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Review article

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Antibiotic-induced collateral damage to the microbiota and associated infections

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Abstract

Antibiotics have transformed medicine, saving millions of lives since they were first used to treat a bacterial infection. However, antibiotics administered to target a specific pathogen can also cause collateral damage to the patient's resident microbial population. These drugs can suppress the growth of commensal species which provide protection against colonization by foreign pathogens, leading to an increased risk of subsequent infection. At the same time, a patient's microbiota can harbour potential pathogens and, hence, be a source of infection. Antibiotic-induced selection pressure can cause overgrowth of resistant pathogens pre-existing in the patient's microbiota, leading to hard-to-treat superinfections. In this Review, we explore our current understanding of how antibiotic therapy can facilitate subsequent infections due to both loss of colonization resistance and overgrowth of resistant microorganisms, and how these processes are often interlinked. We discuss both well-known and currently overlooked examples of antibiotic-associated infections at various body sites from various pathogens. Finally, we describe ongoing and new strategies to overcome the collateral damage caused by antibiotics and to limit the risk of antibiotic-associated infections.

Sections

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Introduction

Antibiotic treatment is a double-edged sword: although these drugs are crucial for the treatment of bacterial infections, they can also strongly disrupt the commensal microbiota, select for resistant pathogens and facilitate subsequent infections. Although most courses of antibiotics do not result in adverse events, these drugs are prescribed in prolific quantities, with more than 40 billion doses of antibiotics estimated to be taken annually[1], and we still have much to learn about the personal risks of antibiotic exposure[2].

At the individual-patient level, the unwanted consequences of antibiotic treatment fall broadly into two categories (Fig. 1). Firstly, antibiotics prescribed to treat a specific infection also act on the commensal species living within the patient, leading to disruption of microbiota homeostasis and subsequent disease[2–5]. Humans are host to trillions of microorganisms that form diverse microbial communities within the gut, the skin and various epithelial surfaces at other body sites[6]. Most of the commensal microbiota reside in the colon[7], which forms a relatively stable ecological habitat in healthy adults[8]. However, exposure to antibiotics can drastically perturb the ecological equilibrium of the microbiota. Although antibiotic-induced imbalances in the composition and behaviour of the microbiota have been associated with various non-communicable diseases such as obesity, diabetes and asthma[9–14], in this Review we focus specifically on the risk of infectious disease following antibiotic use. In particular, perturbation of the commensal microbiota can cause loss of protection against colonization by foreign pathogens, increasing the risk of subsequent bacterial[15,16], fungal[17,18] and even viral[19] infections.

Secondly, the use of antibiotics selects for drug resistance, thereby limiting their own efficacy[20,21]. This is often perceived as primarily a population-level problem, but the selective pressures that antibiotics exert can have a direct negative impact on the individual patient being treated. Even a single course of antibiotics can lead to overgrowth of pre-existing resistant strains residing in the patient's microbiota[22–24]. Ever increasing rates of antibiotic resistance have led to a high risk that patients harbour resistant potential pathogens within their microbiota prior to therapy[25–27]. Therefore, although the microbiota confers protection against colonization by foreign pathogens, it can also act as a potential source of infection. Indeed, antibiotic-induced proliferation of a typically low-abundance species to a high-abundance state can cause disease or can facilitate translocation of potential pathogens to other body sites, leading to hard-to-treat resistant superinfections, during or soon after treatment[28].

Despite both perturbation of microbiota homeostasis and selection for the spread of resistance being well-known side effects of antibiotic therapy, these are often treated as separate issues and the relationship between these phenomena remains poorly understood[15]. In this Review we will outline the factors that contribute to the interlinked processes of antibiotic-induced disruption of microbiota homeostasis and overgrowth of resistant pathogens. We give examples of diverse infections that are associated with antibiotic therapy and describe new approaches to reduce the risk of such infections.

Antibiotic-induced disruption of microbiota homeostasis

Antibiotics administered to target a specific pathogen have off-target effects that can kill or suppress the growth of commensal strains. This can lead to altered species richness and diversity within the microbiota as well as a reduced total number of bacteria[29]. There are many factors that determine the extent and manner in which antibiotic treatment can perturb the microbiota. These include drug-specific factors such as the drug mechanism of action, spectrum of activity, route of administration and route of elimination[30–33] (Fig. 2). Host-specific factors are also important. It is becoming increasingly apparent that the response to antibiotics is highly variable between individuals[34] and determined by factors such as the make-up of the patient's microbiota and the resistance of strains within it, as well as host comorbidities and immune status[35–38]. Furthermore, the microbiota at different body sites are highly distinct[6,39]; although most studies on the impact of antibiotics on normal microbiota have been carried out on the microorganisms inhabiting the intestinal tract[30], antibiotics can lead to perturbation of the oral, skin and vaginal microbiota[30].

Drug-specific factors

The disruption to the microbiota caused by antibiotics can vary substantially between different drugs[40]. Much of our understanding of how specific antibiotics perturb the microbiota derives from studies in patients or healthy volunteers, particularly metagenomic analyses of swabs or stool samples. Other reviews discuss these effects on a drug by drug level[30,31,40,41], and here we give examples and outline some key trends. For example, the colon is home to ~98% of the microbiota and a major factor determining the disruption caused by an antibiotic is therefore the concentration it reaches in the large intestine. The route of administration and pharmacokinetics are the main factors that determine the drug concentration reached at a specific body site. Orally administered antibiotics are directly carried to the gastrointestinal tract[33], but the absorption within the intestine strongly affects the concentration which reaches the densest population of microorganisms residing in the colon. Absorption of peroral macrolides, such as erythromycin, is incomplete and high faecal concentrations strongly affect the normal intestinal microbiota[30]. By contrast, peroral nitrofurantoin, which is readily absorbed in the intestine, does not reach high concentrations in the colon and has not typically been associated with major perturbations to the gut microbiota[42].

Although topical antibiotic application is likely to induce the least collateral damage, it can still perturb the local microbiota[43]. Intravenous administrations can indirectly reach the intestine, but the level depends on the route of elimination of the drug[44]. Drugs which undergo biliary excretion are secreted into the gastrointestinal tract and excreted in the faeces. In mice, intravenous administration of antibiotics excreted mainly by renal clearance, such as ampicillin, perturb the intestinal microbiota less than drugs with higher excretion via the bile, such as tetracyclines[44]. Other animal studies have found that oral and intravenous administration of the same antibiotic both led to similar levels of intestinal microbiota disruption, but oral administration led to a slower return of species richness and diversity levels to pre-treatment levels[45], and promoted higher levels of antibiotic resistance dissemination within the gut microbiome[46]. However, there remain few studies directly comparing the effect of antibiotic administration route on microbiota disruption in humans.

Beyond the drug pharmacokinetics, its spectrum of activity is also very important[32]. Most bacteria inhabiting the intestinal tract are anaerobes from the Bacteroidota, Bacillota and Actinomycetota phyla[7,47,48]. The next most represented phylum is Pseudomonadota, which includes a wide variety of pathogenic Gram-negative genera, such as *Escherichia*, *Salmonella* and *Acinetobacter*. The activity of an antibiotic against these bacteria is therefore particularly important for determining the disruption it causes[49]. Drugs broadly active against commensal anaerobes include β-lactams, metronidazole,

