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EDITORIAL

Strategies for overcoming anti-tumor necrosis factor drug antibodies in inflammatory bowel disease: Case series and review of literature

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Abstract

Anti-tumor necrosis factor (TNF) biologics are currently amongst the most widely used and efficacious therapies for inflammatory bowel disease (IBD). The development of therapeutic drug monitoring for infliximab and adalimumab has allowed for measurement of drug levels and antidrug antibodies. This information can allow for manipulation of drug therapy and prediction of response. It has been shown that therapeutic anti-TNF drug levels are associated with maintenance of remission, and development of antidrug antibodies is predictive of loss of response. Studies suggest that a low level of drug antibodies, however, can at times be overcome by dose escalation of anti-TNF therapy or addition of an immunomodulator. We describe a retrospective case series of twelve IBD patients treated at the University of California-Irvine, who were on infliximab or adalimumab therapy and were found to have detectable but low-level antidrug antibodies. These patients underwent dose escalation of the drug or addition of an immunomodulator, with subsequent follow-up drug levels obtained. Eight of the twelve patients (75%) demonstrated resolution of antidrug antibodies, and were noted to have improvement in disease activity. Though data regarding overcoming low-level anti-TNF drug antibodies remains somewhat limited, cases described in the literature as well as our own experience suggest that this may be a viable strategy for preserving the use of an anti-TNF drug. Low-level anti-TNF drug antibodies may be overcome by dose escalation and/or addition of an immunomodulator, and can allow for clinical improvement in disease status. Therapeutic drug monitoring is an important tool to guide this strategy.

Key words: Inflammatory bowel disease; Adalimumab; Anti-tumor necrosis factor; Infliximab; Therapeutic drug monitoring; Drug antibody; Antidrug antibodies; Dose escalation

Core tip: One of the main challenges of anti-tumor necrosis

factor use in inflammatory bowel disease is immunogenicity, or the immune-mediated formation of drug antibodies. Therapeutic drug monitoring allows for measurement of serum drug levels and antidrug antibodies. Previously it was thought that antibody formation was indication to switch to an alternate agent; however, more recent literature, which we review in this article, suggests that a low level of antidrug antibodies can be overcome by dose escalation of the biologic drug and/or addition of an immunomodulator. We describe a small case series of patients in whom this strategy was used, in conjunction with therapeutic drug monitoring, with some success.

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INTRODUCTION

Since the initiation of their use for inflammatory bowel disease (IBD) in the late 1990s, tumor necrosis factor (TNF) inhibitors have drastically changed the face of IBD treatment. Anti-TNFs are monoclonal antibodies that inhibit the pro-inflammatory cytokine tumor necrosis factor[1]. These drugs have shown significant efficacy in the treatment of ulcerative colitis (UC) and Crohn's disease (CD)[2]. Currently approved anti-TNFs for IBD in the United States include infliximab, adalimumab, certolizumab, and golimumab.

As the use of anti-TNFs has become more widespread, we seek out tools that will help us to use these drugs more efficaciously and economically. Therapeutic drug monitoring (TDM) allows for measurement of drug levels and drug antibodies. As inadequate serum drug levels and/or development of immunogenicity are possible etiologies for treatment failure, TDM has become a helpful tool to guide therapy.

DRUG LEVELS

In the United States, there are currently commercially available assays to measure serum drug levels of infliximab, adalimumab, certolizumab and golimumab, though the therapeutic cutoffs for certolizumab and golimumab are overall less certain[3]. There are various types of assays, including enzyme-linked immunosorbent assay (ELISA), homogeneous mobility shift assay (HMSA), radioimmunoassay (RIA), reporter gene assay (RGA), and electrochemiluminescence (ECLIA)[4]. It is beyond the scope of this article to discuss details regarding the mechanism of these various assays; however, although analytic properties of the tests vary somewhat, it is thought that overall detection of drug levels and antidrug antibodies (ADAs) correlate with each other and result in similar interventions and clinical outcomes regardless of the assay used[5]. It should be noted that the newer generation assays allow for the detection of drug in the presence of drug antibodies or when bound to drug antibodies[4].

Numerous studies have clearly demonstrated that therapeutic levels of drug in the serum are associated with induction and sustaining of clinical remission, decreased inflammatory markers, endoscopic healing, and decreased risk for requiring surgery[6-9].

Anti-TNF drug levels are typically measured as a trough. There have been multiple attempts to identify target therapeutic levels; due to variable study end points (including clinical remission, decreased inflammatory markers, endoscopic and mucosal healing and lack of antibody formation), these studies have yielded mixed results[3]. A retrospective analysis in 2015 by Yanai *et al*[10] using an ELISA-based assay demonstrated trough infliximab levels of > 3.8 mcg/mL and trough adalimumab levels of > 4.5 mcg/mL to be 90% specific in identifying patients who failed to respond to dose intensification. Other studies suggest that slightly higher trough levels are necessary for the end point of mucosal healing[11,12].

ANTI-DRUG ANTIBODIES

Formation of antidrug antibodies occurs as an immune response to exposure to the TNF inhibitor, which is a foreign protein. Immunogenicity results in inability of the TNF inhibitor to bind to TNF molecules and also results in increased immune-mediated clearance of the drug from the body[13,14]. Factors thought to predict development of immunogenicity include episodic anti-TNF dosing, lack of induction dosing[15], chimeric monoclonal antibody drugs[16], route of administration, and possibly the presence of certain genetic alleles[17,18]. Commercially available assays for quantitation of anti-drug antibodies are currently available for infliximab and adalimumab only[3]. Due to lack of data on this topic with regard to other biologics, this article will focus on application of TDM for infliximab and adalimumab only.

The significance of ADAs has been evaluated in multiple studies. A relatively early study by Baert *et al*[19] in 2003 showed that antibodies to infliximab were associated with infusion reaction and decreased duration of response to the drug. Subsequent studies confirmed that ADAs are associated with decreased drug levels[20,21], and demonstrated association with flare, loss of clinical response, and discontinuation of the anti-TNF drug[20-23].

Dose escalation of the anti-TNF drug is less successful in patients with antibodies and will be discussed further below. Therefore, determining the presence or absence of drug antibodies is a useful tool to guide decision-making.

Determination of a clinically significant level of antibodies has been evaluated in multiple studies. Baert *et al*[19] determined that patients with antibodies

Table 1 Management of secondary loss of response

	No/low antibody level	High antibody level
Low drug level	Increase drug dose	Change therapy (within class or alternate class)
Normal/high drug level	Change therapy (alternate class)	(Not clinically relevant scenario)

to infliximab in a titer ⩾ 8 mcg/mL (using ELISA) had a reduced duration of drug effect. Mazor *et al*[24] showed an inverse correlation between drug levels and antibodies levels, with antibody to adalimumab ⩾ 3 mcg/mL (using ELISA) predictive of active disease. The Yanai study from 2015 determined that antibodies to infliximab > 9 mcg/mL or antibodies to adalimumab > 4 mcg/mL (using ELISA) identified patients who did not respond to dose escalation with 90% specificity[10].

Given the above, prevention of immunogenicity is regarded to be an important consideration in the approach to using a TNF inhibitor. Strategies to prevent antibody formation include maintenance, rather than episodic, dosing[25], and concomitant use of an immunomodulator[26].

However, if antidrug antibodies are identified, the subsequent management strategy is less clear. Options to salvage the current anti-TNF therapy may include dose adjustment of the TNF inhibitor and/or addition of an immunomodulator.

DOSE ESCALATION OF ANTI-TNFS

Dose intensification of the anti-TNF drug, in the form of increased dosage or frequency, can be a useful strategy for the management of secondary loss of response. The success of this strategy has been described with and without the assistance of drug monitoring, but appears to be more cost-effective when TDM is used as evidenced in multiple reviews[14,15,27]. Additionally, as recapturing of response is only demonstrated in patients who achieve measurable increase in drug levels after dose intensification[28,29], TDM may be helpful to better identify patients who will respond to this intervention.

The usefulness of dose escalation in patients with antidrug antibodies, however, is less certain. A 2010 study found that patients who underwent dose escalation of infliximab had a decreased response when antibodies to infliximab were present[30]. Similar findings were noted during a prospective study of patients on adalimumab done in 2014[31]. Vande Casteele *et al*[28] also reported in 2013 that patients with sustained levels of infliximab ADAs were more likely to fail dose adjustment, with a likelihood ratio of 3.6 to fail dose escalation when antibodies to infliximab were > 9.1 U/mL (using HMSA). Based on these data, some treatment algorithms would advocate changing drug therapy if presence of ADAs is identified.

Though studies have been able to identify with relatively reasonable consistency a cutoff beyond which dose escalation is unlikely to be successful (10, 28), the question remains whether lower levels of ADAs can be overcome by manipulation of therapy. This phenomenon has been described, albeit not in great number, in multiple studies throughout the years. Ternant *et al*[32] described as early as 2008 patients in whom infliximab antibodies resolved with dose adjustment, though disappearance seemed to occur spontaneously in other patients. In another prospective study by Bartelds *et al*[33] in 2011, 6 cases were described in which patients had loss of antibodies to adalimumab after dose escalation. Pariente *et al*[34] described a decrease in antidrug antibody titers after dose intensification. More recently, the previously cited retrospective study by Yanai noted that low level of ADAs were overall less specific for failure to respond to dose escalation[10], and a 2015 study by Steenholdt *et al*[35] demonstrated resolution of anti-infliximab antibodies in patients who underwent dose escalation.

Based on the limited information from (but not limited to) the studies listed above, and the theoretical pharmacokinetics of overcoming the presence of antibodies, more recent treatment algorithms advocate that a low level of antidrug antibodies can be overcome[14,28,36-38]. These algorithms suggest that in patients who are found to have low drug level and low level of ADA, dose intensification be performed in an attempt to avoid changing to an alternate drug (Table 1).

ADDITION OF IMMUNOMODULATOR THERAPY

An alternate strategy to mediate immunogenicity to anti-TNF biologics is to use a concurrent immunomodulator.

