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The evolutionary logic of sepsis

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ABSTRACT

The recently proposed Microbiome Mutiny Hypothesis posits that members of the human microbiome obtain information about the host individuals' health status and, when host survival is compromised, switch to an intensive exploitation strategy to maximize residual transmission. In animals and humans, sepsis is an acute systemic reaction to microbes invading the normally sterile body compartments. When induced by formerly mutualistic or neutral microbes, possibly in response to declining host health, sepsis appears to fit the 'microbiome mutiny' scenario except for its apparent failure to enhance transmission of the causative organisms.

We propose that the ability of certain species of the microbiome to induce sepsis is not a fortuitous side effect of within-host replication, but rather it might, in some cases, be the result of their adaptive evolution. Whenever host health declines, inducing sepsis can be adaptive for those members of the healthy human microbiome that are capable of colonizing the future cadaver and spread by cadaver-borne transmission. We hypothesize that such microbes might exhibit switches along the 'mutualist – lethal pathogen – decomposer – mutualist again' scenario, implicating a previously unsuspected, surprising level of phenotypic plasticity.

This hypothesis predicts that those species of the healthy microbiome that are recurring causative agents of sepsis can participate in the decomposition of cadavers, and can be transmitted as soil-borne or water-borne infections. Furthermore, in individual sepsis cases, the same microbial clones that dominate the systemic infection that precipitates sepsis, should also be present in high concentration during decomposition following death: this prediction is testable by molecular fingerprinting in experimentally induced animal models.

Sepsis is a leading cause of human death worldwide. If further research confirms that some cases of sepsis indeed involve the 'mutiny' (facultative phenotypic switching) of normal members of the microbiome, then new strategies could be devised to prevent or treat sepsis by interfering with this process.

1. Introduction

The recently proposed Microbiome Mutiny Hypothesis posits that some members of the human microbiome (the assemblage of mutualist and commensal microbes within a host individual) might be able to switch to an intensive host exploitation strategy, when the survival of the host is compromised (e.g., by old age, serious injury or infection), to maximize short-term transmission in the remaining time (Rózsa et al., 2015). It is hypothesized that in such cases microbiome mutiny may aggravate the already weakened condition of the hosts, potentially contributing to their death (Rózsa et al., 2015). In this paper we argue that some cases of sepsis, a condition that causes approximately 6 million human fatalities per year globally (Fleischmann et al., 2015), might be interpreted as a particular manifestation of this phenomenon. Specifically, we aim to show that sepsis, although it is usually a non-contagious condition, does enhance the transmission of the causative microbes to new hosts in a rather surprising way.

Sepsis occurs in animals (both vertebrates and invertebrates), including humans. It is an acute systemic reaction to microbes (induced by their endo- or exotoxins) that invade the normally sterile body

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compartments, accompanied by an unusually strong innate immune response that leads to organ dysfunction (Lever and Mackenzie, 2007; Vincent et al., 2013). Sepsis and its sequelae are a leading cause of mortality in intensive care units and thus have a prominent public health importance in both developing and developed countries. Microorganisms initiating sepsis may originate from a recent acute infection (as in the case of sepsis caused by *Yersinia pestis*, the plague pathogen, or *Bacillus anthracis*, the causative agent of anthrax), but more often they are normal mutualist members of the healthy human microbiome located on skin and mucosal surfaces. The infectious agents most commonly implicated are bacteria including *Streptococcus pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiella* species (Lever and Mackenzie, 2007; Vincent et al., 2013; Williams et al., 2004; Angus and van der Poll, 2013). A significant proportion of cases are caused by fungi, *Candida* yeasts in particular (Wisplinghoff et al., 2004).

Nearly 10% of the fatal cases of cancer terminate by sepsis (Williams et al., 2004); moreover, major burns (that cause sterile wounds), appendicitis, volvulus etc. can also initiate sepsis by the invasion of mutualistic or commensal microbes into the blood stream (Podnos et al., 2002). Even severe sleep deprivation can induce lethal sepsis in laboratory rats without any apparent outside source of infection (Everson and Toth, 2000). In humans, sepsis is more frequent and more often fatal in inherently frail age groups such as the new-born (especially in infants with very low birth weight) (Nizet and Klein, 2011) and elderly people (Podnos et al., 2002). Other comorbidities, and the use of immunosuppressive agents are also among the well-known risk factors (Lever and Mackenzie, 2007; Vincent et al., 2013; Williams et al., 2004; Angus and van der Poll, 2013).

