated in developed nations. A snapshot of currently ongoing or planned industry trials shows the US leading the pack with 14 active studies. The EU claims the next four positions with France and Spain at nine and eight studies, respectively. Interestingly, this ranking is upended if the search is expanded to trials of any sponsor type. China leapfrogs to first place with 42 ongoing studies, well ahead of the US's 32, and indicating that industry and institutional support for sepsis research do not necessarily march in lockstep, as well as speaking to the significant regulatory obstacles in conducting clinical trials within China10 (Figure 5).

**Figure 5. Geographic distribution of ongoing and planned sepsis trials**

![Geographic distribution chart](source: Trialtrove®, November 2017)

Sponsors

Following decades of research and the exit of several key players such as Eli Lilly, the landscape of industry research has now tilted toward medium-sized companies. Although the number of trials has remained relatively constant, aside from a recent uptick, the proportion of industry sponsors belonging to Top 20 Pharma\(^{11}\) has shifted to 21% for trials initiated in the last five years versus 53% in the five years prior. This is accounted for less by a waning interest among larger pharmaceuticals than by increased activity from all other sponsors, who initiated 55 trials in the first timeframe versus 23 in the second (data not shown).

Over half of ongoing activity is in the early stage pipeline, with Phase III comprising just 18% of the landscape. As well, although research of novel compounds is dominated by industry players, there is significant institutional support for the sepsis space: academic centers and co-operative groups comprise 80% of all trials completed in the last ten years, and 9% of industry trials have government funding or co-sponsorship (Figure 6).

Figure 6. Sepsis trials by sponsor type and phase

![Graph showing sepsis trials by sponsor type and phase](image)

Note: Phase II and I/II; Phase III and II/III; Phase IV and Other are grouped.

Source: Trialtrove®, November 2017

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11. Top 20 Pharma as defined by latest available sales revenue rankings, found in Scrip100: http://www.scrip100.com.
Over the last ten years within ongoing, completed, and terminated studies, we see Eli Lilly and Merck spearheading sepsis research with 24 and 20 trials, respectively. The Eli Lilly platform has since been retired, with Xigris developed and commercialized only to be withdrawn from market. Merck was primarily pursuing the tail end of Cubicin’s expanded indication for bacteremia, a precursor condition to sepsis prior to the host response. Pfizer’s 13 trials bring up the rear with an antifungal in Ecalta built out for invasive candidiasis, the most common cause of fungal sepsis (Figure 7).

**Figure 7. Initiated industry trials by sponsor and phase**

![Trial Count](chart.png)

Note: Phase II and I/II; Phase III and II/III; Phase IV and Other are grouped.

Source: Trialtrove®, November 2017
Other sponsors rounding out the cast of key historical players are AstraZeneca, which had an anti-tumor necrosis factor-alpha polyclonal antibody fail a pivotal Phase IIb trial, and Takeda with Resatorvid (Tak-242), which was discontinued after a DMC interim analysis found a failure to suppress cytokine levels in patients with severe sepsis. This has unfortunately been a recurring theme for a parade of other candidates, such as Eisai’s eritoran and oral talactoferrin, for which an interim analysis in a pivotal Agennix-sponsored trial found all-cause mortality to be 7% lower in the placebo arm (Table 1).

Table 1. Pivotal trials by outcome

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Drug</th>
<th>Primary Endpoints Reported</th>
<th>Protocol ID</th>
<th>Status</th>
<th>Trial Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eli Lilly</td>
<td>Xigris</td>
<td>March 8, 2001</td>
<td>PROWESS</td>
<td>Completed</td>
<td>Completed, positive outcome</td>
</tr>
<tr>
<td>Takeda</td>
<td>Resatorvid</td>
<td>May 29, 2008</td>
<td>01-04-TL-242-011</td>
<td>Terminated</td>
<td>Study prematurely terminated for lack of efficacy after the DSMB determined there was insufficient cytokine suppression.</td>
</tr>
<tr>
<td>Eisai</td>
<td>Eritoran</td>
<td>January 25, 2011</td>
<td>ACCESS</td>
<td>Completed</td>
<td>Study failed to meet primary endpoint of 28-day all-cause mortality.</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>CytoFab</td>
<td>August 8, 2012</td>
<td>N/A</td>
<td>Terminated</td>
<td>Planned pivotal trial was terminated and drug discontinued after Phase IIb program failed to meet primary endpoints.</td>
</tr>
<tr>
<td>Agennix</td>
<td>Talactoferrin Alfa</td>
<td>September 1, 2015</td>
<td>OASIS</td>
<td>Terminated</td>
<td>Study prematurely terminated after DSMB identified higher mortality among talactoferrin-treated cohort.</td>
</tr>
</tbody>
</table>

Note: For the CytoFab trial, the date of program discontinuation was used in place of the primary endpoints reported date.