Concomitant therapy with an immunomodulator is a strategy already used to prevent immunogenicity. Previous data has shown that use of an immunomodulator, in the form of a thiopurine *vs* methotrexate, when used together with a biologic agent has been associated with decreased formation of antidrug antibodies[26]. Use of dual therapy is associated with lower disease activity, increased mucosal healing, increased rates of steroid-free remission, and decreased need to switch to an alternate drug. These findings are evidenced in multiple studies, including the SONIC trial[39-41]. This benefit has been postulated to be at least in part related to decreased immunogenicity of the biologic therapy when an immunomodulator is used. Additionally, studies do not show significant increase in adverse events such as malignancy, infection or death when using combination therapy *vs* monotherapy[42].

There is limited data regarding the addition of an immunomodulator drug after antidrug antibodies have already formed, but it suggests that this may be a viable strategy. In a small retrospective study of 5 patients who developed antidrug antibodies and loss of response to infliximab, Ben-Horin *et al*[43] showed

that after addition of an immunomodulator (either azathioprine/6-mercaptopurine or methotrexate), all 5 patients had gradually decreasing levels of ADAs and restored clinical response. A later study by Yarur *et al*[44] showed that 6-thioguanine (6-TG) levels > 125 pmol/8 × 10^8 RBCs correlated with more optimal levels of infliximab, and 6-TG levels lower than this threshold were associated with presence of antidrug antibodies. These studies did not include patients on adalimumab.

Though a distinct cutoff for antidrug antibody levels was not delineated in these studies, they do suggest that the addition of an immunomodulator is a viable strategy when ADAs form. This strategy has not yet been widely added to treatment algorithms, presumably pending the availability of additional supportive data.

PRACTICAL EXPERIENCE

We describe a retrospective case series of patients on anti-TNF therapy that were found to have low-level antidrug antibodies and underwent escalation of drug therapy or addition of an immunomodulator, with subsequent follow-up drug levels obtained. These patients were receiving care at the University of California-Irvine in the 36-mo period from November 2013 to October 2016.

A total of twelve patients on either infliximab or adalimumab were included in the case series - eight patients with CD and four patients with ulcerative colitis. Median patient age was 43.5 years, ranging from 21 to 71 years. Disease activity in all patients was moderate to severe. Disease extent in Crohn's patients disease included ileal, colonic, and ileocolonic disease, with some patients having stricturing or perianal disease. Disease extent in UC patients included either left-sided disease or pancolitis. The median duration of disease (from the time of diagnosis) was 8 years, ranging from 1 to 30 years. Four patients had previously been on an alternate anti-TNF drug. Four patients were being treated concurrently with immunomodulator at the time of initial evaluation. Of note, all patients had been advised to take a concurrent immunomodulator at the time of anti-TNF initiation but eight of the twelve patients had previously declined due to concern for adverse effects.

Of the twelve patients, seven were being treated with infliximab and five with adalimumab at the time of the study. Median duration of treatment on the respective anti-TNF was 18.5 mo, ranging from 4 to > 120 mo. Drug and antibody levels were checked using an ECLIA or HMSA. Reference values were defined as had been previously determined for the respective assays. Indication for checking drug and antibody levels included presence of symptoms and/or active disease noted on endoscopy. All patients had some subjective or objective evidence of active disease at the time that drug level testing was performed. In our experience, most patients either had the test covered by insurance or paid up to about $250 after subsidization from drug company assistance programs, though the list price for drug level testing is as high as $2500.

The median drug levels prior to alteration of therapy were 4.1 mcg/mL and 3.0 mcg/mL for infliximab and adalimumab, respectively. The median antidrug antibody level for infliximab was 5.5 U/mL using HMSA (negative < 3.1 U/mL). The median antidrug antibody level for adalimumab was 3.1 U/mL for patients tested using HMSA (negative < 1.7 U/mL), and was 52 ng/mL for patients tested using ECLIA (negative < 25 ng/mL). The twelve patients were determined to have a low level of antidrug antibody present, which was determined at the clinical discretion of the treating physician.

After presence of low-level antibodies was noted, eleven patients underwent dose escalation of the anti-TNF drug in the form of either increase in drug frequency or dosage, and one patient had an immunomodulator (methotrexate) added. Addition of an immunomodulator was discussed with all of the patients who were not already treated with one, but most patients declined due to concern for side effects. Those who were already on immunomodulator therapy were continued on dual therapy.

Follow-up drug level testing demonstrated resolution of anti-drug antibodies in eight patients (75%). These patients were found to have increase in drug level: Median levels drug levels increased to 20.2 mcg/mL and 7.9 mcg/mL for infliximab and adalimumab, respectively. These patients were also noted to have improvement in disease activity in the form of decreased inflammatory markers and/or symptomatic improvement. The remaining four patients did not have resolution of anti-drug antibodies after dose escalation and were therefore switched to an alternate IBD therapy. Of note, the four patients who did not have resolution of ADAs carried a diagnosis of CD, though given the small study size, it is unclear whether this is significant (Tables 2 and 3).

CONCLUSION

Though IBD treatment continues to evolve, biologic therapies still remain limited in number; therefore it may be prudent to exhaust a drug therapy before switching to an alternate drug. Therapeutic drug monitoring allows for measurement of drug levels and drug antibodies, and has become instrumental in optimizing anti-TNF drug therapy. In the case of active disease, when drug levels are low, dose escalation of the anti-TNF is recommended; when drug levels are high, therapy may need to be changed. Management of antidrug antibodies is an evolving area of interest, as immunogenicity one of the most common reasons for changing drug therapy. Antidrug antibodies have been demonstrated in multiple studies to be associated with decreased drug levels, loss of response to the drug, and active disease. Strategies to prevent antibody formation include maintenance dosing and concurrent use of an immunomodulator. A small amount of data exists about the possibility of overcoming antidrug antibodies, as reviewed above. Several studies have

Table 2 A total of twelve patients on either infliximab or adalimumab were included in the case serie

Patient	Age (yr)	Sex	Diagnosis	Montreal classification	Duration of disease (yr)	Previous anti-TNF therapy?	Immunomodulator therapy?
1	24	M	CD	A2L3B1	5	Y	Previous - MTX
2	46	M	UC	E3	10	N	Previous - 6MP
3	71	M	CD	A3L1B2	4	N	Previous - 6MP
4	31	F	CD	A2L1B2	9	Y	Current - 6MP
5	46	F	CD	A2L3B2p	5	N	None
6	41	M	UC	E2	18	N	Current - AZA
7	53	F	UC	E2	24	Y	Previous - MTX
8	21	M	UC	E3	1	N	Current - MTX
9	67	M	CD	A3L2B1	3	N	None
10	26	M	CD	A1L2B1	11	N	None
11	49	F	CD	A2L3B2	30	N	None
12	25	M	CD	A2L1B2	7	Y	Current - MTX

Montreal classification CD: Age at Diagnosis (A1: Less than 16 years; A2: Between 17 and 40 years; A3: Over 40 years). Location (L1: Ileal; L2: Colonic; L3: Ileocolonic; L4: Isolated upper digestive tract). Behavior (B1: Non-stricturing, non-penetrating; B2: Structuring; B3: Penetrating; p: Perianal). Montreal classification UC: Location (E1: Proctitis; E2: Left-sided; E3: Extensive or pancolitis). M: Male; F: Female; CD: Crohn's disease; UC: Ulcerative colitis; MTX: Methotrexate; 6-MP: 6-mercaptopurine; AZA: Azathioprine; TNF: Tumor necrosis factor.

Table 3 Adjustment therapy at the time of the study

Pt	Dx	Anti-TNF drug	On immuno-modulator?[1]	Reason for TDM	Predrug level	Pre-Ab level	Adjustment in therapy	Post-drug level	Post-Ab level	Resolved ADAs?	Did patient have improvement?
1	CD	ADA	N	Endoscopic disease	3.0 μg/mL	38 ng/mL	Frequency	10 μg/mL	< 25 ng/mL	Y	Symptom improvement; fecal calprotectin
2	UC	ADA	N	Flare symptoms	< 1.6 μg/mL	4.6 U/mL	Dose/ frequency	13.7 μg/mL	< 1.7 U/mL	Y	Symptom improvement; decreased CRP
3	CD	ADA	N	Flare symptoms	3.3 μg/mL	2.6 U/mL	Frequency	5.8 μg/mL	0	Y	Symptom improvement
4	CD	ADA	Y - 6MP	Flare symptoms, Endoscopic disease	2.6 μg/mL	66 ng/mL	Frequency	4.8 μg/mL	< 25 ng/mL	Y	Symptom improvement
5	CD	IFX	N	Flare symptoms	4.1 μg/mL	4.5 U/mL	Dose/ frequency	23.4 μg/mL	< 3.1 U/mL	Y	Symptom improvement; CRP
6	UC	IFX	Y - AZA	Flare symptoms	1.1 μg/mL	8.2 U/mL	Dose	16.9 μg/mL	< 3.1 U/mL	Y	Symptom improvement
7	UC	IFX	N	Flare symptoms; Endoscopic disease	10.4 μg/mL	5.0 U/mL	Added immuno-modulator (MTX)	11.3 μg/mL	0	Y	Symptom improvement; ESR
8	UC	IFX	Y - MTX	Flare symptoms	0	5.5 U/mL	Dose	26.8 μg/mL	0	Y	ESR/CRP
9	CD	IFX	N	Flare symptoms	23.1 μg/mL	8.6 U/mL	Dose	< 1 μg/mL	88.6 U/mL	N	-
10	CD	IFX	N	Endoscopic disease	< 1.0 μg/mL	3.7 U/mL	Frequency	< 0.4 μg/mL	34 ng/mL	N	-
11	CD	ADA	N	Flare symptoms	5.6 μg/mL	3.1 U/mL	Frequency	4.6 μg/mL	113 ng/mL	N	-
12	CD	IFX	Y - MTX	Flare symptoms	< 1 μg/mL	8.2 U/mL	Frequency	8.2 μg/mL	9.0 U/mL	N	-

[1]Refers to concurrent immunomodulator therapy. Pt: Patient; Dx: Diagnosis; TDM: Therapeutic drug monitoring; Ab: Antibody; ADA: Antidrug antibody; CD: Crohn's disease; UC: Ulcerative colitis; ADA: Adalimumab; IFX: Infliximab; AZA: Azathioprine; 6MP: 6-mercaptopurine; MTX: Methotrexate; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

described resolution of ADAs with therapy modification in the form of dose escalation and/or addition of an immunomodulator. Based on this strategy, recent algorithms for management of secondary loss of response now advocate that patients with low drug levels and low level ADAs undergo adjustment of therapy using these two strategies.