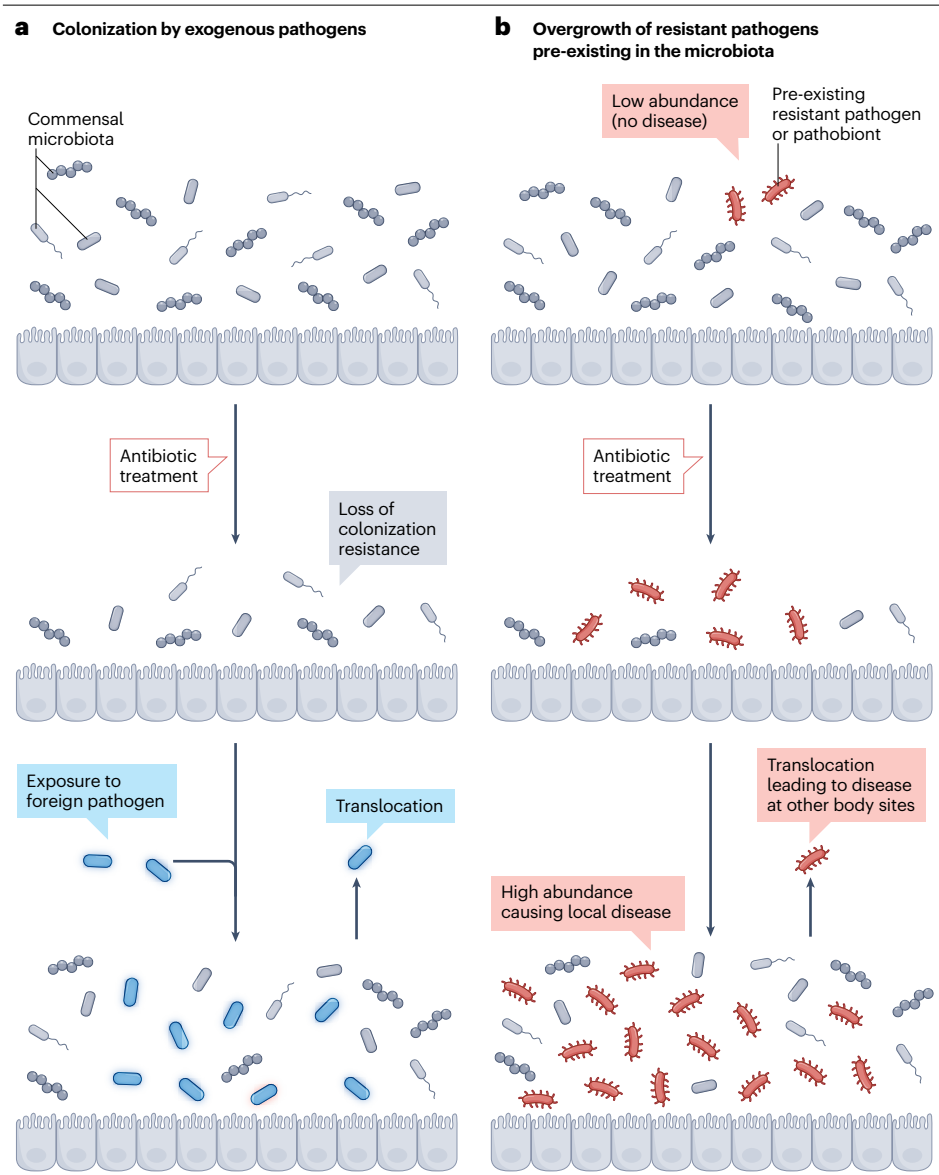


Fig. 1 | Two mechanisms of infection following antibiotic treatment. a, A healthy microbiota provides protection against colonization by foreign pathogens. Antibiotic therapy can suppress commensal bacteria living within the host and significantly increase the risk of colonization and infection upon exposure to foreign pathogens. **b**, The microbiota can also harbour potential pathogens, often present in low abundance without causing disease. Antibiotic treatment can lead to overgrowth of any resistant pathogens pre-existing within the microbiota. Overgrowth to high abundance can cause local disease or facilitate the translocation of these pathogens to other body sites where they cause disease, such as the bloodstream.

chloramphenicol, clindamycin, macrolides and tetracyclines[32,50]. Some antibiotics, such as metronidazole, narrowly target obligate anaerobes and can therefore lead to increased relative abundance of oxygen-tolerant bacteria, including potential pathogenic genera such as *Enterococcus* and *Salmonella*[51]. Broad-spectrum β-lactams, by contrast, are active against both obligate and facultative anaerobes. It should be noted that the spectrum of activity can vary strongly even between antibiotics with the same mechanism of action[32]. For example, an in vitro screen of human gut commensals has shown that quinolone antibiotic activity is very dependent on the drug generation, ranging from first-generation variants effective against few species to fourth-generation variants which inhibited almost all tested species[32]. The effects of different antibiotics on oropharyngeal, skin and vaginal microbiota are less studied, but drug-specific effects on the extra-intestinal microbiota have been reviewed[30].

The microbiota disruption caused by a specific antibiotic can also be inferred based on the risk of adverse events such as antibiotic-associated diarrhoea (AAD)[52]. AAD is one of the most common side effects of antibiotics occurring in 5–30% of patients treated with antibiotics, with frequencies varying according to the type of antibiotic administered[4,5,53]. Although almost all antibiotics have been implicated in AAD, higher frequencies of AAD have been associated with exposure to antibiotics active against anaerobic bacteria such as clindamycin, cephalosporins and broad-spectrum penicillins[5,53]. Higher levels of AAD are also often seen in patients treated with combinations of antibiotics[5], such as clindamycin in combination with another antibiotic[53], or combinations of three or more antibiotics[54].

Host-specific factors

Although trends can be observed in how different antibiotics behave, host-specific factors play an equally important role in determining the

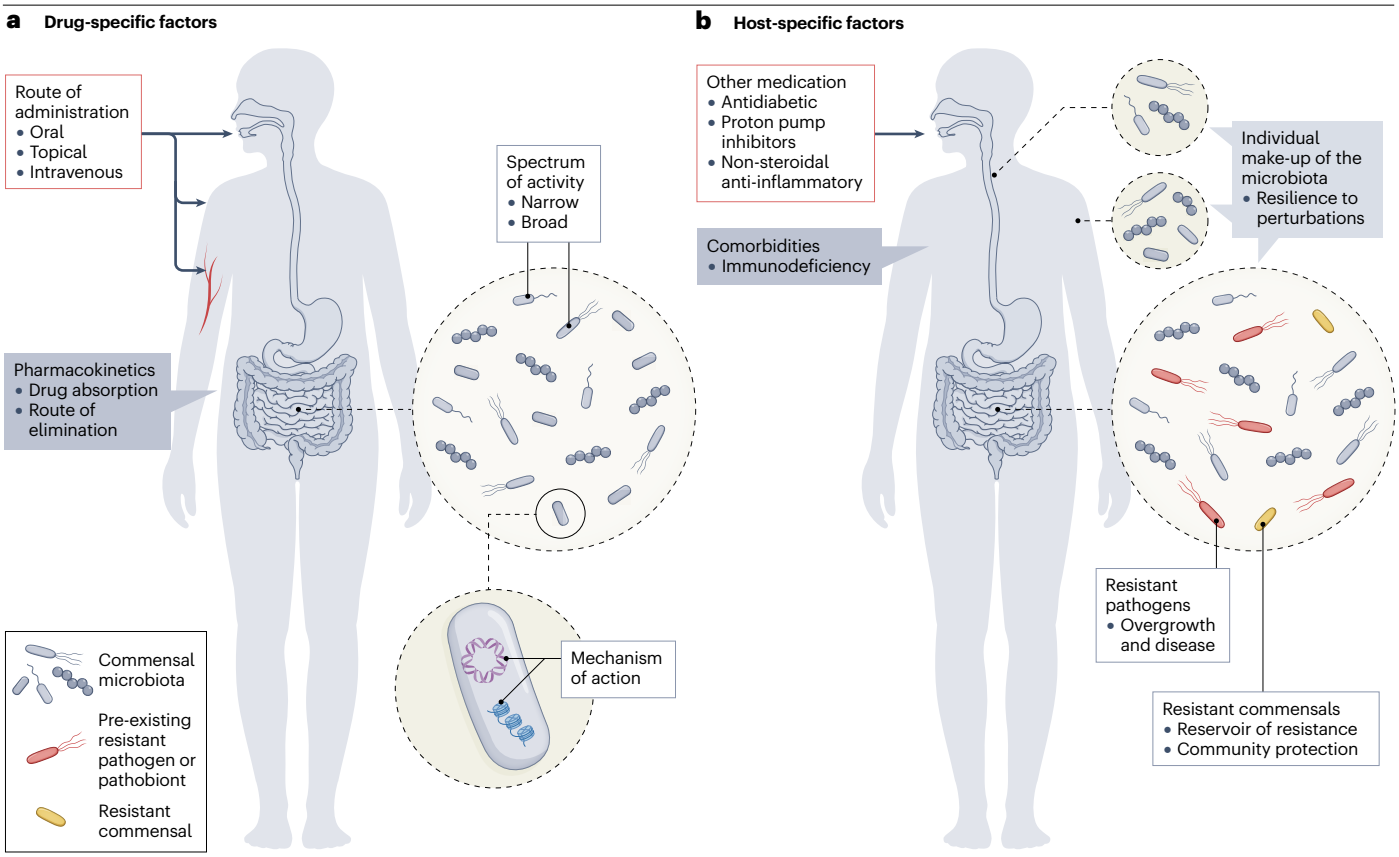


Fig. 2 | Factors contributing to antibiotic-induced disruption of microbiota homeostasis. a, Drug-specific factors include the route of administration, drug pharmacokinetics, mechanism of action and spectrum of activity. **b**, Host factors include the individual make-up of the patient's microbiota, including the presence of antibiotic resistance among both commensals and potential pathogens. Patient comorbidities as well as co-administration of non-antibiotic drugs also determine the level of antibiotic-induced microbiota perturbation.

effect of antibiotics on the microbiota[34,55]. Indeed, the heterogeneous response between individuals can make it difficult to predict the effect of specific antibiotics on the microbiota. For example, the proportion of the antibiotic ceftriaxone secreted in the bile was shown to vary by up to 3-fold between individuals, and the perturbation to the gut microbiota correlated with this biliary excretion rate[56]. Moreover, the microbiota itself is highly heterogenous between individuals. Ecological models and experimental evidence suggest that the species present and their interspecies interactions determine the stability of the microbiota and its response to perturbations such as antibiotics[57]. In studies in which healthy volunteers were administered the same antibiotic, the response of the gut microbiota was highly variable between individuals[34,55,58,59]. In one study, a subset of volunteers showed particularly strong compositional changes and prolonged reduction in microbiome diversity after antibiotics, suggesting that some individuals may be at higher risk of adverse outcomes following antibiotics than others[59]. Lower microbiota stability is also observed in infants[60] and older people[35] compared with healthy adults. Although it is clear that the response to antibiotics depends on the individual make-up of the microbiota, we still have much to learn about the factors that govern this behaviour.