Source: Trialtrove®, November 2017
Challenges and trends in trial design

Although certain subgroups, such as the elderly or immunocompromised subjects, are particularly vulnerable, additional heterogeneity in population (e.g., pathogen, organ and degree of impairment, time to diagnosis, and genetic variants) remains a major compounding factor in the failure of sepsis-targeting therapies. This is exacerbated by a lack of accurate diagnostic criteria: sepsis lacks a universal pathogen, and historically, diagnosis was reliant on interpretive Systemic Inflammatory Response Syndrome (SIRS) criteria represented by various physiological factors, which has led to a fragmented patient population and the diagnosis rate of severe sepsis in ICUs varying by as much as 6–27% when pegged to only minor variations in methodology. However, as the spectrum of sepsis (bacteremia, sepsis, severe sepsis, septic shock) has differing clinical outcomes, depending on the stage of organ dysfunction and attending complications, sponsors are obliged to recruit patients based on the diagnosis of sepsis obtained during screening.

We find that severe sepsis is the most common target across all industry trials, likely due to a mortality rate up to 30% higher than the previous stage, but sepsis and septic shock are well-represented with 69 and 64 studies, respectively. Non-bacterial sepsis makes a modest appearance at 14 trials, although this comes hand in hand with fungal sepsis, comprising only some 5% of all cases of septic shock (Figure 8).

Figure 8. Industry trials by patient population

Source: Trialtrove®, November 2017

The above factors contribute to challenges in both recruiting and conducting sepsis trials. We find that the landscape features a relatively large amount of trials that fail to close out with viable data: within the industry sector, of the 106 trials for which outcomes are available, over half were either terminated or were unable to meet primary endpoints. Termination for poor enrollment was the most common reason for premature discontinuation of a trial, highlighting the difficulty of identifying suitable concentrations of patients that can satisfy relatively unreliable screening criteria (Figure 9).

Figure 9. Outcomes of completed and terminated sepsis trials

Completed, Positive Outcome
Completed, Outcome Indeterminate/Unknown
Terminated, Poor Enrolment
Terminated, Other/Unknown
Terminated, Business Decision
Terminated, Planned but Never Initiated
Completed, Negative Outcome
Terminated, Lack of Efficacy
Terminated, Safety/Adverse Effects

Source: Trialtrove®, November 2017
Research has also been hamstrung by the lack of readily available, predictive biomarkers, despite nearly 200 having been evaluated without success.\textsuperscript{15} Although this is perhaps unsurprising given the requirement of a consistent marker in a condition with inconsistent pathogens, the interest has recently fueled an increase in the number of trials which evaluate novel biomarkers relative to overall trials completed in a given year. Among trials completed in the last five years, 33 had an explicit objective of evaluating novel biomarkers as indicators of therapeutic efficacy versus only 13 in the five years prior (Figure 10). Other gaps in the clinical space have also been addressed or incorporated into trial design, such as the traditionally poor pharmacokinetic (PK) performance of candidates. Taking the same ten-year snapshot, 78\% of industry trials evaluating PK among endpoints did so in the more recent five-year window. This figure is 70\% for trials with an active comparator arm (data not shown).

Figure 10. Biomarker use across completed sepsis trials

Note: Trialtrove defines the end date as the date a trial completes or is expected to complete, or the report of primary endpoints.

Source: Trialtrove®, November 2017

Drugs in active development

Turning to the current landscape and therapeutics with ongoing development, the standout is Asahi Kasei’s thrombomodulin alpha (ART-123). Currently in an ongoing Phase III trial (SCARLET) initiated in 2012 that has notably survived an interim safety review and was scheduled to have a topline readout late this year, it is a soluble recombinant human thrombomodulin intended for treatment of septic patients with disseminated intravascular coagulation, and is perhaps the only first-in-class drug for sepsis that is on the immediate horizon of regulatory approval (Table 2).