1.1. The classical interpretation of sepsis

Sepsis most often occurs in patients with poor immune capabilities, such as in new-borns or injured, diseased and elderly people, respectively. Therefore, the classical interpretation of this process is that a healthy immune system can spatially constrain commensal and mutualistic bacteria to those body compartments where they do not cause harm (or might even yield benefits), whereas a deteriorating immune system is no longer capable of that. When constraints posed by host defences disappear, opportunistic microbial populations invade the formally sterile vital organs like the circulatory system and the central nervous system. Finally, this infection provokes a dysregulated host response causing life-threatening organ dysfunction, called sepsis (Singer et al., 2016). Below we call this causation the 'classical hypothesis'.

1.2. Interpreting sepsis as a microbial mutiny

The Microbiome Mutiny Hypothesis rests on three basic tenets (Rózsa et al., 2015). First, the microorganisms involved must be able to switch between alternative phenotypes that correspond to low and high virulence behaviour in the host, respectively. Second, the low-virulence (possibly even cooperative) phenotype must be optimal in a healthy host with a long life expectancy, while the high-virulence phenotype must involve a means of intense short-term transmission that allows maximal residual transmission over the reduced life expectancy of a diseased/aged host. And, third, the microorganisms must possess some detection mechanism that can assess the health status of the host and distinguish between the short-term and long-term settings, to be able to switch phenotype in an adaptive way. These three components can be regarded as the mechanism, the driver (fitness benefit), and the trigger of the "microbiome mutiny", respectively.

In the cases of sepsis that are caused by normally harmless members of the microbiome, the mechanism (phenotypic switch) is seen in action. For a list of potential or demonstrated mechanisms for the 'trigger' of the microbiome mutiny (detection of host condition) we refer the reader to our previous publication (Rózsa et al., 2015).

In this paper, we focus on showing that, in contrast to conventional wisdom, the 'driver' of the mutiny might be present in many cases of sepsis. This points to an 'evolutionary logic of sepsis': inducing sepsis likely yields a short-term transmission benefit for certain members of the microbiome.

The microbes involved in sepsis abandon their formerly restricted anatomic site specificity and invade all possible body parts—which can be regarded as a phenotypic strategy switch. In humans and other vertebrates, this practically occurs through the invasion of the blood and lymphatic systems. In case of severe sepsis and septic shock, this causes organ failure and likely kills the host, particularly in the absence of medical interventions.

Systemic dissemination is likely to maximize the colonization of the future cadaver by the sepsis-inducer microbial clone (or clones), enabling the inducers to utilize the cadaver as decomposing (saprobe) microorganisms. Rival clones or species of the formerly healthy microbiome that fail to participate in the mutiny, will start with a handicap in the microbial decomposition of the cadaver. (Naturally, the switch to decomposer lifestyle might be a choice for some mutualistic microbes also when the host dies due to unrelated reasons).

We propose that the ability to induce sepsis might be an adaptive characteristic of some members of the healthy human microbiome that enables efficient cadaver-borne transmission. Such microbes might use two radically different, alternative and, under specific conditions, sequential routes of transmission: low-level continuous transmission from the live host through a long period, and a short period of high-intensity transmission from the decomposing host cadaver. These two kinds of transmission offer benefits to the microbe analogous to collecting the interest and the capital of an investment, respectively. As long as the investment is secure (the host is in good condition with a long life expectancy), the optimal strategy is to patiently accumulate the low-level income from the interests, while preserving the capital (the health of the host). However, if the investment is threatened by market forces outside our control (the host's chances of survival decrease, e.g., due to injury, illness or old age), then the investment would soon be lost anyway, thus our best interest is to liquidate the asset immediately. In terms of the microbes capable of inducing sepsis, this translates literally to liquidating their host, provided that the death of the host offers a final resource for propagation.