Our case series illustrates application of these strategies, with drug levels obtained before and after the adjustment in therapy. In 75% of cases, we were able to achieve resolution of anti-drug antibodies, confirmed with therapeutic drug monitoring, with either escalation of anti-TNF therapy or addition of an immunomodulator. These patients were noted to have improvement in their

disease activity, based on subjective and/or objective measures. With regard to the possibility of de-escalation of anti-TNF dosing or discontinuation of the anti-TNF, the authors of this study generally did not pursue this if patients are tolerating the therapy without adverse effects, due to concern for formation of recurrent drug antibodies.

Based on this literature and our own experience as described, we believe that in certain patients, low-level anti-TNF drug antibodies can be overcome by dose escalation and/or addition of an immunomodulator, and can allow for clinical improvement in disease status. As the efficacy of subsequent anti-TNF drugs generally diminishes in comparison to the initial anti-TNF drug[41], drug manipulation to overcome low-level antibodies may be a valuable strategy to preserve the use of anti-TNFs in IBD; therapeutic drug monitoring is an instrumental tool to assess success or failure of this approach.

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REVIEW

Phage therapy: An alternative to antibiotics in the age of multi-drug resistance

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Abstract

The practice of phage therapy, which uses bacterial viruses (phages) to treat bacterial infections, has been around for almost a century. The universal decline in the effectiveness of antibiotics has generated renewed interest in revisiting this practice. Conventionally, phage therapy relies on the use of naturally-occurring phages to infect and lyse bacteria at the site of infection. Biotechnological advances have further expanded the repertoire of potential phage therapeutics to include novel strategies using bioengineered phages and purified phage lytic proteins. Current research on the use of phages and their lytic proteins against multidrug-resistant bacterial infections, suggests phage therapy has the potential to be used as either an alternative or a supplement to antibiotic treatments. Antibacterial therapies, whether phage- or antibiotic-based, each have relative advantages and disadvantages; accordingly, many considerations must be taken into account when designing novel therapeutic approaches for preventing and treating bacterial infection. Although much about phages and human health is still being discovered, the time to take phage therapy serious again seems to be rapidly approaching.

Key words: Bacteriophage; Bacteriophage therapy; Phage; Phage therapy; Endolysin; Lysin; Multidrug resistance; Antibiotic resistance; Phage safety; Methicillin-resistant *S. aureus*

Core tip: Phage therapy is widely being reconsidered as an alternative to antibiotics. The use of naturally-occurring phages to treat bacterial infection has a contentious history in western medicine. However, the emergent landscape of phage-based antimicrobials has advanced well beyond traditional methods. In this rapidly evolving field, novel technologies such as bioengineered chimeras of phage-derived lytic proteins show potential as a new class of antibacterial pharmaceuticals. This review aims to

provide a topical perspective on the historical context of phage therapy, in order to highlight modern advances in phage research and innovations in the field.

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INTRODUCTION

Almost a decade before the discovery of penicillin, the controversial practice of phage therapy was being developed as a treatment for bacterial infections. Phages, short for bacteriophages, are bacteria-specific viruses that have been used as a treatment against pathogens such as *Shigella dysenteriae* as early as 1919[1]. With an estimated 10^{31}-10^{32} phages in the world at any given time[2], they make up the most abundant biological entity on Earth and play a crucial role in regulating bacterial populations; phages are responsible for the death of approximately 20%-40% of all marine surface bacteria every 24 h[3]. Much of the controversy surrounding phage therapy was due to poor documentation of use and variable success. The complications in implementing phage therapy stemmed from how little was known about phages at the time of their discovery. In fact, the nature of their existence was a topic of contention until they were visualized in the 1940's after the invention of electron microscopy[4]. A number of logistical and technical obstacles in developing phage therapy led to its widespread abandonment after the discovery of antibiotics.

The advent of pharmaceutical antibiotics in the mid-20th century, along with a better understanding of disease and sanitation, revolutionized healthcare and drastically improved both quality of life and life expectancy in the industrialized world. In 1900, life expectancy for men and women in the United States was 46 and 48, respectively, and the major causes of death were infectious diseases, many of which were bacterial (*e.g.*, cholera, diphtheria, typhoid fever, plague, tuberculosis, typhus, scarlet fever, pertussis, and syphilis)[5]. Antibiotics helped usher in a new era in medicine, rapidly becoming an indispensable medical tool with 262.5 million treatment courses prescribed in the United States in 2011 alone (842 prescriptions per 1000 persons) and an estimated 100000-200000 tons of antibiotics used globally between medicine, agriculture, and horticulture each year[6,7]. Antibiotic resistance genes encoding for bacterial resistance to common antibiotics, including β-lactams, aminoglycosides, chloramphenicols, and tetracycline, are posing a major threat to current medical treatment of common diseases, and these genes now appear to be abundant in the environment[8]. The spread of antibiotic resistance genes carries a unique danger in that many antibiotics have diminishing efficacy against common infections, particularly the difficult-to-treat nosocomial infections caused by the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.).

Admonitions of a return to "the pre-antibiotic era" have become increasingly common and regulatory organizations such as the Centers for Disease Control (CDC) and WHO have declared antibiotic resistance a threat to global health[9,10]. The CDC estimates antibiotic-resistant infections result in 2 million illnesses and at least 23000 deaths a year, with many more dying from conditions complicated by antibioticresistant infections, costing the United States $55 billion annually[7]. According to the United Kingdom government's 2016 Review on Antimicrobial Resistance, an estimated 700000 people die each year globally from resistant infections with a projected cost of $100 trillion and a death toll of 10 million by 2050[7]. In the United States, methicillin-resistant *S. aureus* (MRSA) infections alone account for more deaths than HIV/AIDS and tuberculosis combined[11]. Since the discovery of antibiotics, there has been a steady stream of novel antibacterial pharmaceuticals in what has been dubbed the "antibiotic pipeline". However, due to the rate at which bacteria evolve resistance to antibiotics, there has been less commercial interest in the research and development of novel compounds. In the years of 1983-1987, there were 16 new pharmaceutical antibiotics approved by the Food and Drug Administration (FDA) for use in the United States, this number has steadily trended downwards and between 2010-2016 only 6 new antibiotics were approved[12]. At the end of the antibiotic pipeline is the carbapenem class of antibiotics, often reserved as the "last resort" due to their adverse effects on health. Beginning in 2000, the incidence of carbapenem-resistant, hospital-acquired *K. pneumoniae* infections began to increase in the United States; due to the lack of treatment options these infections are associated with a 40%-50% mortality rate[13]. Reaching the end of the antibiotic pipeline could signal a shift in the global culture of infectious disease treatment and some claim is the imminent return to a pre-antibiotic era of medicine.

On September 21, 2016, the United Nations General Assembly convened to discuss the problem of antibiotic resistance and deemed it "the greatest and most urgent global risk"[14]. In the hunt for alternative strategies for prophylaxis and control of bacterial infection, one of the more popular suggestions involves revisiting the practice of phage therapy. Proponents of phage therapy tout several major advantages that phages have over antibiotics such as host-specificity, self-amplification, biofilm degradation, and low toxicity to humans[15,16]. Owing to the development of analytical tools capable of studying these small biological entities

(approximately 25-200 nm in length), such as next-generation sequencing and electron microscopy, the field of phage biology is only now reaching maturity. These technological advancements have ushered in a renaissance of phage therapy research as indicated by a wave of recent human clinical trials and animal research. The complex story of the human phageome in regards to health and disease is only beginning to unfold and will not be included in this review (for current literature review see Wahida, Ritter and Horz[17] 2016). This review aims at discussing historical use of phage therapy and current research on the feasibility of phage-based infection control with a focus on multidrug-resistant infections.

PHAGE BIOLOGY BASICS

Phages are simple, yet incredibly diverse, non-living biological entities consisting of DNA or RNA enclosed within a protein capsid. As naturally-occurring bacterial parasites, phages are incapable of reproducing independently (*i.e.*, non-living) and are ultimately dependent on a bacterial host for survival. Phages typically bind to specific receptors on the bacterial cell surface, inject their genetic material into the host cell, and then either integrate this material into the bacterial genome (so-called "temperate" phages) and reproduce vertically from mother to daughter cell, or hijack the bacterial replication machinery to produce the next generation of phage progeny and lyse the cell (so-called "lytic" phages). Upon reaching a critical mass of phage progeny, which can be anywhere from a few to over 1000 viral particles depending on environmental factors, the lytic proteins become active and hydrolyze the peptidoglycan cell wall, releasing novel phage to reinitiate the lytic cycle[18,19].

Most phages are infectious only to the bacteria that carry their complementary receptor, which, in turn, determines lytic phage host range[20]. Host specificity varies among phages, some of which are strain-specific, whereas others have demonstrated the capability of infection across a range of bacterial strains and even genera[21,22]. Bacteria have evolved numerous mechanisms to resist infection by lytic phages, and phages have an equally impressive diversity of mechanisms for breaking this resistance. For bacteria, this can include alteration or loss of receptors and integration of phage DNA into the clustered regularly interspaced palindromic repeats/CRISPR associated system (CRISPR/Cas) system[23], while for phage this can include recognition of new or altered receptors and anti-CRISPR genes[24]. The most common lytic phages associated with human pathogens and the gut microbiota are in the orders *Caudovirales*, commonly known as "tailed phages" which contain double-stranded DNA genomes, and *Microviridae*, which are tailless, single-stranded DNA viruses[25,26].