Table 2. Pipeline drugs in active development for sepsis

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Primary Indication</th>
<th>Pipeline Phase</th>
<th>Likelihood of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asahi Kasei</td>
<td>ART-123</td>
<td>thrombin inhibitor</td>
<td>sepsis</td>
<td>III</td>
<td>54%</td>
</tr>
<tr>
<td>Spectral Diagnostics</td>
<td>Toraymyxin</td>
<td>membrane integrity inhibitor</td>
<td>sepsis</td>
<td>III</td>
<td>n/a</td>
</tr>
<tr>
<td>AM-Pharma</td>
<td>reCAP</td>
<td>alkaline phosphatase stimulator</td>
<td>sepsis</td>
<td>II</td>
<td>24%</td>
</tr>
<tr>
<td>Cidara</td>
<td>CD101 (IV)</td>
<td>1,3-Beta-glucan synthase inhibitor</td>
<td>fungal sepsis</td>
<td>II</td>
<td>27%</td>
</tr>
<tr>
<td>ContraFect</td>
<td>CF-301</td>
<td>unidentified pharmacological activity</td>
<td>bacteremia</td>
<td>II</td>
<td>27%</td>
</tr>
<tr>
<td>Inotrem</td>
<td>MOTREM</td>
<td>TREM-1 antagonist</td>
<td>septic shock</td>
<td>II</td>
<td>n/a</td>
</tr>
<tr>
<td>Revimmune</td>
<td>CYT107</td>
<td>interleukin 7 agonist</td>
<td>sepsis</td>
<td>II</td>
<td>27%</td>
</tr>
<tr>
<td>Adrenomed</td>
<td>Adrecizumab</td>
<td>immunostimulant</td>
<td>septic shock</td>
<td>I</td>
<td>n/a</td>
</tr>
<tr>
<td>Roche/Genentech</td>
<td>RG-7861</td>
<td>unidentified pharmacological activity</td>
<td>bacteremia</td>
<td>I</td>
<td>19%</td>
</tr>
</tbody>
</table>

Note: The Likelihood of Approval represents the probability of reaching US Food and Drug Administration approval from a current phase. The average is calculated for a specified disease group based on the historical performance of drugs within the same disease group and development phase.

Source: Biomedtracker, November 2017; Pharmaprojects®, November 2017
Other sponsors with a hand in late-stage development include AM-Pharma, which recently completed a Phase II trial (STOP-AKI) for human recombinant alkaline phosphatase in sepsis-associated acute kidney injury and for which results are still pending, and Spectral Diagnostics, which is currently conducting a Phase III trial in Toraymyxin, a hemoperfusion adsorption column for removing bloodstream endotoxin. Although approvals for Toraymyxin have already been obtained in the EU and Japan, a pivotal Phase III trial (EUPHRATES) is now being conducted in the US (Table 2).

All three compounds exemplify a recent trend wherein only narrow patient segments are targeted in an attempt to bypass the traditional pitfalls of viewing sepsis as a holistic condition afflicting all populations in equal measure. AM-Pharma, for instance, has adopted creatinine clearance rather than all-cause mortality as a primary endpoint in its Phase II trial – a novelty among sepsis, but one which could guide future research. Although most trials rely on 28-day mortality, a somewhat arbitrarily-decided timeframe, there is an established body of data that supports the presence of lifelong complications for patients who survive the initial onset of sepsis. To combat this, there have been calls to use long-term mortality or other surrogate endpoints for efficacy as the primary drivers of clinical trial design. There is some evidence that this has translated into clinical practice: in a representative set of trials initiated in the five-year window between 2012 and 2017, 31% of trials evaluated primary endpoints over a timeframe longer than a month. An equivalent snapshot of trials from 2007 to 2012 only had 21%.

Similarly, although length of ICU stay is inadequate as a primary endpoint due to compounding factors unrelated to drug therapy (variations in standard of care, etc.), an increasing number of trials are incorporating it as a secondary endpoint. In the same set of trials over the same period, 73% of trials having length of ICU stay as an endpoint belonged to the more recent five-year block (data not shown).

We see a similar situation played out in the inclusion criteria of Asahi Kasei’s ART-123 Phase III trial, in that targeting coagulopathy as an indication allowed the incorporation of international normalized ratio >1.40 among inclusion criteria as a supplement to SIRS criteria, thereby facilitating a more homogeneous patient population and, looking further, a smoother regulatory pathway for demonstrating efficacy. Spectral’s EUPHRATES inclusion criteria screens for Endotoxin Activity Assay ≥ 0.60 on the same principle.

This may become the eventual norm of sepsis research. As sepsis cannot be treated as a distinct nosologic entity, and lacks either predictive biomarkers or a quantitative consensus of clinical definitions beyond a shared outcome, there has been considerable variance in the populations tasked with demonstrating clinical efficacy. This recognition has translated into clinical practice, and sponsors are increasingly attempting to stratify patients by homogeneity. For instance, of the trials in sepsis which exclusively recruit from an elderly population and have completed within the last 15 years, 78% have done so in the second half of this time period (data not shown).

Final thoughts

Clinical development in sepsis continues in earnest, with 43% of pipeline activity being in novel compounds. However, the landscape has evolved from the one-size-fits-all therapies of only a decade past to those targeting homogenous population subtypes. By setting their sights on more specific indications such as endotoxemia and coagulopathy, sponsors have found a strategy which serves as a hedge against the challenges of sepsis clinical development. Thus far, sponsors appear willing to shoulder the tradeoff that any resulting therapy would have a smaller patient pool upon obtaining regulatory approval. It remains to be seen whether this is the future of clinical research, or if the holy grail of a universal sepsis-specific therapeutic agent will be realized.

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