We therefore propose that the cases of sepsis that affect weakened hosts and are caused by facultative pathogens capable of cadaver-borne transmission, might perfectly fit the criteria for microbiome mutiny (Rózsa et al., 2015). The facultative pathogens might be able to detect host stress or declining health, and respond by switching to a high-virulence mode that induces sepsis, to maximize residual transmission from the host. Further, the ability of these species to induce sepsis might be the result of adaptive evolution, rather than a fortuitous side effect of within-host replication, and a series of phenotypic switches along the 'mutualist → lethal pathogen → decomposer → cadaver-borne infection → mutualist (or lethal pathogen)' sequence (Fig. 1A) might be an evolved life history strategy of these microbes. This implicates a formerly unsuspected, surprising level of adaptive phenotypic plasticity in these species.

2. Comparison of the two hypotheses

2.1. The role of sepsis-inducers in cadaver decomposition

Interpreting sepsis induction as an adaptive strategy switch of microbes implies that in sepsis victims, the facultatively pathogenic microbes that provoked sepsis would play an important role in the decomposition of the cadaver, and should then be capable of cadaver-borne transmission to healthy individuals. Contrarily, the classical hypothesis yields no specific prediction: if sepsis is simply an accidental sequela of declining host defences then potentially any mutualistic

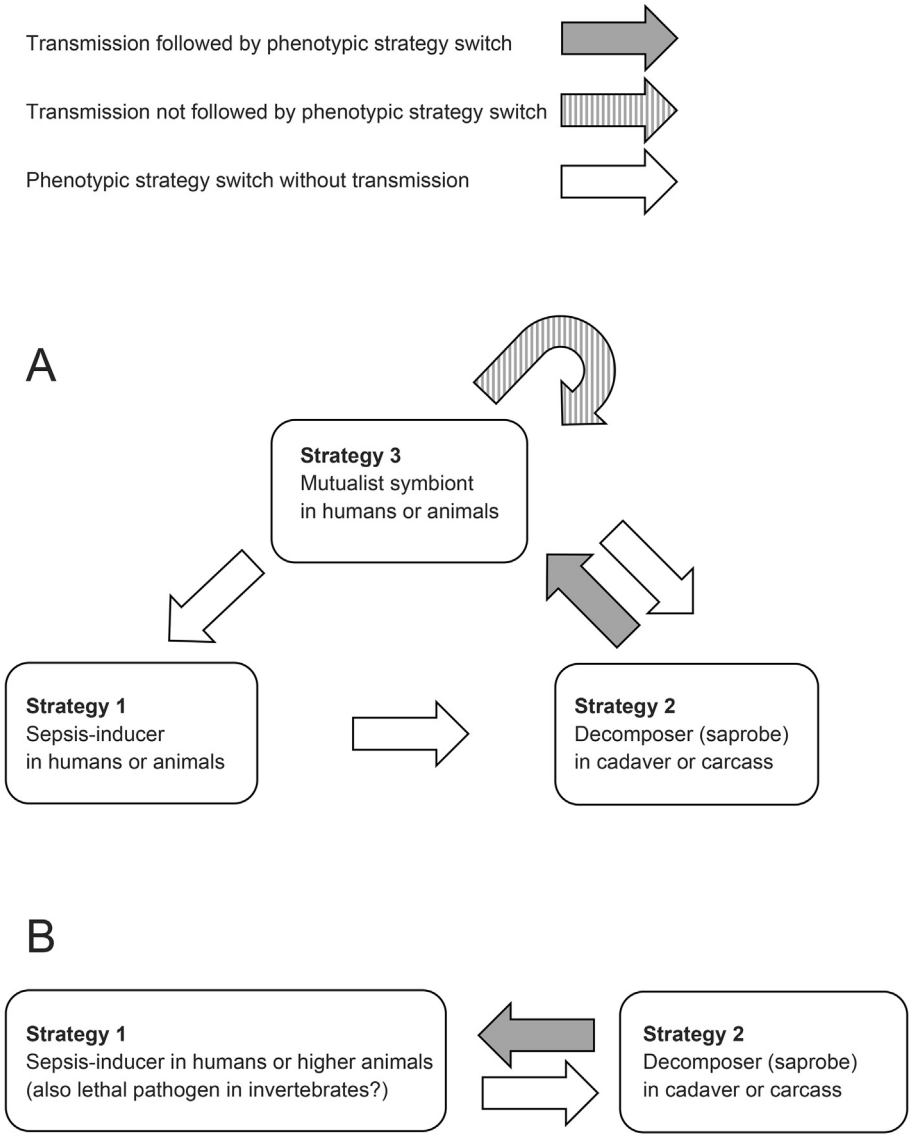

Fig. 1. Phenotypic strategy switches and transmission routes of facultative sepsis causing organisms.
A: microbes capable of changing lifestyles between (1) lethal sepsis inducer, (2) decomposer and (3), then, through cadaver-borne transmission, to mutualist. Only those transitions are illustrated here that we presume to be relatively frequent. B: microbes like virulent *Anthrax* strains exhibit a somewhat similar, though much simpler network of phenotypic strategy switches and transmission routes; they (1) kill their host (2) to utilize their carcass/cadaver as decomposers. Then cadaver-borne transmission channels spores to new host individuals through contaminated soil or water.