The presence of antibiotic resistance within the microbiota also determines the resulting effect of antibiotics. Antibiotic-resistant pathogens present within the microbiota can lead to overgrowth and subsequent infections, as covered in detail later. Resistance among commensals can have different effects. On the one hand, these commensals can act as a reservoir for resistance genes that can spread horizontally to pathogenic species. On the other hand, commensals which are resistant to a particular antibiotic will be less perturbed by drug treatment and, hence, lead to lower overall disruption to the microbial community. Furthermore, the bacteria present in the microbiota can also modulate the effect of drugs, providing protection for their antibiotic-susceptible neighbour[36]. The secretion of antibiotic-degrading enzymes, such as β-lactamase enzymes, by the microbiota may compromise antibiotic efficacy and, in turn, provide passive resistance to a microbial community[37,61,62]. The composition of an individual's microbiota is influenced by environmental factors. For instance, exposure to environmental reservoirs, for example livestock or wastewater, likely promotes the transmission of not only environmental microorganisms but also their antimicrobial resistance genes to the human microbiome[63]. As the initial state of the microbiota impacts how it is perturbed by antibiotics[55], these environmental factors ultimately also affect the individual response to antibiotics.

The microbiota is also highly regulated by the host immune system, with the host playing an essential role in microbiota homeostasis[64]. The microbiota, in turn, influences the function of the immune system[38,65]. As such, patient immune status and comorbidities can

impact the disruption caused by antibiotics. The gut microbiota of individuals who are immunosuppressed, such as patients receiving chemotherapy or stem cell transplants, can be highly distinct from those of healthy individuals, and hence are likely to have altered risk of antibiotic-induced microbiota perturbation[51]. Furthermore, some non-antibiotic drugs, such as proton pump inhibitors (PPIs), anti-inflammatory drugs and antipsychotics, have been shown to supress various gut commensal species in vitro[66], and have been associated with changes to the microbiota composition in humans[67]. The use of these drugs in parallel with antibiotics can change the host's risk of antibiotic collateral damage[66,68]. For example, PPIs strongly inhibit gastric acid production and are a known risk factor for AAD[69,70].

Loss of colonization resistance and increased infection risk

An intact microbiota confers protection against a wide range of invading pathogens, a concept termed colonization resistance. There are various mechanisms by which a healthy microbiota provides colonization resistance (Box 1). These can be direct, through interbacterial interactions such as nutrient competition[71,72] or secretion of bacteriocins and other antimicrobials[73]. The microbiota can also provide colonization resistance indirectly, for example by preparing the host immune system to combat infection[74–76]. It has long been known that antibiotic-induced perturbations can disrupt colonization resistance and drastically increase the risk of infection. Indeed, studies performed as early as the 1950s showed that antibiotic administration to mice or guinea pigs rendered these animals up to 100,000-fold more susceptible to subsequent infection by enteric pathogens such as *Vibrio cholerae* and *Salmonella enterica* than untreated animals[74,77–80].

Clinically, *Clostridioides difficile* is one of the most well known and widely studied pathogens which cause infections following antibiotic treatment. *C. difficile* infections (CDIs) are responsible for between 10% and 25% of all diagnosed cases of AAD, and can cause serious intestinal infections such as antibiotic-associated pseudomembranous colitis[4]. Various antibiotics have been associated with risk of CDIs, but particularly high-risk drug classes are clindamycin and various β-lactams, including monobactams, carbapenems and cephalosporins[15,81]. The dosage and the duration of antibiotic treatment are important factors determining the risk for CDIs, with risks increasing for longer treatments and when multiple antibiotics are administered[81]. The essential role that a healthy gut microbiota plays in protecting against CDIs has been demonstrated by numerous studies showing that CDIs could be cured by administration of a consortium of commensal gut species[82] or donor faeces[83]. A healthy gut microbiota provides protection against CDIs through several mechanisms. In particular, metabolism of host-produced bile acids by certain members of the healthy microbiota makes them toxic to *C. difficile* vegetative growth. It has been shown in mice that colonization resistance to *C. difficile* can be restored with the addition of a single species, *Clostridium scindens*, which generates secondary bile acid through 7α-dehydroxylation[84]. Other mechanisms also important for colonization resistance against *C. difficile* – for example, competition by members of the microbiota for nutrients essential for *C. difficile* growth – can protect against CDIs independently of bile acid effects[85,86]. In mice, antibiotic treatment increased the amounts of sugars, amino acids and other nutrients which *C. difficile* uses for growth[72].

Beyond the well-studied example of *C. difficile*, there is evidence that infections with various other enteric pathogens are also associated with antibiotic-induced loss of gut microbiota-mediated colonization resistance. For example, *Klebsiella oxytoca* has been identified as a causative organism of antibiotic-associated haemorrhagic enterocolitis[16]. Other pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are likely also responsible for cases of non-*C. difficile* antibiotic-associated enterocolitis[87,88]. Numerous studies in animals have shown that antibiotics can facilitate *Salmonella* infection[79,89]. In humans, epidemiological evidence suggests that prior antibiotic use is a significant risk factor for infections from both non-typhoidal[90–92] and typhoidal[93,94] *Salmonella*, although the causality of these associations remains to be established.

Colonization resistance and antibiotic-associated infections at other body sites

Although the gut represents the largest and most diverse microbial reservoir in the human body, colonization resistance also extends to other body sites and prior antibiotics have been associated with increased risk of various extra-intestinal infections in both communtiy[94] and hospital settings[95]. For example, the skin microbiota has an essential function against invasion of exogenous pathogens. Similar to the intestinal microbiota, these microorganisms may metabolize host proteins and lipids to produce bioactive molecules, such as antimicrobial peptides, for their competitive advantage[96]. For instance, various commensal *Staphylococcus* spp., commonly found on the skin, were previously shown to produce antimicrobial peptides which inhibited the growth of *S. aureus*[39,97,98]. Moreover, commensal skin microbiota, or their metabolic products, may stimulate production of host-derived antimicrobial peptides[99,100].

The niche-specific microbial community of the upper respiratory tract also has an important function for inhibiting the dissemination of pathogens to the lungs[101], and therefore for the prevention of respiratory infections[101–104]. An intact upper respiratory microbiota can provide indirect protection from infection through its role in regulating the host immune response. Indeed, in mouse models the commensal microbiota regulates T cell and antibody responses following influenza virus infection, and antibiotic treatment has been shown to exacerbate disease severity in various viral infections[19,105]. Antibiotic perturbation to the microbiota of the oropharynx has been observed to cause increased colonization by various Enterobacteriaceae[30] and *Streptococcus pyogenes*[43], and prior antibiotic treatment may be associated with upper respiratory infections in humans[106]. Studies have also shown that prior antibiotics significantly increase the risk of urinary tract infections (UTIs); women treated with antibiotics for other illnesses were three to six times more likely to experience a subsequent UTI than untreated women[107].

