At least it won’t hurt: the personal risks of antibiotic exposure
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This review presents recent evidence regarding the adverse effects of antibiotic therapy mediated by collateral damage to commensal flora. Two major drivers have characterized recent research in this field: new perspectives into human microbiota afforded by next-generation DNA sequencing techniques and ongoing attention to antimicrobial resistance. New molecular techniques have illustrated that antibiotic therapy can disturb human microbiota, and that these changes are associated with infection. Concurrently, epidemiologic studies using patient-level data offer new insights into the role of antibiotics in the emergence, selection and spread of antimicrobial resistance, and Clostridium difficile infection (CDI).

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Introduction
‘It may not do any good’, can be the line of thought when prescribing antibiotics to a patient with a possible bacterial infection, ‘but it at least won’t hurt.’ Indeed, it is not always possible to link the emergence and spread of antimicrobial resistance with antibiotic prescribing as a day-to-day clinical practice. Increasingly, public health campaigns — such as the recent WHO World Health Day, ‘No Action Today, No Cure Tomorrow’ (URL: http://www.who.int/world-health-day/2011) — aim to make this connection and recent clinical practice guidelines include reference to ‘ecological adverse effects’ or ‘collateral damage’ [1,²]. But more than the comparatively intangible concept of globally increasing antimicrobial resistance, an antibiotic prescription can have a direct and negative impact on the individual patient at hand.

With this review, we aim to challenge conventional wisdom (‘at least it won’t hurt’) and update the reader on recent research describing the ‘biological impact’ of antibiotic agents directly on the patient who consumes them. In keeping with this clinical focus, we deliberately excluded articles reporting animal, in vitro and purely ecological studies [3]. We have also avoided discussion of direct toxic effects, allergic reactions and pharmacologic interactions [4], concentrating instead on phenomena specific to antimicrobial therapy; those involving perturbation of commensal flora.

Collateral damage: new perspectives from the microbiome
The rich community of commensal bacteria in the human gut — which are implicated in nutrition, immune system maturation and homeostasis, and in resisting colonization by pathogenic organisms — are subject to the effects of antibiotics that either pass directly through the gastrointestinal tract after oral administration or are excreted through the biliary tract in an active form [5,6,7]. Recent advances in DNA sequencing techniques permit culture-independent sampling of the human microbiome (the genetic material belonging to the wealth of microbiota in the human body), offering novel insights into the risks of antibiotic exposure.

Antibiotic therapy leads to perturbation of the human intestinal microbiota. In early infancy, antibiotic exposure has been associated with decreased numbers of intestinal bifidobacteria and Bacteroides spp. [8,9] and a significant increase in Enterobacteriaceae [10]. In adults, a course of ciprofloxacin has a marked effect on intestinal microbiota diversity within three days of commencement, but cessation of therapy is associated with a relatively rapid return to the pretreatment state, a characteristic labeled ‘compliance resilience’ [11]. This resilience, however, is not complete: after two five-day courses of oral ciprofloxacin during a 10-month period, a steady state of intestinal microbiota is established that is different to the pretreatment state, as shown in a recent landmark study [12]. Similarly, residual effects of a short course of metronidazole and clarithromycin on oral and gut microbiota are seen for up to four years [13]. The important question remains what, if any, influence do these short-term and long-term effects exert on patient health?

Two healthcare-associated infections — vancomycin-resistant Enterococcus (VRE) bacteremia and Clostridium difficile infection (CDI) — provide interesting examples of the potential clinical significance of such changes. Ubeda et al. [14] demonstrated that VRE bloodstream infection in patients undergoing stem cell transplant is preceded by complete domination of the intestinal microbiota by this
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organism. During antibiotic therapy (including vancomycin and ciprofloxacin) the intestinal microbiota of two of the five highly immunosuppressed patients underwent a striking change, with Enterococcus spp., a minor component of intestinal flora at baseline — accounting for greater than 97% of detected organisms. These two patients subsequently developed VRE bacteremia with their own intestinal strains [14] (Figure 1). Concurrently reported mouse model data provide support for the role of antibiotic-mediated perturbation of intestinal microbiota in this process [14].