microbe could induce sepsis; however, most of these species would not be able to take advantage of cadaver-borne transmission.

Unfortunately, there is no direct information available about the microbial composition of the cadavers of sepsis victims. However, the scarce information on the microbial decomposition of human cadavers and animal carcasses indicates that the so-called decomposer (or saprophage, saprophyte, saprobe) microorganisms of the outside environment (soil, mud, or water) play a subordinate role in this process (though it may still be relevant in small-bodied animals, see Lauber et al., 2014). The main direction of bacterial decomposition is from the inside out: in nematodes (Cabreiro and Gems, 2013), arthropods (Butler et al., 2015), as well as in humans (Hyde et al., 2013; Palmiere et al., 2015; Can et al., 2014) it is members of the former healthy microbiome that constitute the dominant actors of microbial decomposition of carcasses and cadavers. Of note, the formerly commensal bacteria that participate in the decomposition can persist for at least 24 weeks in the soil surrounding the cadaver (Cobaugh et al., 2015).

Studies on decomposing human cadavers (cause of death not specified) revealed that *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Enterobacteriaceae* (like *E. coli*, *Proteus* spp.) play a predominant role in the first stage of decomposition (Hyde et al., 2013). Similarly, viable strains of *Streptococcus pneumoniae* can be cultured from the cerebrospinal fluid of a large proportion of severely decomposed human cadavers (Palmiere et al., 2015). These species greatly overlap with the opportunistic pathogens implicated as frequent causative agents of human sepsis (Lever and Mackenzie, 2007; Vincent et al., 2013; Williams et al., 2004; Angus and van der Poll, 2013). Then, due to a gradual loss of redox potential in the tissues, microaerophils and anaerobes take precedence in the cadaver microbiome, like *Clostridium*, *Lactobacillus* (Kaufman et al., 2013), and *Bacteroides* (Cobaugh et al., 2015) species. They also constitute regular members of the healthy human microbiome (*Lactobacillus* is even marketed as probiotics) and infrequently they also induce sepsis in response to traumatic injuries or surgery (Kaufman et al., 2013; Kochan et al., 2011).

Furthermore, the cadaver microbiome is not limited to bacteria: fungi also contribute significantly to the decomposition of dead bodies. Yeasts, particularly *Candida* species, are regular and important members of the healthy human microbiome on skin and mucosal surfaces. At the same time, *Candida* species constitute the most frequent agents of fungal-related human mortality (Pfaller and Diekema, 2007), being the 4th leading cause of nosocomial bloodstream infection in the United States (accounting for 8–10% of all such infections acquired in hospitals) (Wisplinghoff et al., 2004). Remarkably, such *Candida* species are also the most frequently isolated fungal saprobes in human cadavers (Martínez-Ramírez et al., 2013).

Unlike symbionts, saprobes inhabiting cadavers cannot rely on host

body-to-body contacts or blood-sucking insect vectors for transmission to new host individuals. Therefore, they need to utilize soil-borne or water-borne transmission routes. Accordingly, several potential sepsis-inducers (*Bacteroides* spp., *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* spp., *Clostridium* spp., *Lactobacillus* spp., *Candida* spp., *Streptococcus pneumoniae*) are known to contaminate soil or water resources (Baron, 1996; Cobaugh et al., 2015; Evstigneeva et al., 2009; Schulz et al., 2012). We predict that once infecting a healthy host individual, these microbes will often initiate mutualist partnerships again.