Overgrowth of pre-existing pathogens within the microbiota

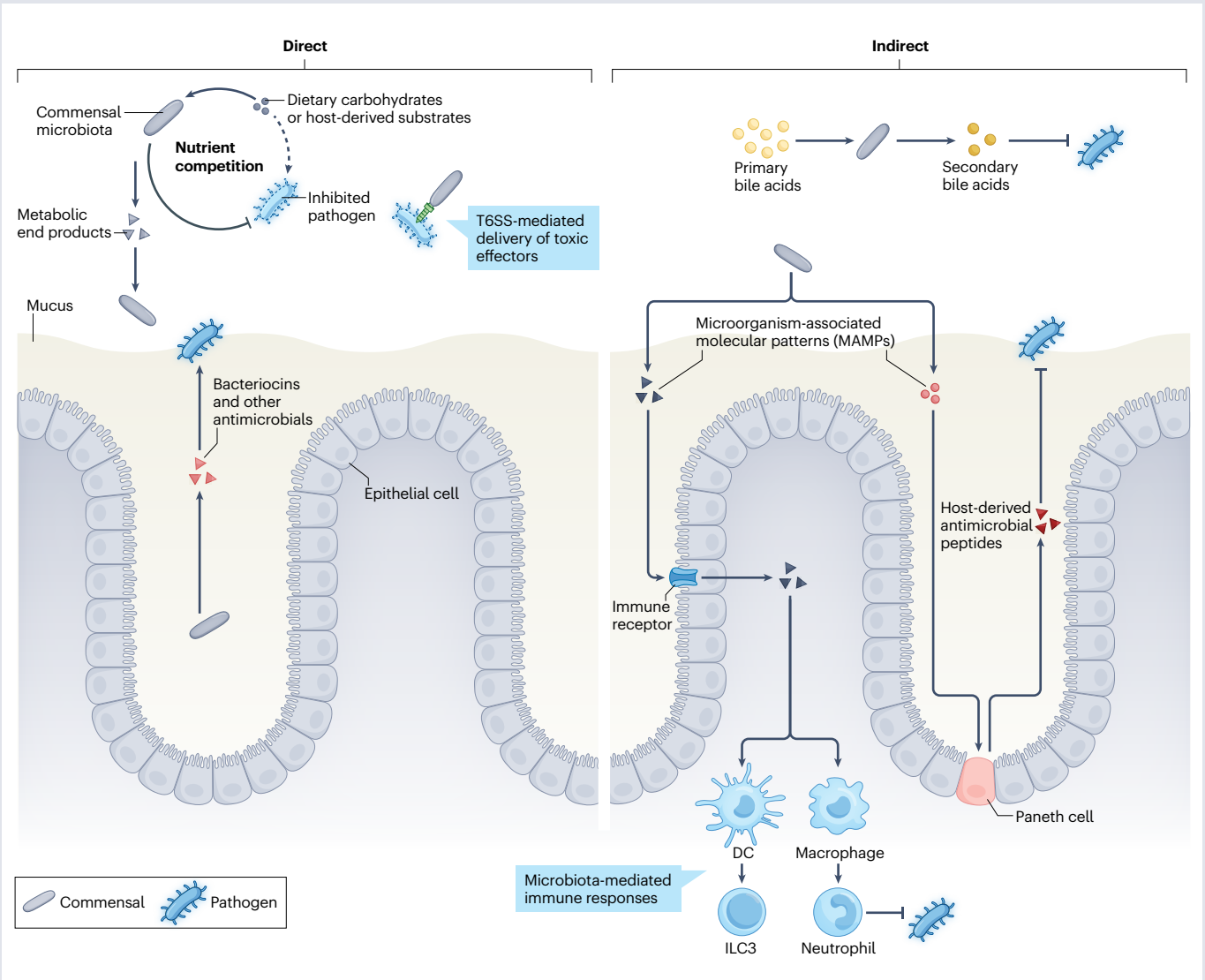
It is well established that a disrupted microbiota following antibiotics can increase the risk of colonization and infection by foreign pathogens[108]. Experimental models of colonization resistance typically recapitulate this by measuring infection by an exogenous pathogen introduced to the animal following antibiotic treatment. However, in many cases, potential pathogens are already present in the patient's microbiota prior to therapy[109–113] (Box 2), sometimes at low levels or undetectable in surveillance cultures, known as occult or subclinical colonization[114]. Self-infection can also be caused by 'pathobionts': commensal species typically not considered pathogens, but which can cause disease in certain contexts, such as individuals who are

Box 1

Colonization resistance

Commensal bacteria can protect against exogenous pathogens by various mechanisms. These fall into two categories: direct mechanisms via bacterial–bacterial interactions, or indirect mechanisms via microbiota-mediated modification of host factors (see the figure). Microbial competition and subsequent depletion of nutrition represent one aspect of direct colonization resistance. Dietary carbohydrates or host-derived substrates may be metabolized by different microbial groups, whereas metabolic end products may become metabolic inputs for other syntrophic microorganisms[6]. Additionally, whereas some bacteria can catabolize both monosaccharides and polysaccharides, others are restricted to specific glycans. As such, commensal microorganisms that share similar nutrition preferences or glycan restrictions, as pathogens, compete for the same metabolic niche, which in turn limits pathogen colonization[181–183]. Other mechanisms include direct attacks via type VI secretion systems (T6SSs) used by Gram-negative species to kill competing species via contact-dependent transport of toxin proteins[184,185]. Furthermore, many gut commensals secrete bacteriocins, a subgroup of antimicrobial peptides, that directly inhibit other bacterial species, including pathobionts and pathogens[166,186].

Indirect mechanisms of colonization resistance, on the other hand, require host–microorganism interactions to inhibit exogenous



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bacteria. Although the mucus layer forms a physical barrier limiting pathogen interaction with the underlying epithelium, commensal microorganisms may further limit pathogen colonization by inducing mucus production and maintaining the mucosal barrier. Moreover, interaction of the microbiota with host receptors can elicit the production of host-derived antimicrobial peptides by epithelial cells. Simultaneously, interactions of the microbiota with innate immune receptors lead to downstream production of pro-inflammatory cytokines[6,74]. Besides promoting the host's immune system[75,76], members of the microbiota may also interact with host-derived molecules themselves. Primary bile acids are secreted into the intestinal tract[187]. Hydrolases produced by a wide range of bacterial taxa deconjugate the primary bile acids, which can be converted into various secondary bile acids that are known to inhibit the growth of pathogens such as *Clostridioides difficile*[84]. DC, dendritic cell; ILC3, type 3 innate lymphoid cell.

immunocompromised[110]. Antibiotic treatment can lead to overgrowth of these opportunistic pathogens or pathobionts that were previously persisting at low levels in the patient's microbiota[23]. Knowing whether an antibiotic-associated pathogen is of exogenous or endogenous origin is important for developing preventative strategies, as described later in this Review.

The main mechanism by which a potential pathogen can outcompete other species during antibiotic treatment is when it is more resistant to the drug than its competitors, either due to intrinsic or acquired resistance (Fig. 3a). However, an antibiotic can affect particular bacteria differently depending on the interspecies interactions with other microorganisms within the community[115–117]. As such, even apparently susceptible pathogens can overgrow within the microbiota during antibiotic treatment as a result of preferential loss of commensal species that confer colonization resistance to them[49,51,77]. Here, the role of the resident microbiota might more accurately be described as 'proliferation resistance': preventing the proliferation of a low-abundance microorganism to a high-abundance, disease-causing state.

Overgrowth of intrinsically resistant pathogens

One of the most well-known examples of overgrowth of intrinsically antibiotic-resistant pathogens is post-antibiotic fungal infection. Various fungi are found in the microbiota of healthy humans in various body sites, including the skin, oropharynx, intestine and lower reproductive tract[118]. Although usually benign, antibiotic-induced loss of commensal bacteria can lead to the proliferation of fungi and subsequent disease. In particular, the overgrowth of the opportunistic pathogen *Candida albicans* leading to vulvovaginal and oral candidiasis[119] is a very common adverse effect of antibiotic treatment[17,120,121], particularly β-lactams[122]. Moreover, *C. albicans* is a common cause of nosocomial bloodstream infections and past antibiotic treatment is a strong risk factor for candidaemia[18,123–125]. Antibiotics, particularly with anaerobic activity or high concentrations in the intestine, caused sustained increase in intestinal colonization by yeasts[126]. Intestinal domination by *Candida* spp. has been observed to precede bloodstream infections[125], suggesting that overgrowth in the gut may facilitate these systemic yeast infections.

Other antibiotic-associated infections may also be caused by overgrowth of intrinsically resistant pathogens persisting within the microbiota. Gram-negative species are intrinsically resistant to antibiotics such as clindamycin and vancomycin, and can overgrow in the intestine during treatment with these drugs[114]. In mice, treatment with a single dose of clindamycin resulted in a marked expansion of Enterobacteriaceae species, followed by multiple shifts in microbiota composition over the next 4 weeks[24]. Metronidazole is active against commensal obligate anaerobes, but generally ineffective against oxygen-tolerant bacteria and has been shown to lead to increased *Enterococcus* abundance in humans[51]. *C. difficile* is intrinsically resistant to various broad-spectrum antibiotics used against other pathogens[127,128]. Despite being one of the most common nosocomial infections, studies have shown that many CDIs are not a result of transmission events within hospitals, suggesting they may instead be a result of antibiotic-induced overgrowth of *C. difficile* already present in the microbiota[129]. In agreement with this, a systematic review has shown that patients colonized with *C. difficile* are at significantly higher risk of CDIs than patients who are not colonized[109].