In contrast to lytic phage, lysogenic phages integrate their genetic material into the bacterial chromosome in the form of an endogenous prophage (less commonly phage DNA can remain separate as a plasmid but still be stably transmitted across bacterial generations). The bacterial lysogen then propagates the prophage with each cell division. Environmental stressors on the bacterial host are capable of inducing the lysogenic phage from the latent prophage form, triggering a transition to the lytic cycle and the release of phage progeny into the environment. When incorporating their genetic material into the bacterial genome, prophage-encoded genes become available for transcription by the host. Up to 18 prophages have been found in one bacterial genome, as in the food pathogen *Escherichia coli* (*E. coli*) O157:H7 strain Sakai[27], with prophage-encoded genes comprising up to 20% of bacterial chromosomal content[28]. These genes can be beneficial to the bacterial host and can encode for virulence factors (*e.g.*, diphtheria toxin, shiga toxin, and botulinum toxin), metabolic genes, and antibiotic resistance genes (*e.g.*, β-lactamases)[29-32]. Phage biologists now recognize that phage lifecycles fall on a spectrum between these two extremes with pseudolysogenic, chronic, and cryptic lifecycles as examples of recent classifications[19,33]. Conventional phage therapy relies on strictly lytic phages, which obligately kill their bacterial host. For treatment, lytic phages are compiled into preparations called "phage cocktails" which consist of multiple phages proven to have *in vitro* efficacy against the target pathogen.

HISTORY OF PHAGE THERAPY

Although the idea of using bacterial viruses therapeutically against bacterial infections has recently gained traction in response to the emergence of multidrug-resistant pathogens, the practice has been around for nearly a century. Since the initial observations of phage-induced bacterial lysis, the biological nature of phage, as well as their therapeutic value, has been controversial. Frederick Twort first described the characteristic zone of lysis associated with phage infection in 1915, but it was Felix d'Herelle who identified the source of this phenomenon, attributed the plaques to bacterial viruses, and coined the term "bacteriophage" (literally "bacteria-eater"). It was also d'Herelle who conceived of the idea to use phages therapeutically and is responsible for the first documented clinical use of phage in 1919 at the Hôpital des Enfants-Malades in Paris where phages were successfully used to treat 4 pediatric cases of bacterial dysentery[1]. Despite several successful trials, d'Herelle's early experiments were notorious for being poorly controlled and his research was vigorously disputed by the scientific community[3]. Nevertheless, d'Herelle continued to pioneer phage therapy with the treatment of dysentery, cholera, and the bubonic plague in the early 20th century with a series of phage therapy centers and commercial phage production plants throughout Europe and India[34]. One 1931 trial of phage therapy as a treatment for cholera in the Punjab region of India involved a cohort of 118 control

subjects and 73 experimental subjects who received phage treatment; d'Herelle observed a 90% reduction in mortality with 74 lethal outcomes in the control group and only 5 in the experimental group[1].

Along with d'Herelle, several other entrepreneurs attempted to commercialize phage production in Brazil and the United States with phage preparations for *Staphylococcus*, *Streptococcus*, *E. coli*, and other bacterial pathogens[34]. These preparations were shipped throughout the world to willing clinicians but treatment was met with mixed success; this lack of reliability, in large part, added to the preference for antibiotics in western medicine[1].

Many mistakes were made during these early trials of phage therapy and most can be attributed to a poor understanding of the biological nature of phages. Rudimentary purification and storage protocols resulted in low titers of active phage, contamination from bacterial antigens, and the inappropriate choice of a phage that lacked specificity to the target pathogen. Furthermore, delivery of phage to the site of infection was confounded by the medical limitations of the day. For example, the role of the patient's innate immune response in removing active phage and diminishing the efficacy of phage therapy was only observed recently as a potentially confounding physiological mechanism[35]. As a result, phage therapy was widely dismissed by most of western medicine after the introduction of pharmaceutical antibiotics in the 1940's. The exception to this is in the former Soviet Union and Eastern Europe where clinical phage therapy has been used extensively to treat antibiotic-resistant infections caused by a range of infectious bacteria such as *Staphylococcus*, *Pseudomonas, Klebsiella*, and *E. coli*[36,37].

PHAGE AGAINST CLINICALLY SIGNIFICANT PATHOGENS

Recent investigations using animal models have explored phage treatment against a range of clinically significant pathogens. When challenged with gut-derived sepsis due to *P. aeruginosa*, oral administration of phage saved 66.7% of mice from mortality compared to 0% in the control group[38]. In a hamster model of *Clostridium difficile* (*C. difficile*)-induced ileocecitis, a single dose of phage concurrent with *C. difficile* administration was sufficient prophylaxis against infection; phage treatments post-infection saved 11 of 12 mice whereas control animals receiving *C. difficile* and clindamycin died within 96 h[39]. Phage combinations also significantly reduced *C. difficile* growth *in vitro* and limited proliferation *in vivo* using a hamster model[40]. Intraperitoneal administration of a single phage strain was sufficient to rescue 100% of mice in bacteremia models using vancomycin-resistant *E. faecium*[41], extended spectrum β-lactamase producing *E. coli*[42], and imipenem-resistant *P. aeruginosa*[43]. Phage cocktails have also been used to treat antibiotic-resistant *P. aeruginosa* infections of the skin, lungs, and gastrointestinal tract in animal models[38,44]. Additional animal studies show similarly promising results for multidrug-resistant *E. coli* O25:H4-ST131[45], *Vibrio parahaemolyticus*[46], *S. aureus*[44,47], and *A. baumanii*[38]. There is even an indication that phage are capable of restoring antibiotic sensitivity in antibiotic-resistant bacteria, as in the case of multidrug-resistant *P. aeruginosa*[48].

Human trials for phage therapy have taken place for almost a century at several institutes in Eastern Europe, the most famous of which are the Eliava Institute of Bacteriophage and the Institute of Immunology and Experimental Therapy in Wroclaw, Poland. The Eliava Institute has extensively used phage in preclinical and clinical treatment of common bacterial pathogens such as *S. aureus*, *E. coli*, *Streptococcus* spp., *P. aeruginosa*, *Proteus* spp., *S. dysenteriae*, *Salmonella* spp., and *Enterococcus* spp.[49]. Effective applications range from surgical to gastroenterological, both therapeutic and prophylactic. In a six patient case series of antibiotic-unresponsive diabetic foot ulcers, topical application of *S. aureus*-specific phage was sufficient for recovery in all individuals[50]. In a 1938 clinical trial, 219 patients with bacterial dysentery (138 children and 81 adults) were treated solely with a phage cocktail consisting of a variety of phage targeting *Shigella flexneri*, *Shigella shiga*, *E. coli*, *Proteus* spp., *P. aeruginosa*, *Salmonella typhi*, *Salmonella paratyphi* A and B, *Staphylococcus* spp., *Streptococcus* spp. and *Enterococcus* spp.; cocktails were administered both orally and rectally. Within 24 h, 28% of patients with blood in their stools were relieved of this symptom, with a further 27% showing improvement within 2-3 d. Overall, 74% of the 219 patients showed improvement or were completely relieved of symptoms[51]. Additionally, during a 1974 typhoid epidemic, a cohort of 18577 children was enrolled in a prophylactic intervention trial using typhoid phages. Phage administration resulted in a 5-fold decrease in typhoid incidence compared to placebo[49]. The potential for phage therapy has yet to be fully realized since phages tend to be more effective against the target pathogen when used in combination with antibiotics[52], a treatment option that has not yet been investigated in humans.

Currently there are no phage therapy products approved for human use in the EU or United States. However, in the food industry, there are several commercial phage preparations used for biocontrol of bacterial pathogens that are approved by the FDA under the classification of "generally considered as safe." These preparations are used against *Salmonella* spp., *Listeria monocytogenes*, MRSA, *E. coli* O157:H7, *Mycobacterium tuberculosis*, *Campylobacter* spp., and *Pseudomonas syringae*, among others[53-56]. Phages also have potential value for pathogen detection, an example of which is using bioluminescent reporter phage to detect *Bacillus anthracis*[56]. In 2011 there was an estimated 48 million cases of food poisoning in the United States alone[55].

Table 1 Published findings on phage therapy in humans and in animal models

Causative agent	Model	Condition	Oral	Result summary[1]	Ref.
Shigella dysenteriae	Human	Dysentery	Oral	All four treated individuals recovered after 24 h	[1]
Vibrio cholerae	Human	Cholera	Oral	68 of 73 survived in treatment group and only 44 of 118 in control group	[1]
Pseudomonas aeruginosa	Murine	Sepsis	Oral	66.7% reduced mortality	[38]
Clostridium difficile	Hamster	Ileocecitis	Oral	Co-administration with *C. difficile* prevented infection	[39]
	Hamster	Ileocecitis	Oral dose every 8 h for 72 h	92% reduced mortality	[39]
Vancomycin-resistant Enterococcus faecium	Murine	Bacteremia	i.p.	100% reduced mortality	[41]
β-lactamase producing Escherichia coli	Murine	Bacteremia	i.p.	100% reduced mortality	[42]
Imipenem-resistant P. aeruginosa	Murine	Bacteremia	i.p.	100% reduced mortality	[43]
Acinetobacter baumannii, P. aeruginosa and *Staphylococcus aureus*	Murine	Sepsis	i.p.	Animals protected against fatal dose of *A. baumannii* and *P. aeruginosa* but not *S. aureus*	[44]
Escherichia coli	Murine	Meningitis and Sepsis	i.p. or s.c.	100% and 50% reduced mortality for meningitis and sepsis, respectively	[45]
MDR Vibrio parahaemolyticus	Murine	Sepsis	i.p. and oral	92% and 84% reduced mortality for *i.p.* and oral routes, respectively	[46]
S. aureus	Rabbit	Wound infection	s.c.	Co-administration with *S. aureus* prevented infection	[47]
MDR S. aureus	Human	Diabetic foot ulcer	Topical	All 6 treated patients recovered	[50]
Unclassified bacterial dysentery	Human	Dysentery	Oral	Phage cocktail improved symptoms of 74% of 219 patients	[51]
Salmonella typhi	Human	Typhoid	Oral	In cohort of 18577 children, phage treatment associated with 5-fold decrease in typhoid incidence compared to placebo	[49]
Antibiotic-resistant *P. aeruginosa*	Human	Chronic Otitis	Oral	Phage treatment safe and symptoms improved in double-blind, placebo-controlled Phase I/II trial	[61]

[1]Reduced mortality is for phage-treated groups and are relative to 100% mortality in control animals, unless otherwise specified. MDR: Multi-drug-resistant; i.p.: Intraperitoneal injection; s.c.: Subcutaneous injection.