2.2. Invasion of the host circulatory system

Pathogens, parasites, and mutualists tend to exhibit restricted anatomic site specificity within the host body, e.g., humans harbour different microbial assemblages in the intestines, the lungs, the urogenital system etc. On the one hand, it is a vital host interest to restrict microbes to anatomical sites where they cause no harm or even yield benefits. On the other hand, there may be several adaptive reasons why symbionts may restrict their own occurrence to certain body parts: most likely to avoid host defences or to limit virulence (Reiczigel and Rózsa, 1998). These particular reasons, however, are no longer relevant for the saprophytic microbes. Their adaptive interest is to consume as large a proportion of the cadaver as possible, to utilize this resource for their replication, and subsequent spread. Indeed, the late phase of sepsis is associated with an anergic immune state and an increase of opportunistic bacteria and fungi in blood cultures (Otto et al., 2011). This may also explain why the different organs of the same human cadaver are typically decomposed by a rather similar set of microbe species (Can et al., 2014), although different organs harbour different microbiomes through the host's life.

The classical hypothesis implies that crossing the endothelial wall lining the blood and lymphatic vessels is a consequence of declining host defences. As it is not presumed to enhance transmission to new hosts, we do not expect to find any specific mechanism that pathogens evolved to increase their capability for this function.

Contrarily, if inducing sepsis is a particular manifestation of microbiome mutiny, then the invasion of the circulatory system by means of bacteremia or fungemia is an essential part of the microbial life cycle, and is expected to involve active targeted mechanisms. Of note, opportunistic pathogens that are capable of inducing sepsis (e.g. *Streptococcus pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus*) are also known to exhibit a diverse set of advanced mechanisms that enable them to establish intimate interactions with endothelial cells. They trigger local inflammatory responses and coagulation processes, and modify endothelial cell plasma membranes and junctions to adhere to their surfaces to invade and then cross the endothelial barrier (Lemichez et al., 2010).

2.3. The bacterial toxins involved in sepsis induction

Several bacteria involved in sepsis produce neurotoxins or enterotoxins (Popoff and Poulain, 2010), and some of these toxins appear to contribute actively to the induction of sepsis (Choi et al., 2016; Qin et al., 2017). The classical hypothesis of sepsis induction implies that these molecules have evolved for functions unrelated to pathogenesis, and their toxic action is a non-adaptive, accidental by-product.

Contrarily, presuming that sepsis may arise as a microbiome mutiny implies that these toxins serve an adaptive role. Given the potency of these toxins (some of them are among the most potent biotoxins known to date), and their parallel presence in unrelated species with similar lifestyles, it is likely that their adaptive role for the bacteria is indeed their toxicity. This appears to indicate that the high-virulence phenotype, and in particular its ability to cause sepsis, is an evolutionary adaptation rather than a fortuitous “accident” in these species. Remarkably, the expression of the sepsis toxin is inducible in at least one species, *Bacteroides fragilis* (Choi et al., 2016), consistent with the notion of an inducible switch to the high-virulence phenotype.

2.4. Host health detection and strategy switch mechanism in microbes

Finally, as mentioned above, the microbiome mutiny scenario of sepsis implies that microbes involved should be capable of detecting changes in host health, and also of switching to a highly virulent host exploitation strategy whenever expected host survival declines. These capabilities require the presence of molecular health detection and genetic switch mechanisms. Contrarily, if sepsis arises simply as a side effect of declining immune function, as posited by the classical hypothesis, then we do not expect to find complex and costly molecular mechanisms serving such non-adaptive functions.

2.5. Sero venientibus ossa (bones for those who come late – Latin proverb)

Evidently, a single individual of the causative organism is not capable of inducing sepsis, let alone monopolizing a large proportion of the cadaver biomass. Thus the success of a mutiny requires that it is a coordinated strategy switch carried out by a population of microbes. This synchronization might be based on producing and sensing quorum molecules, a mechanisms known to play a role in the regulation of virulence genes in several pathogens, including those most often responsible for initiating sepsis (Boyen et al., 2009; Vogt et al., 2015). For evident evolutionary reasons, this coordination is more beneficial among clone-mates than across different clones or species (Czárán and Hoekstra, 2009). Though communication by means of quorum molecules may occasionally involve some degree of cross-talk between bacterial species (Diggle et al., 2007), this argument may still explain why monomicrobial sepsis (initiated by a single species of microbes) is far more frequent than polymicrobial sepsis (Lin et al., 2010). The latter type constitutes only 4–24% of all sepsis cases (Faix and Kovarik, 1989; Pammi et al., 2014), although several species capable of inducing sepsis coexist in the human microbiome.