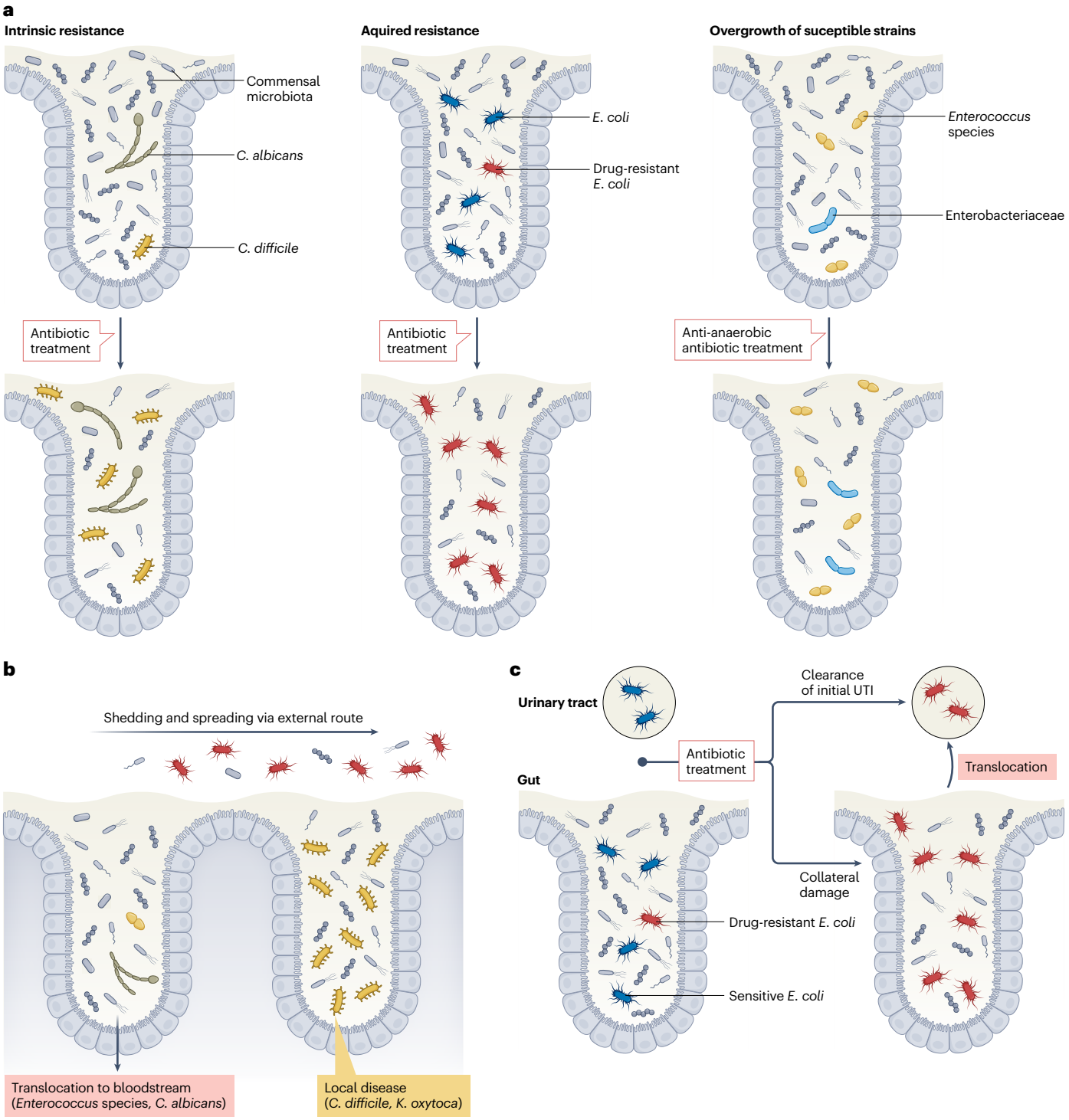
Overgrowth of pathogens with acquired resistance

Antibiotics can also lead to overgrowth of strains from typically sensitive species which have evolved or acquired resistance to

Box 2

Infection from within

Many bacterial pathogens are members of species that are primarily commensals which do not cause disease as an obligate part of their life cycle[112,188]. Indeed, globally, more than half of the deaths associated with bacterial pathogens come from five species that are commonly identified in the microbiota of healthy individuals: *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*[189]. Disease from these species, as well as many other opportunistic pathogens, can be self-infections, that is, caused by bacteria pre-existing in a patient's microbiota rather than transmission events[110,113,188]. For example, in one prospective study of patients with nasal colonization by *S. aureus*, 86% who went on to experience *S. aureus* bacteraemia had blood isolates clonally identical to the isolates identified in their nasal swabs up to 14 months prior[151]. Carriage of uropathogenic *E. coli* (UPEC) in the gut microbiota is common, and these uropathogens can act as a reservoir for urinary tract infections (UTIs)[150,190]. Potential pathogens may be able to persist in the microbiota over very long periods of time. In one study, a multidrug-resistant UPEC strain was found to move between the gut and the bladder of a patient suffering from recurrent UTI over a 5-year period[143]. For all of these potential pathogens within the host microbiota, various drivers can trigger the transition from a low-abundance, commensal state to a high-abundance, disease-causing state[110].



specific drugs. Antibiotic-resistant opportunistic pathogens and pathobionts can frequently persist asymptomatically within an individual's microbiota, including hard-to-treat pathogens such as carbapenem-resistant Enterobacteriaceae (CRE) and vancomycin-resistant enterococci (VRE)[25–27,49,113]. When resistant strains are present in the microbiota prior to therapy, antibiotics can lead to 'blooms': overgrowth of a strain that was previously persisting at low levels leading to transient domination of the microbiota by a single strain resistant to the drug[23,113]. Antibiotic-induced blooms of drug-resistant *Escherichia coli* and *Klebsiella pneumoniae* have been observed in humans[22], with the relative abundance of these species increasing from a few per cent before treatment to account for nearly

Fig. 3 | Overgrowth and infection from pre-existing pathogens within the microbiota. a, Potential pathogens are frequently present in the patient's microbiota prior to therapy. Antibiotic-induced overgrowth can occur when these pathogens are intrinsically resistant to the administered drug, such as *Clostridioides difficile*, and fungi such as *Candida albicans* (left). Pathogens with acquired resistance, such as drug-resistant *Escherichia coli* and other Enterobacteriaceae, can overgrow by outcompeting not just other species but also sensitive members of the same species (centre). Even susceptible pathogens can overgrow due to antibiotic-induced loss of species conferring colonization resistance. Antibiotics active against commensal anaerobes can promote overgrowth of potentially pathogenic oxygen-tolerant species such as enterococci and Enterobacteriaceae despite in vitro activity against these species (right). **b**, Antibiotic-induced overgrowth can directly lead to local disease, such as colitis caused by the overgrowth of enteric pathogens *C. difficile* and *Klebsiella oxytoca* in the gut. Alternatively, microbiota disruption can lead to a weakened intestinal barrier, or reduced host defences, allowing overgrowing pathogens, such as *Candida* spp. and *Enterococcus* spp., to cross into the bloodstream. Overgrowth within the intestine can lead to increased shedding in the faecal matter, facilitating spread to other body sites via external routes. **c**, Antibiotic-associated infections may be easily misidentified as treatment failures if the treatment promotes reinfection at the same body site as the original infection. For example, an antibiotic may clear a susceptible pathogen from the urinary tract, but at the same time lead to overgrowth of resistant uropathogens in the gut microbiota, thereby facilitating resistant reinfection of the urinary tract. UTI, urinary tract infection.

a quarter of the entire microbiota following treatment. Even resistant strains present at initially very low abundance can overgrow to high levels during antibiotic treatment. In a mouse model of occult colonization, treatment with various antibiotics including ampicillin and azithromycin caused overgrowth of multidrug-resistant *K. pneumoniae* from initially undetectable levels to high abundance in the stool[114]. Furthermore, in antibiotic-treated mice, overgrowth of a multidrug-resistant *E. coli* previously benignly inhabiting the gut led to systemic spread and rapid sepsis-like death[130].