Evidence suggests that phage biocontrol can be an effective method for improving food safety at numerous stages in meat production and processing, and also has potential to reduce bacterial contamination in fruits, vegetables, and dairy products[55]. These investigations into phage biocontrol in food production, as well as recent placebo-controlled human trials that demonstrated the safety of oral phage administration[57-60], are gradually beginning to fill the knowledge gap in phage therapy safety. The evidence on phage safety will continue to strengthen with further randomized, double-blind, and placebo-controlled phase Ⅰ/Ⅱ clinical trials of phage therapy, such as the one that established both safety and efficacy in treating chronic otitis caused by antibiotic-resistant *P. aeruginosa*[61].

Innovations in the programmable gene editing tool CRISPR/Cas have created novel opportunities for phage therapy. One example of which is the use of bioengineered phage to deliver a CRISPR/Cas programmed to disrupt antibiotic resistance genes and destroy antibiotic resistance plasmids[62]. These phages may be applied to hospital surfaces to reduce frequency and spread of antibiotic resistance genes. The field of bioengineered phages is still in its infancy but will undoubtedly yield many invaluable technologies such as this (Table 1).

DEVELOPMENT AND APPLICATION OF PHAGE-DERIVED LYTIC PROTEINS

Among the most promising of advances in phage therapy is the isolation of phage-encoded lytic enzymes, which are functionally similar to the eukaryotic enzyme lysozyme. Genes for these enzymes are expressed by the bacterial host during the lytic cycle and assist the phage by hydrolyzing the cell wall to release viral progeny. The discovery and analysis of these proteins opens the possibility for the development of novel phage-based pharmaceuticals.

Two major protein classes are employed by the majority of phage species during the lysis of the bacterial host. One of which is the transmembrane protein holin and the other is a peptidoglycan cell wall hydrolase called endolysin (lysin). These two proteins work together in triggering the lysis of the bacterial cell. The holin protein acts as a molecular "clock" in the lytic cycle. During the process of viral assembly within the cytoplasm, holin molecules accrue in the cell membrane. At the end of the lytic cycle the holin proteins trigger an opening on the cytoplasmic side of the cell membrane, allowing the lysin proteins to access and hydrolyze the cell wall[63]. Although both of these enzymes are present

across the majority of phage species, there is huge structural and biochemical variability and therefore little sequence conservation among species. Each phage can encode for several unique lysin and holin enzymes, some of which are highly specific but others can exhibit broad-spectrum activity between strains and even between species as in the case of recently discovered lysin ABgp46. ABgp46 has the ability to lyse several gram-negative and multidrug-resistant pathogens, including *A. baumannii*, *P. aeruginosa*, and *Salmonella typhimurium*[64].

Phage lysins alone are capable of bacterial cell lysis, whereas holins are not; therefore lysins have received a lot of attention as potential antimicrobial agents. These proteins are fast acting, potent, and inactive against eukaryotic cells. Lysins have successfully saved mice from bacteremia caused by multidrug-resistant *A. baumannii*[65], *Streptococcus pneumoniae*[66], and MRSA[67], among others[63]. A combination of phage lysins and antibiotics has been shown to be much more effective than antibiotics alone in eliminating *C. difficile* colonization in both an *in vitro* and an *ex vivo* colon model in the presence of intestinal contents[68]. Not all lysins show equal therapeutic potential, however, as demonstrated by Gilmer *et al*[69] who identified a uniquely potent lysin, PlySs2, which was highly effective against a range of pathogenic *Streptococcus* and *Staphylococcus* species, including MRSA, and was fully functional after 10 freeze-thaws. A single dose administered intraperitoneally to mice in a mixed *S. pyogenes* and MRSA bacteremia model provided a significantly higher survival rate than treatment with 3 previously characterized lysins[69]. A recent study exploring the isolation and application of phage proteins has revealed that lysins are even capable of crossing epithelial cell membranes to eliminate difficult to treat intracellular infections of *S. pyogenes*[70]. In addition, phage lysins can disrupt vegetative cells such as in the case of *B. anthracis* lysin PlyG which is capable of attacking endospores of bacillus, a distinct advantage over antibiotics[71]. Lysins can also be mass produced through common recombinant techniques. The gene for bacteriophage-derived cysteine, histidine-dependent amido hydrolase/peptidase (CHAPK) has been cloned and inserted into *E. coli* to be overexpressed for purification. Not only is the CHAPK lysin highly effective against MRSA, but it can disperse *S. aureus* biofilms[72].

Efforts to optimize lysins through bioengineering have yielded some promising results. Yang *et al*[73] produced a novel chimeric lysin, by combining the active site of a lysin with a cell wall binding domain, that was capable of saving mice challenged with MRSA bacteremia. Research on chimeric lysin enzymes is still in the early stages, but some of these modified lysins have also been shown to prevent death from *S. pneumoniae* bacteremia[74] and prevent development of methicillin-sensitive *S. aureus* endophthalmitis in a mouse model[75]. Since lysins act by enzymatically cleaving the bacterial cell wall, they are inherently less effective against gram-negative bacteria which have an impermeable lipopolysaccharide outer membrane. In an attempt to broaden lysin activity to target gram-negative pathogens, several researchers have begun to bioengineer artificial lysin molecules, termed Artilysins, that are capable of penetrating the outer membrane. Some of these lysins are created by combining the active site of the lysin enzyme with lipopolysaccharide-destabilizing peptides which allows the molecule to penetrate the outer membrane. So far Artilysins have been shown to decolonize *P. aeruginosa* in a nematode gut model and protect human keratinocytes when challenged with *A. baumannii*[76].

Adding to the appeal of lysins as antibacterial agents, it is widely considered unlikely that bacteria will evolve resistance to lysins due to the fact that they target sites on the peptidoglycan cell wall critical for bacterial viability[63]. Engineered recombinant phage lytic proteins would be far easier to mass produce and administer than preparations of actual phage, which can be limited by a short shelf life, removal by the reticuloendothelial system of the host, and the potential for generating neutralizing antibodies[35]. Future potential for phage lysin application includes combination therapy of lysins in conjunction with antibiotics, which has been shown to be more effective than antibiotics or lysins alone against pathogens such as MRSA and *C. difficile* in a murine model[77-79] (Table 2).

PHAGE THERAPY *VS* ANTIBIOTIC THERAPY

Both antibiotics and phages function as antibacterials that disrupt bacterial colonies through lysis or inhibition, yet several key differences make each antibacterial more or less appropriate depending on the situation.

Safety

Adverse reactions to antibiotics are well documented and include instances of anaphylaxis, nephrotoxicity, cardiotoxicity, hepatotoxicity, and neurotoxicity, as well as a number of gastrointestinal and hematological complications[80]. The majority of adverse reactions are allergic reactions and in these rare instances, the anaphylaxis is associated with specific classes of antibiotics or is the product of high tissue concentrations[81-83]. In contrast to the comprehensive literature on antibiotic safety, phage therapy has only recently gained attention by western medicine and, as a result, much of the available information on phage safety is new. Although oral phage administration is generally considered to be safe[57-60], a major consideration for phage therapy is the translocation of phage across the intestinal epithelium where they subsequently circulate within the blood[84]. Some data show that phage translocation may benefit the host by downregulating the immune response to indigenous gut microbe antigens through the inhibition of interleukin-2, tumor necrosis

Table 2 Recently published findings on phage lytic enzymes

	Lytic enzyme	Model	Target pathogens	Result summary	Ref.
Phage-derived lysins	ABgp46	*In vitro*	MDR *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium*	Cross-inoculation significantly reduced bacterial density	[64]
	PlyF307	Murine	MDR *A. baumannii*	*i.p.* treatment rescued mice from lethal bacteremia	[65]
	Cpl-1	Murine	*Streptococcus pneumoniae*	*i.p.* treatment rescued mice from lethal pneumonia	[66]
	Cocktail of 6 distinct lysins	*In vitro* and murine *in vivo*	MRSA	Effective against biofilms *in vitro* and protected mice from lethal sepsis	[67]
	PlyCD	*In vitro* and *ex vivo*	*Clostridium difficile*	Reduced *C. difficile* colonization	[68]
	PlySs2	Murine	*Streptococcus pyogenes* and MRSA	i.p. treatment reduced mortality from lethal bacteremia	[69]
	PlyG	*In vitro*	*Bacillus anthracis*	Eliminated *B. anthracis* spores and vegetative cells	[71]
Bioengineered chimeric lysins	CHAPK	*In vitro*	MRSA	Eliminated MRSA and dispersed biofilms	[72]
	ClyH	Murine	MRSA	Treatment rescued mice from bacteremia	[73]
	Cpl-711	Murine	*S. pneumoniae*	Treatment rescued mice from bacteremia	[74]
	Ply187	Murine	*Staphylococcus aureus*	Prevented bacterial endophthalmitis	[75]
	Artilysins	Nematode gut	*P. aeruginosa*	Decolonized *P. aeruginosa* from gut	[76]
		Human keratinocytes	*A. baumannii*	Protected cells from bacterial challenge	[76]
Lysin and antibiotic combination therapy	CF-301	Murine	MRSA	Lysin treatment was most effective when combined with vancomycin or daptomycin	[77]
	MR-10	Murine	Burn wound infection	Lysin treatment was most effective when combined with minocycline	[78]

MDR: Multi-drug-resistant; *i.p.*: Intraperitoneal injection; MRSA: Methicillin-resistant *S. aureus*.

factor, and interferon gamma production[84]. Other studies discovered a host innate immune response aimed at removing phage after administration in mice[35,85]. While potentially beneficial in a healthy individual, the immunological response to phage may be indicative of a potential adverse immunogenicity of phage in immunocompromised patients, which could hypothetically worsen a patient's condition. On the contrary, other researchers argue it is unlikely phage therapy will elicit such an adverse response in immunocompromised patients[86].