The Microbiome Mutiny Hypothesis predicts that this process is likely to be self-reinforcing (Rózsa et al., 2015). As one clone (or species) switches to high virulence, it will further deteriorate host health, inducing other microbial species to switch, too. However, in the case of sepsis as a particular manifestation of the hypothesis, it appears that rival species often do not react at all. This suggests that sepsis induction is a process that escalates fast among clone members, thus rival clones and species may not have enough time to join. The speed of this process might be a further hint that the mechanisms of the switch have been shaped by adaptive evolution. We presume that all members of the microbiome that fail to switch to systemic dissemination in a sepsis event (initiated by other members) will suffer a competitive disadvantage during the decomposers' race for the cadaver biomass.

In contrast, the classical hypothesis of sepsis predicts no mechanisms to coordinate the strategy switch even within the same microbial clone.

2.6. Host specificity

The classical hypothesis on sepsis induction yields no prediction about the host specific or generalist nature of the pathogen species involved.

Contrarily, however, interpreting sepsis as a particular type of microbiome mutiny implies that the pathogen species involved are not likely to be specific to human hosts. Necrophobia is a widespread phenomenon in mammals, including humans. Decomposing corpses had been recognized as a serious health hazard long before microbes were discovered and identified as the causative agents of disease. Throughout the history of our species, human cadavers were mostly buried or cremated. Since this practice may hinder cadaver-borne transmission to some degree, it should, at first sight, select microbes not

Table 1
A brief summary of predictions of the two hypotheses on the evolutionary background of sepsis.

Phenomenon	Classical hypothesis	Sepsis as microbiome mutiny
Which species of the healthy microbiome are capable of inducing sepsis?	Random	Enriched in species capable of cadaver-borne transmission
Fitness consequence of sepsis for the causative organism	None or negative (dead-end in the cadaver)	Positive due to cadaver-borne transmission
Systemic invasion	Accidental/opportunistic process, elicited by changes in the host	Facilitated by active mechanisms of the microbes
Toxins involved in sepsis	Toxic effect a by-product of molecules evolved for unrelated functions	Toxins have no function other than harming the host
Host health detection and strategy switch mechanism in microbes	Not present	Inevitably present
Most sepsis cases are caused by a single strain or species of bacteria	Because a single strain or species was present at breaking through the epithelial wall of the blood or lymphatic vessel	Because sepsis-inducers use a communication system to coordinate sepsis induction among clone members
Host specificity of microbes	No prediction, either generalists or specialists	Must be generalists, not specific to humans

to induce sepsis. Therefore, we predict exclusively human-specific members of the microbiome to have given up the sepsis-inducer strategy. Indeed, most species responsible for inducing human sepsis are not specific to human hosts. Since they occur in the gut microbiome of a wide range of other animal hosts, both vertebrates and invertebrates, human burial habits cannot exert a strong selection pressure on their populations.

We summarize the comparison of the two hypotheses of sepsis in Table 1.

3. Limitations of the hypothesis

Evidently, not all cases of sepsis arise from microbiome mutiny. First of all, the scenario does not apply to sepsis initiated by microbes that are unable to participate in the decomposition of cadavers. Neither does this hypothesis apply to microbes that do not occur as members of a healthy microbiome, like virulent strains of *Bacillus anthracis* and *Yersinia pestis*. Virulent strains of *Bacillus anthracis*, persist in the soil and can spread by cadaver-borne transmission (Van Ness, 1971; Van Ert et al., 2007), facilitated by their participation in the microbial decomposition of the cadaver (Dragon and Rennie, 1995), but are not capable of mutualistic coexistence. The life history of these pathogens cycles through a simpler 'lethal pathogen → decomposer → cadaver-borne infection → lethal pathogen' sequence (Fig. 1B) that is broadly analogous to a parasitoid lifestyle.

Furthermore, the two possible causes of sepsis (accidental by-product of the deterioration of the host immune system, or an adaptive microbial strategy switch) are not mutually exclusive. As the classical hypothesis claims, it seems very likely that a compromised immune defence may facilitate the systemic dissemination of opportunistic pathogens independently of their adaptive interests. Thus, even if the microbiome mutiny scenario is real, it will be superimposed on this immunological host effect, and the individual contribution of both is hard to distinguish.