CDI is also closely related to disturbance of the intestinal microbiome, frequently mediated by antibiotics [15,16]. Moreover, restoration of a ‘healthy’ intestinal microbiota has therapeutic potential for refractory CDI, through instillation of faecal flora from a healthy donor into the patient’s large intestine (known as faecal transplantation or bacteriotherapy) [17,18]. Khoruts et al. [18] report the successful application of this process in a patient who developed recurrent CDI (and a perturbed intestinal microbiome) following antibiotic therapy. Resolution of symptoms occurred in conjunction with a change in her intestinal commensal flora to closely resemble the donor’s [18]. This innovative approach remains investigational, however.

Selection of antimicrobial resistance

A synthesis of the studies exploring the relationship between antibiotic consumption and colonization or infection with antimicrobial-resistant bacteria is complicated by the heterogeneity of both the methodologies employed and the permutations of antibiotic class, dosage regimen, bacteria and resistance mechanism studied. Taking up this challenge, Costelloe et al. [19**] conducted an excellent meta-analysis of the impact of primary care antibiotic prescription on the risk of acquisition of antimicrobial-resistant organisms in individual patients. Key findings of this important review included a pooled odds ratio for antimicrobial resistance in a patient presenting with a urinary tract infection as 2.5 (95% confidence interval [CI] 2.1–2.9) within two months of antibiotic treatment, falling to 1.3 (95% CI 1.2–1.5) within 12 months. For respiratory tract bacteria, the equivalent pooled odds ratios were 2.4 (95% CI 1.4–3.9) and 2.4 (95% CI 1.3–4.5) for the same periods, respectively [19**]. For the first time, a systematic review quantified the short-term and long-term risks of individual antibiotic resistance in primary care. Thus, risks of antibiotic resistance can be conveyed to the individual patient.

Gram-negative bacteria

In keeping with its global significance, a number of recent studies have examined risk factors for the acquisition and detection of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae. Most of these associate prior antibiotic therapy with carriage of [20–22] and infection with [23–27] this group of resistant organisms. Interestingly, three observational studies taking stool samples

VRE dominates the intestinal microbiota in humans before invading the bloodstream. Phylogenetic classification of 16S rDNA frequencies in stool samples collected from allo-HSCT patients. Samples were collected upon hospital admission and periodically during the transplant course; five patients were studied. Each bar represents the microbiota of one stool sample. The timing of sample collection relative to the day of transplant (day 0) is indicated below each bar. The most predominant bacterial populations identified are color coded as indicated. The timing of VRE bloodstream infection relative to analyses of the microbiota for patients A and B is indicated by red horizontal bars. Reproduced with permission from Ref. [14].
from healthy volunteers were unable to demonstrate a significant association between recent antibiotic exposure and intestinal carriage of ESBL-producing bacteria [20,28,29], though the association did become significant in one study when focusing only on fluoroquinolone exposure, with an odds ratio of 1.33 (95% CI 1.04–1.69) [20]. The other two studies demonstrated an association at a community level — either over time or geographic location [28,29]. This observation confirms that individual and group-level antibiotic effects may interact and should be carefully examined.

In contrast, several recent studies have identified previous antibiotic exposure as a predictor of bacteremia with ESBL-producing Enterobacteriaceae [26] or Escherichia coli [23,25,27]. Furthermore, ESBL-production was associated with mortality, with this link explained by inadequate empiric therapy [23,25,27]. Prior antibiotic exposure was also an independent risk factor for bacteremia caused by third-generation cephalosporin-resistant E. coli in a large French cohort [30].

Recent data also exist for other resistance mechanisms in Gram-negative bacteria. In a prospective cohort study, Samore et al. [31*] demonstrated that while not significantly increasing intestinal carriage of ampicillin-resistant (AMP-R) E. coli, antibiotic therapy, particularly macrolides, reduced carriage of ampicillin-sensitive E. coli. This study also demonstrated that both ampicillin-sensitive and AMP-R E. coli cluster within households (Figure 2). Thus, consumption of antimicrobial agents disturbs the ecology of the flora of the household, not just the treated subject. These changes may be mediated through effects on susceptible organisms and may not be manifested as an increased carriage of resistant bacteria in the treated subject [31*]. Other recent studies have also supported the importance of intra-household transmission of antimicrobial resistance [32,33].