Additional complications include the possibility that phage cocktails induce a state of intestinal barrier dysfunction, otherwise known as "leaky gut". Tetz and Tetz used a mouse model to demonstrate that oral administration of a commercial Russian phage cocktail was capable of increasing intestinal permeability and elevating serum levels of inflammatory circulating immune complexes in the blood, which are associated with a number of pathological conditions[87]. However, another study observed no significant increase in cytokine levels in response to phage treatment[88]. The potential for phage therapy to disrupt normal intestinal barrier function would have serious implications for several disorders recently linked to intestinal barrier dysfunction such as Crohn's disease, inflammatory bowel disease, and type 1 diabetes[87]. Pincus *et al*[89] found that inflammatory response to phage was dependent on site of infection. Clearly, many considerations for the safety of phage therapy still need to be addressed. It is likely that the physiological response to phages also differs between individuals and is dependent on the specific phage strains used. To determine the safety of phage treatments in regards to human health, future investigations will need to focus on human clinical trials as much of the current research on the immunological response to phage is limited to animal models.

Specificity

Relative to antibiotics, phages tend to be specific towards both species and strain. In certain situations this can be a major advantage considering the well-documented, collateral effects of broad-spectrum antibiotics on commensal gut microbes, which are notorious for secondary outcomes such as antibiotic-associated diarrhea and *C. difficile* infection[90]. Other consequences of antibiotic perturbations in the gut microbial community include risk of asthma, obesity, and diabetes[91-93]. The current understanding of collateral damage due to phage therapy is limited, but compared to antibiotics, phage therapy has been reported to result in less perturbation of the gut microbiome while still effectively reducing gut carriage of pathogens such as *Shigella sonnei* and uropathogenic *E. coli*[94,95].

Strain and species specificity of antibacterial action has many advantages, however, increased specificity also comes with several limitations. By targeting a single pathogen, phage therapy could be less effective against certain infections, such as infected burn wounds, which are often colonized by more than one strain of bacteria[96]. This can be accounted for by creating phage cocktails infective against a range of known pathogens, but the success of this approach depends on knowledge of which pathogens are being treated. With regard to logistical considerations, this

specificity significantly impacts treatment development and testing, and also limits the possibility of large-scale production and distribution, a distinct advantage of broad-spectrum antibiotics. Bourdin *et al*[15] cross-inoculated phages from 2 distinct geographic regions (Mexico and Bangladesh) against diarrhea-associated *E. coli* from the same regions and found that phage showed high strain specificity to the *E. coli* of their indigenous region. In a randomized clinical trial, Sarker *et al*[60] administered a commonly used Russian *E. coli* phage cocktail to a cohort of 120 Bangladeshi children with microbiologically-proven enterotoxogenic *E. coli* diarrhea. No improvement of clinical outcome was observed in patients receiving the phage cocktail compared to placebo[60]. These findings are in line with the *in vitro* work that suggests phage cocktails are better adapted to local bacterial populations[15], and bacterial host range can be restricted both spatially and temporally[97]. In contrast, in an *in vitro* cross-inoculation of a phage cocktail against shiga toxin-producing *E. coli* O157:H7, lysis occurred in isolates of both human and bovine origin, suggesting the possibility of regional phage cocktails for both clinical and agricultural settings[98]. Latz *et al*[99] found that phages targeting antibiotic-resistant bacteria are more likely to be found within the environment of the infected patient, which, in this case, was the hospital effluent where the antibiotic-resistant bacteria were isolated.

Regional specificity may be helpful in finding phages with the greatest infectivity towards the target pathogen, this would especially benefit regions with limited access to antibiotics. Together, the mounting evidence for the local adaptivity of phage suggests that regulatory pipelines must also be rapidly adaptable (*i.e*., allowing for the replacement or addition of phages into cocktails without requiring further clinical trials) for phage therapy to work on a global scale.

Biofilm penetration

Antibiotic therapy is highly effective with planktonic bacteria, such as *V. cholerae* and *Yersinia pestis*, yet is limited in treating biofilm-based bacterial infection[100]. Phages, however, are equipped with enzymes (*e.g*., EPS depolymerase) on the exterior of the capsid that degrade the extracellular polymeric substances (EPS) and disperse bacterial biofilms, allowing the phage to access bacteria embedded within the EPS matrix[83]. The phage progeny released upon completion of the lytic cycle propagate the dispersal of the biofilm through the removal of biofilm-embedded bacteria in subsequent layers[83,101]. In order to penetrate dense biofilms, high doses of antibiotics are typically required to observe any inhibition of bacterial growth, yet complete eradication is rare and regrowth of colonies begins after the end of antibiotic treatments[102,103]. Although low concentrations of many antibiotics are generally considered non-toxic, high concentrations of antibiotics can result in tissue toxicity[83]. Gabisoniya *et al*[104] at the Eliava Institute of Bacteriophages in Tbilisi, Georgia found that the application of phages on *in vitro* colonies of the pathogen *P. aeruginosa* not only prevented additional biofilm formation by the pathogen but also degraded existing biofilm. Phage treatments have eliminated biofilms formed by *L. monocytogenes, P. aeruginosa,* and *Staphylococcus epidermidis* on the surface of medical devices[22]. These findings are highly relevant to the problem of persistent infections caused by implanted medical devices such as catheters, lenses, and prostheses where biofilm formation is common.

Phage cocktails

Due to the massive diversity of environmental phages, designing a phage cocktail is substantially more complicated than designing a regimen for combination antibiotic therapy. Composition of the phage cocktail is critical for the success of phage therapy. Factors in the construction of a phage cocktail are beyond the scope of this review and have been thoroughly discussed elsewhere[105], but one of the major logistical challenges is whether to approach phage therapy with a standardized or a customized cocktail. Customizing phage cocktails to each infection is time consuming and costly but on the other end of the spectrum, a "one-size-fits-all" approach may not provide the strain specificity required for favorable clinical outcomes[105]. Other considerations are the collateral effects of phages on the indigenous microbiota, a topic that has not yet been fully explored[88,94,95]. In cocktail design, one must also take into account phage lifecycle. Lysogenic phages appear to be very common in the indigenous gut microbiota, with prophages comprising the majority of the gut virome[25]. Some therapeutically promising lysogenic phages effectively silence virulence genes in pathogenic bacteria or provide genes for short chain fatty acid metabolism, whereas other lysogenic phages supplement genes for virulence and antibiotic resistance[29,30,106].

Antibiotic resistance genes have been collected from the phage fraction of DNA in wastewater and have been reported to persist longer in phage when compared to bacteria[107]. Antibiotic resistance genes are also present in the phage fraction of human fecal samples and antibiotic treatment in mice enriches the abundance of phage-encoded antibiotic resistance genes, indicating a possible role for phages as a reservoir for antibiotic resistance genes[30-32]. The hypothetical potential for lysogenic phages to complicate existing infections through the horizontal transfer of antibiotic resistance genes to infectious bacteria largely excludes them from consideration for most phage cocktails. Yet, Regeimbal *et al*[106] demonstrated the possibility for an innovative application of lysogenic phages by designing an "intelligent" 5 phage cocktail that eliminated *A. baumannii* skin wound infection in a mouse model. This intelligent phage cocktail was composed of 4 phages that were incapable of lysing the *A. baumannii* host and 1 phage that only inhibited growth *in vitro*. The growth-inhibiting phage targeted capsulated *A. baumannii*, selecting for

the loss of the capsule. The removal of the capsule, a known virulence factor, decreased the virulence of the bacterium and made it susceptible to lysis from the 4 additional phages[106]. This "intelligent" cocktail represents the beginning of novel treatment options for eliminating bacterial infections that are resistant to conventional treatment. Lysogenic phages have many intriguing properties that may be useful for this type of *in situ* manipulation of individual bacterium, and potentially the human gut microbiome metagenome[108], but first much more needs to be known about the role of lysogenic phages in the human gut phageome for this to be done safely and effectively.

CONCLUSION

The available literature on the use of phages and phage-derived proteins for combating bacterial infections, specifically those of multidrug-resistant bacteria, increasingly shows promise for the prospect of phage therapy as either an alternative or a supplement to antibiotics. However, recent findings on the immunomodulatory effects of phages make it abundantly clear that we need a better understanding of the interaction between phage, microbiome, and human host before implementing phage therapy on a large scale. Phage lysins may thus be a much more practical therapeutic tool for their decreased immunological potential, among other reasons such as ease of production, purification, and storage. In spite of the promise offered by phage and phage-derived lytic proteins, it is more than likely that no panacea for antibiotic-resistant infections will arise. The increased efficacy of antibacterial agents when used in conjunction implies that therapy using some combination of phage, phage-derived lytic proteins, bioengineered phage, and/or antibiotics will be necessary for addressing the growing problem of antibiotic-resistant infections.

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MINIREVIEWS

Critically ill patients and gut motility: Are we addressing it?

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Abstract

Gastrointestinal (GI) dysmotility is a common problem in the critically ill population. It can be a reflection and an early sign of patient deterioration or it can be an independent cause of morbidity and mortality. GI dysmotility can be divided for clinical purposes on upper GI dysmotility and lower GI dysmotility. Upper GI dysmotility manifests by nausea, feeding intolerance and vomiting; its implications include aspiration into the airway of abdominal contents and underfeeding. Several strategies to prevent and treat this condition can be tried and they include prokinetics and post-pyloric feeds. It is important to note that upper GI dysmotility should be treated only when there are clinical signs of intolerance (nausea, vomiting) and not based on measurement of gastric residual volumes. Lower GI dysmotility manifests throughout the spectrum of ileus and diarrhea. Ileus can present in the small bowel and the large bowel as well. In both scenarios the initial treatment is correction of electrolyte abnormalities, avoiding drugs that can decrease motility and patient mobilization. When this fails, in the case of small bowel ileus, lactulose and polyethylene glycol solutions can be useful. In the case of colonic pseudo obstruction, neostigmine, endoscopic decompression and cecostomy can be tried when the situation reaches the risk of rupture. Diarrhea is also a common manifestation of GI dysmotility and the most important step is to differentiate between infectious sources and non-infectious sources.