As an illustrative example, neutropenia often accompanies sepsis; however, rather than being a (facilitating) cause of sepsis, the depletion of neutrophil granulocytes appears to be a consequence of sepsis (Christensen and Rothstein, 1980), that can in some cases be linked to targeted toxins produced by sepsis-inducing bacteria (do Vale et al., 2016).

4. The natural history context of the 'sepsis as a mutiny' hypothesis

From an evolutionary point of view, a particularly interesting example is presented by the sepsis-causing bacterial flora that inhabits the mouths of Komodo dragons (*Varanus komodoensis*) (Bull et al., 2010). In this case, the bacteria appear to cycle through the extended sequence 'mutualist (in Komodo dragon) → lethal pathogen (in prey) → decomposer → cadaver-borne infection → mutualist (in Komodo dragon)'. According to this hypothesis, the close association between the dragons and bacteria offers mutual benefit: the lizards effectively act as vectors for the bacteria, while the bacteria effectively function as a slow-acting venom for the lizards, improving predation success. Bull et al. (2010) discuss which peculiarities of Komodo dragon life history might have facilitated the evolution of this relationship, which very likely involved an increase in the sepsis-inducing potential of the bacteria, and the evolution of (possibly mutual) mechanisms to protect the lizard host from sepsis.

Another possible example of considerable ecological relevance might involve the massive die-off events that have been observed in the populations of saiga antelopes (*Saiga tatarica*). Remarkably, no obligate pathogen could be identified as the causative organism, and facultative pathogens such as *Pasteurella multicoda* have been proposed to be the underlying cause of the haemorrhagic septicemia that was the apparent direct cause of death in these animals (Samuel, 2017). The latest of these events followed a period of adverse weather conditions, which brings up the possibility that large herds of saiga fell victim to a dramatic instance of the microbiome mutiny, precipitated by the weakened condition of the hosts. Strains of *P. multicoda* also constitute a dominant element in the Komodo dragon mouth microbiome (Bull et al., 2010). The possible role of this bacterium in the saiga die-offs indicates that it might have been pre-adapted to cause sepsis even before being acquired by the Komodo dragons, and the widespread occurrence of these bacteria underscores the evolutionary success of this strategy.

In a broader context, the microbial strategy outlined in this paper greatly differs from other environment-borne infectious strategies that have been described in the literature. First, the so-called 'sit-and-wait' strategy (a capability to remain infectious through long, inactive periods spent outside the host, such as seen in anthrax spores) has been proposed to allow pathogens to increase virulence because the 'sit-and-wait' strategy eliminates the selection pressure for low virulence at transmission (Walther and Ewald, 2004). Contrarily, the microbiome mutiny scenario implies a selection pressure for high virulence at one particular type of transmission, i.e. transmission through sepsis induction.

Second, the category of 'sapronotic agents of disease' has been introduced for those essentially free-living decomposer organisms that rarely and accidentally invade living organisms. These microbes are not adapted to a pathogenic way of life, neither selected for an optimal level of virulence (Kuris et al., 2014).

Third, some authors explained the different virulence levels exhibited at different host anatomical sites by the same pathogen species by invoking the classical "source-sink" models of ecology. Again, this model greatly differs from ours, as it does not imply adaptive switches between alternative phenotypes optimal under different host conditions, but interprets highly virulent invasive infections as dead-end adaptations with no onward transmission (Sokurenko et al., 2006;

Chattopadhyay et al., 2007).

In contrast to the above three categories, the facultative sepsis-inducer strategy relies on some microbes' adaptive capability to switch between mutualist (or at least commensal), lethal pathogenic (sepsis-inducer), and also a decomposer way of life. Such phenotypic switches may occur often enough to subject these strains to selective pressures to maintain all these facultative capabilities in parallel to each other. These steps of strategy changes may occur with or without transmissions to new host individuals (either living or dead) and sometimes even go in opposite directions. The mutualist phase is particularly likely to be repeated several times in successive hosts without strategy switches.

We note that the 'sepsis as microbiome mutiny' scenario incorporates an apparently paradoxical motive, that some microbes incite a devastating host defensive reaction because – under certain circumstances – it serves their own adaptive purposes. Analogous phenomena of pathogens over-stimulating host defences in their own interest are known from host-parasite systems, as well. E.g., gall-forming insects, mites, and nematodes over-stimulate plant defences so that plants produce galls that subsequently serve the protection and nourishment of these parasites (Weis et al., 1988).