Several studies have investigated risk factors for fluoroquinolone resistance. De Lastours et al. [34] found prior fluoroquinolone exposure was significantly associated with fluoroquinolone resistance in nasal coagulase-negative staphylococcus on hospital admission, but not in intestinal E. coli or pharyngeal streptococcus [34]. Regarding infection rather than colonization, three recent observational studies have explored predictors of fluoroquinolone resistance in patients presenting with urinary tract infections caused by E. coli [35–37]. Two showed a significant association between antibiotic exposure in the previous 6–12 months and infection with fluoroquinolone-resistant pathogens [35,36], while the third did not [37]. Though not without its own weaknesses, as a nested case-control study, the report from van der Starre et al. [36] had the highest quality from a methodological perspective. This article reported that fluoroquinolone use within the past six months (odds ratio, 17.5; 95% CI 6.0–50.7), urinary catheter and recent hospitalization were significantly associated with fluoroquinolone resistance.

**Gram-positive bacteria**

A recent meta-analysis including studies published between 1976 and 2007 assessed the risk of acquiring...
methicillin-resistant *Staphylococcus aureus* (MRSA) to be 1.8-fold increased in individuals with recent antibiotic exposure, with the highest risk observed for fluoroquinolones (risk ratio, 3; 95% CI 2.5–3.5) [38]. Given methicillin resistance in *S. aureus* is unlikely to arise *de novo*, this effect is probably explained by the eradication of competing susceptible flora [39]. Since this meta-analysis, two large cross-sectional studies have investigated the association between antibiotic use and community MRSA colonization. Lo et al. [40] analyzed nasal swabs obtained from 3200 Taiwanese children without acute medical problems between 2004 and 2009. Nasal MRSA carriage was identified in a surprisingly high proportion of children (11.6%); antibiotic use within the last 12 months was identified as risk factor for MRSA carriage. The second study did not identify recent antibiotic exposure as risk factor for MRSA colonization, since only 15 of 1163 children were identified as MRSA carriers [41]. Regarding the risk of infection, colonization with MRSA has repeatedly been shown to increase the risk of subsequent *S. aureus* infections as opposed to no colonization or colonization with a methicillin-sensitive strain [42,43].

Another important Gram-positive pathogen frequently colonizing the nasopharyngeal tract of healthy children (and to a lesser degree adults) is *Streptococcus pneumoniae*. In keeping with numerous older studies, a French study of 3507 children aged 6–24 months, most of them consulting with acute otitis media, identified antibiotic use within the last three months as one of the main factors associated with penicillin-non-susceptible pneumococci (PNSP, defined as MIC $\geq 0.12$ µg/ml) carriage (OR = 1.24, 95% CI 1.05–1.47) [44]. A recent cluster-randomized trial examined the effect of mass azithromycin treatment for trachoma in children 1–10 years in several Ethiopian communities [43*]. Nasopharyngeal carriage of azithromycin-resistant *S. pneumoniae* in children from treated communities increased from 3.6% at baseline to 46.9% at 12 months while only 9.2% of the children in the untreated communities carried azithromycin-resistant *S. pneumoniae* at 12 months [45*].

**Dosing to minimize selection of resistance in commensal bacteria**

While optimization of antibiotic dosage and duration to minimize the promotion of antimicrobial resistance in commensal bacteria is an appealing concept, there is little recent evidence to guide the clinician [46]. In their meta-analysis of antimicrobial use in the primary care setting, Costelloe et al. [19**] concluded that longer treatment duration was associated with a higher risk of emergence of antibiotic resistance. This finding stands in contrast to conventional clinical wisdom arguing against short-term treatment (<5 days). Given a set duration of treatment, however, manipulation of ciprofloxacin dosing regimen appears ineffective in minimizing emergence of antimicrobial resistance in intestinal and oral flora [47].

**Antibiotics and Clostridium difficile**

CDI is probably the best-known example of the collateral damage caused by antibiotic therapy. Indeed, the vast majority of cases occur in individuals whose intestinal flora has been altered through recent exposure to antibiotics [15,48,49]. The recent worldwide emergence of virulent strains has been a major motivation for antibiotic stewardship efforts in healthcare [50].

CDI is increasingly observed also outside healthcare settings and in populations, such as children, previously considered at low risk [49,51,52]. About one in five cases of CDI in Canada and the United States are community-associated [51,52], and previous antibiotic exposure remains a significant risk factor [49,51,53,54]. For example, Kutty et al. [51] analyzed community-associated CDI cases among patients treated at six hospitals in North Carolina in 2005 in two separate case-control studies. Exposure to antimicrobial drugs within the previous three months was strongly associated with case status in both subsudies (adjusted OR 17.8 (95% CI 6.6–48) and 9.1 (95% CI 2.9–28.9), respectively).