Key words: Gut motility; Gut dysmotility; Intensive care unit; Gastrointestinal issues in intensive care unit; Ileus

Core tip: This manuscript presents the case for a cautious look at the gastrointestinal (GI) system during critical illness. GI dysfunction can be an early sign of decompensation, but unfortunately is often overlooked due to the natural tendency to gravitate towards the cardiovascular, respiratory and renal systems when looking for decompensation signs. It is our intention to bring attention to this system and help the clinician in using the GI tract as an early marker for decompensation and also to identify and treat potential GI complications common in

this population.

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INTRODUCTION

The gastrointestinal tract is a vast organ system with many key functions during normal state and physiology. Its functions include digestion and absorption of nutrients, immunomodulation, excretion of fluids, electrolyte balance and hormonal control[1]. These functions are integral for maintenance of homeostasis in health, adaptation in sickness and also as a source of disease.

Acute gastrointestinal injury (AGI) can occur as the result of the gastrointestinal tract been a bystander during periods of critical illness with possible grim consequences. The mechanisms responsible of this injury are diverse and include cytokines and ischemia-reperfusion injury. Observational studies have linked AGI with increased mortality and longer ICU-LOS[2].

AGI common manifestations include: Delayed gastric emptying, ileus, malabsorption, diarrhea, GI hemorrhage and GI bleed[3]. Due to this GI dysmotility in the ICU should be addressed seriously and systematically since it could be the manifestation of GI tract failure as well as manifestation of disease.

For the purpose of this review we would like to divide the problem in upper GI dysmotility and lower GI dysmotility.

UPPER GI DYSMOTILITY

Upper GI dysmotility is usually manifested as delayed gastric emptying, regurgitation and ultimately aspiration. These are signs and symptoms that should never be disregarded since they point out at AGI; the difficult questions would be how aggressive should we be monitoring and treating delayed gastric emptying? What is the optimal method of monitoring? What is the optimal treatment?

GASTRIC EMPTYING

Delayed gastric emptying is a common occurrence in the critically ill[4], multiple factors are associated to decreased gastric emptying (Table 1) and once develops there has been concern that this may be linked to aspiration pneumonia and worse outcomes[5].

The challenge for the clinician is to find a way to monitor and prevent significant dysmotility leading to reflux and aspiration.

MONITORING GASTRIC EMPTYING

Multiple direct and indirect methods of measuring gastric emptying have been studied (Table 2). Scintigraphy is the gold standard but is not practical or readily available in the ICU setting. Unfortunately all of the other indirect methods have limitations and the availability is limited and we are left with an imperfect surrogate of gastric emptying measurement: The gastric residual volume (GRV)[6], and also with a promising alternative: The ^{13}C-octanoate breath test.

Gastric residual volumes

The gastric residual volume has been used as an indirect surrogate of gastric emptying. Several limitations of using the GRV have been described. A normal patient's endogenous secretions can confuse this measurement since a patient can produce up to 4500 mL a day of saliva, gastric secretions and duodenal reflux[7].

Other limitations are technical and they include[8]: (1) a lack of standardization on the quantity of a normal GRV, 15 mL to 500 mL has been described as an upper limit; (2) location of the tip of the tube; (3) different volumes depending on the bore of the catheter; and (4) inconsistent frequency of measurements.

Several small studies have looked into the correlation of different volumes of GRV (150-250 mL), and it has been shown to be a sensitive marker for delayed gastric emptying when compared to scintigraphy and acetaminophen absorption test, but, the negative predictive value was low, thus a lot of the patients with a negative test still had abnormal gastric emptying. More importantly having an abnormal GRV did not correlate to any significant clinical outcome[9,10].

The clinical impact from checking GRV is underfeeding and early enteral nutrition has been shown to improve outcomes of critically ill patients, on the other hand checking GRV has not been shown to decrease vomiting or aspiration. In a 205 patients study, subjects were divided in two groups, one group had feedings held if a GRV were > 250 mL, the second group did not have GRV checked. Patients in the non GRV group achieved higher delivery of EN plus vomiting episodes and clinical aspiration events were not statistically different than the patient's in the GRV group[11].

Based on this data we do not recommend monitoring of GRV in the critically ill patient, but this does not mean that we should not address gastric intolerance manifested as nausea and/or vomiting.

^{13}C-octanoate breath test

The octonoate breath test has been developed as a non-invasive technique that is less cumbersome than scintigraphy since does not require patient transportation outside of the intensive care unit. It has been studied against scintigraphy in the critically ill population undergoing mechanical ventilation. In this test, carbon-13 (a non-radioactive isotope) is added to a test

Table 1 Factors associated with decreased gastric emptying

Factors associated with decreased gastric emptying
Hyperglycemia
Opiates
Elevated intracranial pressure
Electrolyte abnormalities
Ischemia
Hypoxia
Sepsis
Burns
Abdominal surgery
Hyperosmolar formulas

Adapted from Hurt RT, McClave SA. Gastric Residual Volumes in Critical Illness: What do They Really Mean? *Crit Care Clin* 2010: **26**: 481-490.

meal of 100 mL of octanoic acid. ^{13}C-Octanoic acid is not absorbed in the stomach but is rapidly absorbed by the duodenum and then metabolized in the liver to produce $^{13}CO_2$. Once the test meal is given, the $^{13}CO_2$ enrichment of the exhaled air is measured with an isotope ratio mass spectrometer at standard times for 3 to 6 h; due to the properties of the isotope this measurement is reflective of gastric emptying. The biggest study to date showed that this test had an 89% sensitivity and a 67% specificity in identifying delayed gastric emptying when compared to scintigraphy, giving it a 92% PPV and a 57% NPV. Also the authors also concluded that the wide confidence interval (45%-88%) made it a good option to test gastric emptying in the research setting but not in a real life clinical setting[12]. Other limitations include the high cost and size of spectrometer units[13].

Prevention and treatment of gastric dysmotility

Interventions to prevent and treat gastric dysmotility include: The use of continuous feeding *vs* intermittent bolus feeding, post-pyloric feeding and prokinetics.

Continuous infusions of enteral feeds have the theoretical advantage of decreasing the amount of regurgitation and aspiration compared to intermittent boluses, unfortunately the evidence is scant. Small trials[14,15] suggest a decreased incidence of elevated gastric residuals and due to this more success in meeting caloric needs with the continuous methods but there is no difference in hard clinical outcomes. The current recommendations of the American Society of Parenteral and Enteral Nutrition (ASPEN) are to choose continuous feedings on those patients that are intolerant to bolus feeding and those that are high risk for aspiration[16].

Another possible solution would be to place the enteral feeding tube past the pylorus to prevent re-gurgitation and aspiration of gastric contents. A recent meta-analysis showed that there was a decrease in the incidence of pneumonias, but there was no significant difference in nutritional outcomes, length of stay or hospital mortality[17]. But, placing a post-pyloric tube can be technically difficult and delay initiation of enteral nutrition, due to that the ASPEN guidelines suggest to use the gastric route routinely and favor the post-pyloric route to patients at high risk of aspiration or those that showed intolerance.

Table 2 Methods of measuring gastric emptying

Methods of measuring gastric emptying
Scintigraphy
Paracetamol absorption
Carbohydrate absorption
Isotope breath test
Ultrasound and MRI
Gastric residual volumes

The use of prokinetics has been associated with decreased GRV but no significant change in length of stay or mortality[18]. The most commonly studied agents include erythromycin at a dose of 3-7 mg/kg per day and metoclopramide at a dose of 10 mg every 4 h. If one chooses to use these agents, we must be aware of the side effects that include QT prolongation and diarrhea with both agents and tardive dyskinesia in the case of metoclopramide.

LOWER GI DYSMOTILITY

Lower GI dysmotility can be manifested in the ICU as ileus, acute colonic pseudo obstruction and diarrhea.

Evaluation of lower GI dysmotility

Unfortunately none of the usual tests used in the outpatient setting to evaluate motility disorders has been validated or found useful in the intensive care unit setting. The clinician is left with his clinical exam acumen and the usual routine tests performed the critically ill, this is why is important to suspect these disorders and look for them on our daily exam. We will describe the most common clinical presentations.

Ileus

Ileus is defined as the absence of physiologic motility in the bowel, leading to a lack of progression of bowel contents through the gastrointestinal tract. A more specific definition has been described and this includes: Absence of a bowel movement for $\geqslant$ 3 d, treatment for constipation, and one of the following: (1) radiologic confirmed ileus; (2) feed intolerance; (3) abdominal distention; or (4) need for gastric decompression. This has to be differentiated from acute mechanical obstruction that may be a surgical emergency. It has been reported to occur in 20%-50% of the ICU population[18]. The average duration of the episode is 6.5 d and is associated with longer ICU stays as well as underfeeding[19].

Risk factors

The critically ill patient population is specially primed to develop ileus. Inflammation, narcotic use, vasopressor use and electrolyte imbalances makes them susceptible

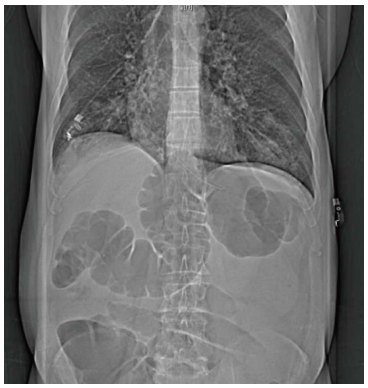

Figure 1 Abdominal plain film showing small bowel ileus and colonic distension.

to a disequilibrium between sympathetic and parasympathetic forces. Common clinical entities that predispose to ileus include: Abdominal surgery, sepsis, pancreatitis, peritonitis, narcotic use, anticholinergic use, hypokalemia, hypomagnesemia, hyperglycemia, acidosis, hypoxia, hypothermia, renal failure and mechanical ventilation[20].