Antibiotic-induced overgrowth of a strain which has evolved resistance is subtly different to that of an intrinsically resistant species. In the former case, this strain can outcompete not just other species but also its closest competitors: susceptible strains of the same species. As they typically compete for an identical set of resources, these same-species competitors are often critical for providing colonization resistance[131,132]. For example, in a recent preprint, the introduction of an engineered non-pathogenic *Salmonella* strain to a mouse microbiota was shown to provide stronger protection against pathogenic *Salmonella* infection compared with other species, as it occupies a near identical metabolic niche[133]. Similarly, germ-free mice mono-associated with a single *Bacteroides* sp. are resistant to colonization by the same, but not different, species[134]. Even antibiotics which cause relatively little perturbation to overall species abundances may therefore still allow resistant strains to overgrow in the microbiota by dominating their species-specific niche[135]. In a study of travellers, a 14-day prophylactic course of trimethoprim–sulfamethoxazole led to no change in total faecal Enterobacteriaceae abundance in most persons, but led to selection for high-level resistance to the drugs in virtually all faecal Enterobacteriaceae strains isolated[135]. Furthermore, a study comparing the gut microbiota of children found that children who had received multiple courses of antibiotics in their first 3 years of life had significantly more species dominated by a single strain compared with children with no antibiotic exposure[22].

Pathogen overgrowth and loss of colonization resistance are interlinked

Importantly, antibiotic-induced overgrowth of pre-existing pathogens and loss of colonization resistance are interlinked processes. Treatment with antibiotics that strongly suppress obligate anaerobes, which make up the majority of the human gut microbiota, can lead to an increased abundance of some oxygen-tolerant, potentially pathogenic bacteria, such as *Enterococcus* and various Enterobacteriaceae[51,77,114,136,137]. As such, antibiotic treatment can lead to overgrowth of a potential pathogen within the microbiota, despite in vitro susceptibility showing it to be sensitive to the administered drug[77]. This has been shown in studies focused on the common nosocomial pathogen VRE. In mice colonized by VRE, treatment with piperacillin–tazobactam, a β-lactam antibiotic and β-lactamase inhibitor combination medication which is broadly active against commensal anaerobes, promoted persistent VRE overgrowth despite moderate in vitro activity against the VRE strain tested[113]. Treatment with bacitracin, an antibiotic with potent activity against both the VRE isolate used and commensal anaerobes, led to suppressed VRE colonization, but then to relapse and overgrowth to moderate levels after discontinuation of treatment. In patients colonized with VRE, the density of VRE in stool increased during treatment not only with vancomycin but also with various antibiotics that target the commensal anaerobes[49,77].

In mouse models it has been shown that antibiotic treatment can lead to downregulation of host expression of an antimicrobial protein, RegIII, which is active against VRE[138], showing that antibiotic-induced loss of indirect colonization resistance factors can potentially facilitate overgrowth, even of pathogens that are apparently susceptible to the treatment. This also highlights that overgrowth of pathogens that are resistant to the administered antibiotic may frequently occur due to a combination of the direct growth advantage against other microorganisms as well as due to the loss of microbiota-mediated colonization resistance and other indirect factors. For example, treatment with β-lactams induces release of large quantities of peptidoglycan fragments from commensal bacteria that potently induce the invasive hyphal growth of *C. albicans*[122].

Antibiotic-induced translocation between body sites

Antibiotic-induced pathogen overgrowth can cause localized disease at the initial colonization site, such as proliferation of *C. difficile* in the intestine leading to colitis. Overgrowth can also facilitate translocation of microorganisms benignly inhabiting one body site to a new body site where it causes disease[139] (Fig. 3b). The gut microbiota can be host to many potential pathogens which rarely lead to enteric disease but can frequently cause infection at other body sites[113]. In particular, antibiotic-induced overgrowth of potential pathogens in the intestine can lead to serious bloodstream infections[139]. Intestinal domination, with a single species accounting for >30% of the gut microorganisms, has been shown to be a risk factor for bloodstream infection with various pathogens, including *Candida*, *Enterococcus*, *Streptococcus* and various Pseudomonadota species[51,125,139,140]. In mouse models, antibiotic-induced overgrowth has been shown to facilitate the systemic spread of pathobionts and commensal gut bacteria[130,141]. This antibiotic-induced translocation from the gut to the bloodstream may

be a consequence of host defences being overwhelmed by pathogen overgrowth or due to increased breakdown of the intestinal barrier caused by disruption of the gut microbiota[142].

Movement of pathogens also occurs between the intestinal microbiota and other body sites, such as the urinary tract[143,144] and respiratory tract[145]. Antibiotic-induced overgrowth within the gut can lead to high levels of shedding of these pathogens in the faecal matter[114,146] and external spread to other body sites, such as the urinary tract, within the host. Antibiotic-induced intestinal overgrowth of VRE leads to increased spreading to the environment in hospital settings[49], suggesting that this mechanism of translocation is also likely to facilitate the spread to other patients. Although relatively poorly studied, antibiotic-induced overgrowth of microorganisms benignly inhabiting other body sites, such as the lower reproductive tract, skin or oral cavity, may similarly facilitate translocation to other body sites where they can cause disease.

Misidentified antibiotic-associated infections

Determining whether antibiotic therapy is a primary cause of a subsequent infection is not straightforward, especially because these drugs are prescribed at very high frequencies and particularly to individuals already at high risk of infection. In acute care settings, three quarters of antimicrobial drugs are prescribed for infections of the lower respiratory tract, urinary tract or skin and soft tissues[147]. The most well-known antibiotic-associated nosocomial infection, CDI, is an enteric disease with very different symptoms to the most common infections for which antibiotics are initially prescribed. Do antibiotics preferentially increase the risk of infections with a different pathology to the original infection? It seems likely that the infections that are most commonly associated with antibiotic use are those where the link between infection risk and antibiotic use is easiest to discern, that is, a completely new infection occurred as a result of antibiotic treatment. However, if antibiotics prescribed for a particular infection also facilitate rapid reinfection at the same body site with similar symptoms, these will be harder to identify.

An example of this is the emergence of antibiotic resistance during treatment, which is a common occurrence for various bacterial infections. Although this can be a consequence of the original pathogen evolving resistance, recent evidence has shown that for several infection types, such as UTIs and wound infections, this is most frequently caused by strain replacement: clearance of the original susceptible pathogen followed by rapid reinfection with a different resistant bacterium likely originating from within the patient's microbiota[148,149]. In the case of UTIs, which are predominantly caused by uropathogenic *E. coli* (UPEC), these rapid reinfections were typically a new strain of the same species. Without frequent culturing and strain-level resolution, such cases could easily be misidentified as simple treatment failures, that is, a failure of the antibiotic to clear the original pathogen (Fig. 3c). Many bacterial infections originate from the patient's own microbiota[110,143,150,151]. Antibiotic treatment can lead to overgrowth of pre-existing pathogens, particularly when they are resistant to the administered drug, and can also facilitate the translocation of strains between body sites. The true prevalence of antibiotic-associated infections therefore remains unknown, but these are important to distinguish from treatment failures because there are many potential strategies to reduce the unwanted collateral effect of antibiotics that cause these infections, as detailed later in this Review.

Recovery of the microbiota following antibiotics

Antibiotic-induced perturbations to the microbiota can be thought of as having both acute and chronic impacts. The strongest disruption occurs during treatment with numerous studies of the gut microbiota showing profound loss of diversity, shifts in community composition and decreases in bacterial counts, occurring within a few days of drug initiation[40,59,136]. Once treatment ends, the microbiota typically returns rapidly towards its initial state, a quality known as resilience (Fig. 4). Most studies of the intestinal microbiota show recovery within 2–8 weeks after the cessation of treatment[40,59,136]. In agreement with a fast initial recovery from a strongly disrupted state once antibiotics are removed, many cases of AAD are self-limiting once antibiotic treatment ends[4,5]. However, the recovery of the microbiota from acute disruption can be incomplete, leading to a long-term altered state[34,59,136]. One study of antibiotic treatment in healthy volunteers found that an acute decrease in species richness and bacterial counts during treatment was followed by a return to pretreatment species richness after 2 months, but with an altered taxonomy, resistome and metabolic output[59]. Similarly, another study observed blooms of Enterobacteriaceae and other pathobionts such as *Enterococcus faecalis* and *Fusobacterium nucleatum* during treatment, followed by recovery to near-baseline composition within 1.5 months. However, multiple common species were lost during treatment and remained undetectable in most of the subjects after 180 days[136]. The resilience of the intestinal microbiota appears to decrease with repeated antibiotic treatments[34].