While clindamycin, cephalosporins, and fluoroquinolones have been classically described as the primary culprits, virtually any antibiotic that disrupts the anaerobic gut flora (including agents used to treat CDI) can cause CDI [48,55]. A study examining the appropriateness of antibiotic use for urinary tract infection by retrospective chart review in 2 US nursing homes illustrates that the risk of CDI after antibiotic therapy is not trivial [56*]. Eleven of 96 (12%) patients receiving treatment for UTI developed CDI within three weeks of treatment. Notably, none of these patients fulfilled the study’s criteria for appropriate initiation of antibiotics.

**Conclusions**

This review is aimed to describe recent evidence of the harmful effect of antimicrobial therapy on the individual patient. In doing so, we hope to provide some concrete evidence to enter into the risk/benefit equation for each antimicrobial prescription, especially when treating relatively mild conditions.

As presented in this review, antibiotic therapy can lead to a significant shift in commensal flora that is not always completely reversible. Recent studies using high-throughput DNA sequencing demonstrate the significance of such a change with regard to VRE bacteremia and CDI. Previous antibiotic therapy is frequently identified as a risk factor for colonization and/or infection with bacteria possessing antimicrobial resistance mechanisms. Specific recent examples include ESBL-production and fluoroquinolone resistance in *Enterobacteriaceae*, MRSA and penicillin-nonsusceptible streptococci.

Unfortunately, the recent literature provides scant evidence that optimization of dosing regimen can signifi-
canently minimize the acquisition or amplification of antimicrobial resistance. Such data would be extremely useful, as would further information regarding the relative effect of different antibiotic classes [46]. For example, what will be the impact of increasing utilization of older agents in urinary tract infections such as nitrofurantoin, trimethoprim/sulfamethoxazole and fosfomycin? In the meantime, minimization of inappropriate antibiotic prescription remains of paramount importance.

Conflicts of interest
SH is a member of the speakers' bureau for bioMérieux and Brahms, participates in scientific advisory boards of bioMérieux, Destiny Pharma, LASCSCO and DaVolterra, and has received research funding for investigator-initiated research by Pfizer. All other authors: no conflicts.

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References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


An overview of national and regional public campaigns to reduce inappropriate antibiotic consumption in high-income countries between 1999 and 2007. By assessing characteristics and outcomes of these widely varying campaigns, the authors conclude that multifaceted campaigns repeated over a number of years appear to have the greatest effect.


These recent guidelines for the treatment of uncomplicated urinary tract infections in women are notable for a sound cross-Atlantic consensus, a return to older agents such as fosfomycin and nitrofurantoin and for recognition of the importance of collateral damage to commensal flora due to antibiotic therapy.


This study provides a detailed examination of the impact of ciprofloxacin therapy on the microbiome of three individuals. The authors used 16S rRNA pyrosequencing to analyse over 50 faecal samples provided by the participants, who took two five-day course of ciprofloxacin each. Ciprofloxacin therapy had a marked, but varying, impact on the gut microbiome of each participant, and each achieved a newly altered steady-state.


A striking example of the silent but profound impact of antibiotic therapy on the immunosuppressed hospitalised patients. Using 16S rRNA pyrosequencing, the investigators demonstrate a remarkable reduction in the diversity of intestinal microbiota of two patients with almost complete domination of the gut flora by VRE, followed by invasive infection.


An excellent paper analysing the risk to which a patient is exposed by receipt of an antimicrobial prescription in primary care. This meta-analysis provides doctors working in the community with concrete evidence that should prompt second thought before the pen hits the pad.


31. Samore MH, Tonnerre C, Hannah EL, Stoddard GJ, • Borotkanics RJ, Haddadin B, Harbarth S: Impact of outpatient antibiotic use on carriage of ampicillin-resistant *Escherichia coli*. *Antimicrob Agents Chemother* 2011, 55:1135-1141. The strengths of this study investigating the relationship between antibiotic exposure and antimicrobial resistance lie in its prospective design and the inclusion of entire households, thereby including the influence of the individual’s close contacts.


The authors take the opportunity presented by a cluster-randomized, placebo-controlled trial on mass azithromycin treatment for trachoma in Ethiopia to study the selection pressure of such a program on macrolide resistance. All investigators performing a placebo-controlled study of antibiotic therapy should consider such an investigation on the possible collateral damage.

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antibiotics for the future: new ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective. Drug Resist Updat 2011, 14:107-117.


This study demonstrated both frequent inappropriate antibiotic prescription in the nursing home context and the consequent harmful effects of such practices in the form of Clostridium difficile infection.