Furthermore, it may also seem inconsistent that sepsis, which is an extreme over-activation of the immune system, occurs preferentially in persons with suppressed or compromised immune systems. Apparently, a yet naive or an already declining immune system is not a protective factor; rather it worsens host chances, partially because it fails to achieve early control of an infection before bloodstream invasion could occur.

5. Testing the hypothesis

Above we provided a point-by-point list of the two hypotheses' predictions that are also summarized in Table 1. Most of these predictions are pairs of a non-specific, general prediction (classical hypothesis) versus a prediction describing a highly specific adaptation. Whenever these very specific conditions are not met, the idea that sepsis arises as a microbial mutiny must be rejected.

On the contrary, since the classical hypothesis on sepsis yields rather unspecified predictions, we cannot falsify it even in cases that fulfil all criteria of a microbiome mutiny. In such cases, we cannot deny that the events occurring as predicted by the classical hypothesis contributed the emergence of sepsis to certain degree.

Practically, investigating the microbiological decomposition of cadavers of sepsis victims would offer the most straightforward way to support or falsify our hypothesis. We predict that the particular microbe species that induced sepsis should gain a relative advantage over other members of the microbiome as a decomposer and, as a consequence, should be able to colonize a large proportion of the decomposing tissues, ultimately resulting in the massive production of spores (or other types of transmissible propagules) and their release into the environment. At present, we lack quantitative estimates on the amount of bacteria and fungi released from decomposing human cadavers into the soil, and also on the amount produced by the healthy human microbiome through a lifetime. Such information would enable us to compare the efficacy of mutualistic versus cadaver-borne transmission routes. Although the latter route is open only for brief period, it might contribute to the overall transmission from a human body quite substantially.

Furthermore, our hypothesis relies on the assumption that the normally mutualistic (or at least non-virulent) members of the microbiome induce sepsis particularly when host survival chances are seriously compromised. We predict, therefore, that these microbes must possess mechanisms to monitor the condition of the host. Some candidate mechanisms are listed in Rózsa et al. (2015).

Our hypothesis also predicts that the same facultative pathogen might be more virulent when transmitted from a cadaver as compared to being transmitted from a healthy host, because cadavers contain the same microbial species in virulent, sepsis inducing mode, while in healthy individuals it is expected to exist in a cooperative/mutualist mode. A possible example of this phenomenon might be hinted at by the increased risk of virulent *Strongyloides* hyperinfection syndrome when the usually commensal parasitic nematode *Strongyloides stercoralis* is transmitted from cadavers (by organ transplantation) (Marcos et al., 2008). The same logic might explain also the risk of serious infection associated with cadavers, and why they are better avoided—when mutinous sailors have just sunk a ship, you don't want to take them on board.

Finally, we predict that the facultative pathogens capable of sepsis as microbiome mutiny should be able to display characteristic patterns of gene expression that correspond to the alternative lifestyles, and the switching between these states should be under tight and coordinated genetic control.

6. Outlook

Human life, and also much of plant and animal life, relies on a durable relationship with indispensable microbial partners. Strangely enough, they sometimes appear to mutiny against us by inducing potentially lethal sepsis in order to benefit from our future cadavers. The recognition that switching to a 'sepsis mode' strategy might be an integral part of the adaptive behavioural repertoire of the facultative mutualist/pathobiont bacteria and fungi potentially opens up a whole new avenue towards preventing and treating sepsis. If we can identify the microbial systems that detect host health and age, we might, in the next step, be able to manipulate these: blocking the microbial signalling pathway or providing false signals of good host health could both prevent the microbial mutiny to sepsis.

While revising an earlier version of our manuscript, we came across the related publication by Krezalek et al. (2016) that discusses human cases of surgical sepsis initiated by injury. They also came to the conclusion that sepsis-inducer bacteria might benefit from cadaver-borne transmission. Their paper focuses on surgical sepsis in a medical context, while our purpose here was to discuss the much broader evolutionary-ecological implications of the phenomenon.

Competing interests

MS has been an investigator in clinical trials supported by Novartis, Bristol-Myers Squibb, Janssen-Cilag, Actelion, Astellas, Sanaria and Abbvie Pharmaceuticals and received speakers' fees from Astellas and Janssen-Cilag. All other authors declared that they have no conflicts of interest.

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