Similar to the changes observed in the composition of the microbiota, its resistome also experiences acute and chronic perturbations following antibiotic treatment. Treatment can lead to transient blooms of resistant strains to extremely high levels within the gut microbiota[22]. As species abundances return to baseline level, resistance levels also decrease; however, they frequently return to an elevated level compared with before treatment. This can be a consequence of resistant strains becoming dominant within their species-specific niche or because of the horizontal spread of mobile resistance genes between species[22]. Indeed, it has been hypothesized that overgrowth or typically low-abundance species within the intestine might act as a driver of horizontal gene transfer, promoting pathogen evolution and the spread of antibiotic resistance[23]. Although the acute phase of microbiota disruption during and immediately following treatment is clearly associated with the highest risk of subsequent infections, there is still much we need to learn about how long-term antibiotic-associated perturbations to microbiota species abundance and resistance levels affect the future risk of infection[152–154].

Strategies to minimize antibiotic-associated infections

Antibiotic-associated infections are a consequence of the collateral damage of administered antibiotics, through the reduction in colonization resistance and by the overgrowth of resistant microorganisms within the microbiota. Strategies to minimize antibiotic-associated infections therefore focus on preventively reducing the collateral damage through antibiotic stewardship, targeted antibiotics and personalized treatment, or on mitigating the infection risk associated with this collateral damage by infection control methods or altering the microbiota to restore or improve colonization resistance (Fig. 5). In the following sections, we describe these potential strategies, highlighting their advantages and current limitations.

Minimizing the collateral damage caused by antibiotics

Antibiotic stewardship. Antibiotic stewardship programmes to promote the accurate use of antibiotics have been one of the major approaches to reduce the occurrence of antibiotic-associated

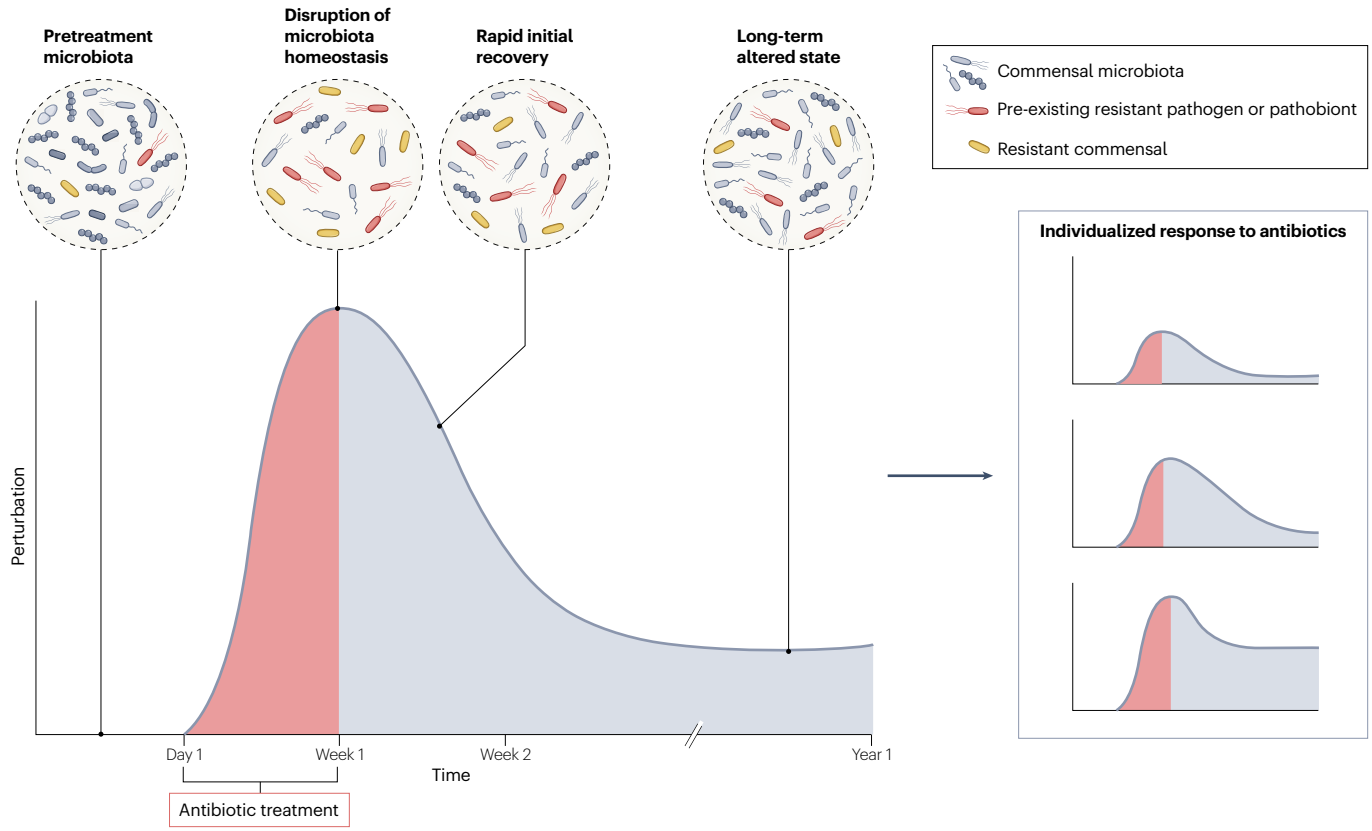


Fig. 4 | Recovery of the microbiota after antibiotic treatment ends. Perturbation of microbiota homeostasis is rapid upon antibiotic administration (left). Disruption of the intestinal microbiota occurs within a few days of treatment starting. After treatment ends, the microbiota rapidly returns towards baseline levels, typically showing recovery within 2–8 weeks. However, recovery can be incomplete, leading to long-lasting changes to species abundance, metabolic activity and antibiotic resistance levels. Both the initial disruption and subsequent recovery can be highly distinct between different individuals (right).

infections[155]. These approaches include auditing, restriction of specific antibiotics, restriction of treatment duration and antibiotic cycling or mixing[156]. Although effective, such approaches have generally been limited to specific antibiotics associated with well-understood infections such as CDIs in hospital settings. For example, restrictions in the clinical use of drugs associated with a high risk of causing CDIs, such as cephalosporins, clindamycin and fluoroquinolones, have been one successful approach to limit CDIs[155–157]. In addition to antibiotic restriction, antibiotic cycling — in which treatment with a first preferred antibiotic is followed by treatment with a second antibiotic of a different class but with a similar spectrum of activity — has been proposed as an effective strategy[156]. Clinical studies, however, have come to contradictory results regarding the true effectiveness of antibiotic cycling[158].

Personalized medicine. There is growing evidence that the response to antibiotics differs strongly between individuals, suggesting that a more personalized approach to antibiotic prescribing could help reduce collateral damage. For example, a better understanding of antibiotic pharmacokinetics in individuals who fall outside typical weight and height ranges may help optimize drug dosing[159]. Data-driven approaches can also reduce the unwanted effects of antibiotics. In a study focusing on UTIs and wound infections, it was shown that antibiotic treatment frequently led to rapid reinfection with a resistant strain probably originating from the patient's own microbiota[148]. These resistance-gaining reinfections could be predicted based on antibiotic susceptibility data from the patient's past infection history and minimized by machine learning-personalized antibiotic recommendations. Although these personalized medicine approaches offer a promising means to reduce the within-host spread of resistant pathogens and other unwanted adverse outcomes, they require significant baseline knowledge of the patient's medical history, which is often not available.

Targeted antibiotics. The collateral damage caused by antibiotics can be reduced by using more targeted drugs. This includes applying targeted drug delivery approaches to reduce the concentrations of antibiotics at off-target body sites[160,161]. Pathogen-specific drugs[162] and drug delivery approaches also offer a promising route to reduce the collateral damage to other species[163]. An alternative strategy has been to use antibiotic combinations that are species specific[164]. Furthermore, antibiotics in combination with other drugs can specifically antagonize the activity against abundant commensal species but not against relevant pathogens. Using this approach, a study identified 'antidote' drugs that selectively protected *Bacteroides* spp. from erythromycin treatment in the gut microbiota of mice, while maintaining its efficacy against the opportunistic pathogen *E. faecalis*[32]. Potential therapeutics such as bacteriophages[165] and bacteriocins[166,167] can also have extremely narrow activity spectra. Bacteriophages are typically

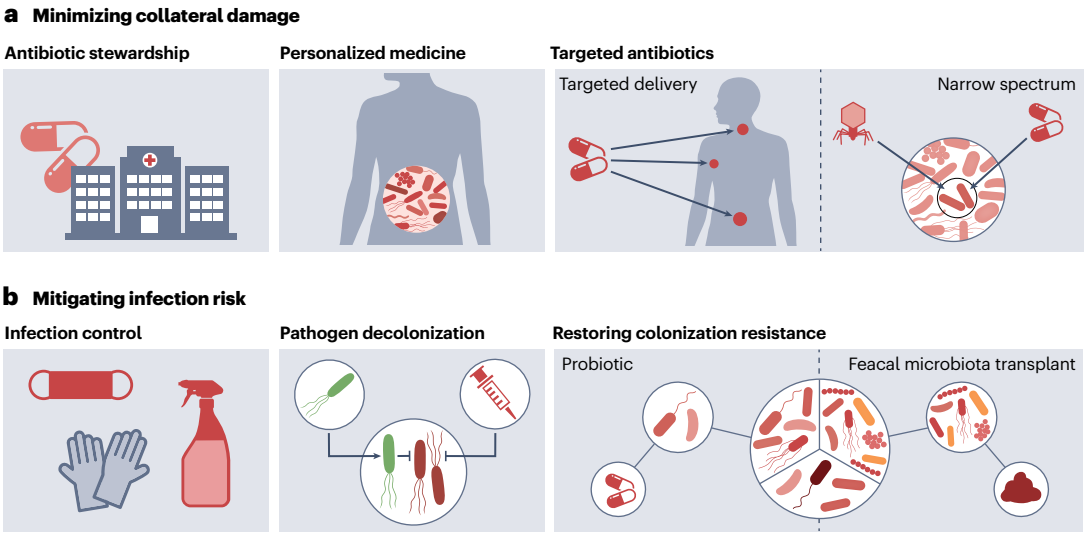


Fig. 5 | Strategies to minimize antibiotic-associated infections. a, The risk of antibiotic-associated infections can be reduced by directly minimizing the collateral damage caused by antibiotics through antibiotic stewardship, personalized medicine approaches and better targeted antibiotics. **b**, This risk can also be reduced by mitigating the infection risk associated with antibiotic collateral damage via infection control strategies, decolonizing patients of potential pathogens, or altering the microbiota to restore or improve colonization resistance.

specific for a particular bacterial host; some bacteriophages can infect several closely related species, but others are specific for a few individual strains within a species[168]. Compared with small molecule antibiotics, the vast natural reservoir of bacteriophages allows for personalized approaches by identifying bacteriophages that target the exact strain causing an infection. Small-scale clinical studies have resulted in the successful clearance of various antibiotic-resistant pathogens, including *Mycobacterium abscessus*[169] and *Acinetobacter baumannii*[170]. Likewise, antimicrobial peptides produced by bacteria, such as bacteriocins, can often have species-specific activity. For instance, the bacteriocin thuricin CD produced by *Bacillus thuringiensis* is active against *C. difficile*, but has little impact on most intestinal commensals[171]. However, narrow-spectrum therapeutics may also not be a viable option for polymicrobial infections. Moreover, the use of narrow-spectrum drugs requires knowing which pathogen is present, which can take days to discover so empirical broad-spectrum therapy is commonly prescribed while waiting for results. As such, the widespread use of pathogen-targeted and narrow-spectrum therapeutics also requires advancement in rapid pathogen detection technologies.

Mitigating infection risk associated with antibiotic collateral damage

Infection control measures. The risk of infection following antibiotic-induced loss of colonization resistance can be partially mitigated by reducing the exposure of these patients to potential pathogens. Infection control measures, such as placing patients with CDIs in single-patient rooms with a dedicated toilet, are standard guidelines in acute care settings[172]. Although such measures are important to reduce the spread of pathogens between patients, many antibiotic-associated infections occur from pathogens already present within the patient's microbiota and, hence, require alternative mitigation strategies.

Restoring colonization resistance with probiotics. Targeted administration of live bacteria to compensate for loss of specific commensal microorganisms has been demonstrated to restore colonization resistance and clear infections[82]. So far, clinical trials have primarily focused on the use of probiotics to alleviate the risk of AAD and CDIs. One study, performing a meta-analysis of randomized controlled clinical trials, reported that probiotics reduced the development of AAD and CDIs[4,5]. CDIs can be cured by administration of a consortium of commensal gut species[82]. Unfortunately, due to limited regulation, probiotics with no evidence for their benefit in reducing antibiotic-associated infections are still used in clinical settings, and in some cases inappropriate use can do more harm than good[173–175]. Nevertheless, various rationally designed live therapeutics show promise for mitigating the antibiotic collateral damage in animal models. For example, a single-species probiotic has been shown to restore bile acid-mediated colonization resistance to CDIs[84]. An engineered strain of *Lactococcus lactis* that secretes β-lactamase provides community protection and prevented the loss of colonization resistance against CDIs in ampicillin-treated mice[62].

Restoring colonization resistance with faecal microbiota transplantation. Faecal microbiota transplantation (FMT) can result in the establishment of a complex, donor-derived microbiota and promote re-expansion of recipient bacterial species[174]. There have been numerous randomized clinical trials documenting the effectiveness of FMT, particularly for treating chronic CDIs[83,176]. The re-established microbiota can suppress *C. difficile* by competing for the same niche or enhancing innate immune defences[177]. FMT is also being explored as a prophylactic measure in patients at particularly high risk of antibiotic-associated infections. During stem cell transplantation, antibiotic administration is essential for optimal clinical outcomes, but also leads to loss of many beneficial microorganisms and an increased risk of subsequent infections. Loss of gut microbiota diversity during stem cell engraftment increases mortality, but post-treatment FMT using autologously derived faecal microbiota has been shown to restore the intestinal microbiota composition[178].

It should be noted, however, that insufficient screening of donor faeces can also lead to recipient colonization and infection with drug-resistant pathogens[179] and that the long-term impacts of FMT are currently poorly understood.

Decolonizing patients of potential pathogens. To mitigate the risk of antibiotics promoting overgrowth and subsequent infection from resistant pathogens within the microbiota, approaches to specifically remove these potential pathogens could be employed. FMT is also being employed as a strategy to decolonize antibiotic-resistant bacteria from patients[177]. A study reported that from 23 studies, 67% of the patients had decolonization of antibiotic-resistant bacteria after FMT[180]. Another more targeted decolonization strategy is to introduce a non-pathogenic niche competitor. This approach can reduce the abundance of enteric pathogens within the gut microbiota, yet complete decolonization with this approach is difficult. A recent preprint reporting a study in mice has shown that vaccination against *S. enterica* combined with a niche competitor strain can achieve sterilizing immunity[133]. However, decolonizing approaches using niche competitors has yet to be trialled properly in humans.

Conclusions and outlook

We are increasingly understanding that commensal microorganisms play an essential role in human health. The concept that the microbiota provides colonization resistance, protecting the host against foreign pathogen invasion, is well established[6,74]. Somewhat paradoxically, an individual's microbiota also acts as a reservoir for potential pathogens and can therefore be the source of infection[111,112,178]. Antibiotics represent the most perturbative factors to which the microbiota is exposed, and are used in enormous quantities. The benefits of antibiotics are clear in the millions of lives they have saved; however, we still have much to learn about both the short-term and long-term effects these drugs can have in perturbing the equilibrium of the microbiota and facilitating subsequent infections. A better appreciation of the personal risks of antibiotics may help in efforts to limit their misuse.

Much of what we know about antibiotic-associated infections comes from several well-studied examples, particularly enteric infections such as CDIs[15,84]. However, it is clear that the impact of antibiotics on the microbiota changes the risk of a diverse number of infections from various pathogens, including extra-intestinal infections. Loss of commensal species can make it easier for foreign pathogens to colonize the microbiota. But antibiotics can also lead to expansion of pre-existing pathogens within the microbiota, particularly when resistant to the drug, leading to the translocation of pathogens between body sites. The source of infection following antibiotics is often not well understood, but is crucial to understand in order to better choose appropriate prevention strategies[129]. Furthermore, many antibiotic-associated infections are easy to misidentify, and the true prevalence remains unknown.

One thing is clear: the personal costs of antibiotic use and the risk of antibiotic-associated infections need not be so high. Perturbations to the microbiota and increased infection risk are not intrinsically related to the ability of antibiotics to cure bacterial infections but, rather, unwanted, off-target effects. Although more work is needed to overcome current limitations, there are a numerous, highly diverse strategies that show promise to minimize and mitigate antibiotic-induced collateral damage. Importantly, many of these approaches will also help reduce the selection and spread of resistance within the microbiota, and are therefore important not just for improving treatment outcomes at the individual-patient level but also for preventing the spread of resistant pathogens between individuals.

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