Clinical manifestations

Ileus is usually manifested as inability to tolerate feeds, nausea, vomiting, abdominal distension, constipation and obstipation. The imaging studies show the presence of gas distension of bowel loops and air fluid levels within them (Figure 1). When severe enough it can develop into abdominal compartment syndrome, which is a life threatening emergency.

TREATMENT

The basic management of ileus includes the correction of electrolyte abnormalities, avoidance of opioid agonists, avoidance of anticholinergic drugs, mobilization and early enteral feedings when possible.

Other therapies may include the use of gastric decompression, osmotive laxatives, opioid antagonists and promotility agents.

A double blinded study comparing the use of placebo *vs* polyethylene glycol *vs* lactulose in ICU patients with 3 or more days without a bowel movement showed that, both lactulose and polyethylene glycol are better in promoting defecation than placebo. Patients receiving polyethylene glycol had a lower incidence of acute intestinal pseudo obstruction. Early defecation was associated to a decreased LOS. Based on these findings is reasonable to start osmotive laxatives in this patient population[21].

The use of promotility agents in ileus seems more controversial. Erythromycin has been tried due to the theoretical effect on the motilin receptor. Despite this theoretical mechanism the trials have consistently failed to show any positive effect and its use comes with risk of a prolonged QT and arrhythmias. So we recommend against its use[22]. Metoclopramide has also been tried but results have been conflicting and no clear role exists for its use.

Acute colonic pseudo obstruction (Ogilvie's syndrome)

Acute colonic pseudo obstruction is a potentially fatal condition defined as an acute dilatation of the colon without a mechanical obstruction. Clinically is characterized by abdominal distension, commonly constipation, but flatus or stools may pass as well, an abdominal exam that may be benign but also it can present with exquisite abdominal tenderness, especially at the level of the cecum. The most feared complication would be perforation that usually happens in the cecum[23].

The pathophysiology is thought to be an imbalance between the parasympathetic/sympathetic signals. Clinical factors predisposing to this condition are multiple and include medications, surgery, critical illness, neurologic factors and metabolic factors (Table 3).

Differential diagnosis

The most important alternative diagnosis to rule out is toxic megacolon and mechanical obstruction. Mechanical obstruction can be easily ruled out by the presence of gas on all colonic segments on an abdominal plain film. If there is doubt a CT of the abdomen and pelvis with oral contrast can clarify the situation. Differentiating between Ogilvie's and toxic megacolon can be more difficult. In the general population the most common cause of toxic megacolon is inflammatory bowel disease, in the critically ill the most common cause is *C. difficile* infection[24]. A thorough history and physical is warranted, other diagnostic tools include stools samples to test for *C. difficile* toxins or *C. difficile* PCR, CT abdomen pelvis and limited endoscopy with biopsies.

Treatment

The first step in management include treating underlying conditions, managing electrolyte abnormalities, avoid opiates, early mobilization when feasible and early enteral nutrition.

When this therapy fail after 24-48 h and the risk of rupture is present, defined as cecum diameter > 12 cm[25]. We must proceed with other options that include neostigmine use, endoscopic decompression, percutaneous cecal decompression or surgical management.

Neostigmine is successful in achieving decompression in more than 88% of cases[26]. The drug is used at a dose of 2 mg intravenously given slowly over 5 min with monitoring of vital signs continuously for at least 30 min. Side effects include bradycardia, hypotension, nausea, vomiting and abdominal cramping.

Endoscopic decompression is les commonly used due to the risk of perforation, when performed this should be followed by the placement of a decompression tube since this increases the success rate from 50% to 80%[27]. In patients in whom these therapies fail, the next step according to the American Society of Gastroenterology

Table 3 Factors predisposing to Ogilvie's syndrome

Factors predisposing to Ogilvie's syndrome
Medications
Opiates
Anticholinergics
Vasopressors
Calcium channel blockers
Cardiovascular factors
Shock
Heart failure
Critical illness
Severe sepsis
Pancreatitis
Mechanical ventilation
Hypoxemia
Post-operative state
Abdominal surgery
Peritonitis
Pelvic or hip fracture surgery
Metabolic factors
Hypokalemia
Renal failure
Hyperglycemia
Neurologic
Spinal cord lesions
Stroke

and Endoscopy guidelines should be either percutaneous cecostomy or surgical management[28].

DIARRHEA

Diarrhea in the ICU can be defined as > 3 loose stools a day[29]. The incidence is around 20%[30]. Diarrhea in the ICU can be divided as infectious and non-infectious. Due to its incidence and possible serious underlying conditions it should never be dismissed and proper workup should be sought.

Infectious diarrhea

Clostridium difficile infection is the most common cause of infectious diarrhea in the ICU been present in 44% of patient with either infectious or non-infectious diarrhea in the ICU[31]. Other enteric pathogens include *Salmonella*, *C. perfringens*, *S. aureus* and *P. aeruginosa*. Antibiotic use is the most widely recognized risk factor for infectious diarrhea in the ICU; other risk factors include gastric acid suppression[27], advanced age and illness severity. A review of *C. difficile* infection is beyond the scope of this review article.

Non-infectious diarrhea

The most common causes for non-infectious diarrhea in the ICU include antibiotic associated diarrhea, enteral feeding associated diarrhea and medications. Regarding antibiotic associated diarrhea, when *C. difficile* is not found the theory behind this condition is the reduction on the concentration of anaerobic organisms in the gut with subsequent reduction of carbohydrate fermentation leading to an osmotic diarrhea[31].

Enteral feeding associated diarrhea is commonly quoted as the cause of diarrhea during ICU rounds. Interestingly a recent meta-analysis comparing total parenteral nutrition *vs* enteral nutrition did not find a higher incidence of diarrhea in the enteral feeds group[32]. A common sense approach would be to avoid high caloric density formulations due to their osmotic effects when possible. Fiber use to decrease diarrhea has been proven effective in the non-icu population, but this effects have not been reproduced in the ICU population. Probiotics also did not change its incidence[33].

CONCLUSION

GI dysmotility is a common but often overlooked occurrence in the critically ill patients. By itself it may be the reflection of end organ damage and deterioration as well as a sign of a serious underlying disorder. The clinician should pay close attention to it and initiate the appropriate work up as soon as possible to prevent grim outcomes.

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ORIGINAL ARTICLE

Retrospective Study

Use of proton pump inhibitors in general practice

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Abstract

AIM

To evaluate the characteristics of the prescription of the proton pump inhibitor drugs (PPI) and the adherence to the indications of the guidelines regulating the reimbursement limitations set forth by the Italian Drug Agency.

METHODS

Thirty general practitioners (GP) participated in the study, providing data on more than 40000 patients in total. The population was divided into non occasional users of PPI drugs (PPI users) and non-users (PPI non-users) based on evidence of a prescription of at least 3 packs of PPIs in the last 90 d before analysis. The data provided allowed an assessment of compliance with the requirements of eligibility for PPI reimbursement according to the Italian Drug Agency rules, in order to obtain subpopulations which complied or not with the rules.

RESULTS

Six thousand three hundred and twenty-two patients were found to be PPI users, accounting for 14.9% of the patient population. PPI users were more frequently female, older and more frequently diagnosed with gastroesophageal reflux disease, gastric or duodenal ulcers, arthropathy, heart disease and cancer than the rest of the population. PPI users had more frequently received prescriptions for non-steroidal ant-inflammatory drugs (NSAIDS), acetylsalicylic acid (ASA), oral anticoagulant therapy (OAT) and systemic steroids. PPI reimbursement resulted applicable to 69.3% of the PPI users, but a potential for reimbursement of PPI prescriptions was identified in the non PPI users for the treatment of peptic or reflux disease (8.5%) and for the protection of gastric damage caused by NSAIDS (6.1%). Patients who are potentially eligible for reimbursement are older, diagnosed with arthropathy and heart disease more frequently and most commonly receive NSAID and ASA prescriptions compared with PPI users who do not satisfy eligibility requirements. Patients in whom it was not possible to identify conditions related to prescription suitability were more frequently associated with use of OAT.

CONCLUSION

A substantial number of patients who apparently do not meet prescription suitability conditions can be identified, but among non PPI users on the contrary, it is possible

to identify an equal number of patients for whom prescription would be suitable. Poor suitability can be identified in the population receiving OAT. Thus, there is scope for decreasing inappropriate use of PPI drugs by adhering to certain criteria and by involving all interested parties.

Key words: Proton pump inhibitors; Appropriateness; General practice; Gastroprotection; Peptic disease

Core tip: This study was carried out in a large unselected population to evaluate the characteristics of proton pump inhibitor (PPI) prescription and the adherence to the guidelines regulating the reimbursement limitations set forth by the Italian Drug Agency. A substantial number of patients who apparently do not meet prescription suitability conditions can be identified, but among non-PPI users on the contrary, it is possible to identify an equal number of patients for whom prescription would be suitable. According to our data the greatest problems in clinical decision originate in patients in antithrombotic therapy.

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INTRODUCTION

Proton pump inhibitors (PPI) are among the most prescribed drugs in the world since their indications for use are manifold, including the treatment of gastro-esophageal reflux disease (GERD), peptic ulcer disease, the prevention of gastric damage by non-steroidal ant-inflammatory drugs (NSAIDS) and acetylsalicylic acid (ASA), dyspepsia and infection by *Helicobacter pylori* (*H. pylori*)[1-4]. There are five PPIs available in Italy (omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole), representing between 5% and 10% of total pharmaceutical prescriptions, similar to other countries[5-7].

PPIs are generally well tolerated and have few side effects but their prolonged use has been associated with various problems due to mechanisms which are especially related to the extensive and persistent inhibition of gastric acid secretion and the competitive inhibition of hepatic cytochrome P450[8-11].

Due to the high efficacy of PPIs in controlling the symptoms of upper gastrointestinal diseases, treatment often becomes ongoing and difficult to suspend[12]. This often makes it difficult to determine the prescription suitability of PPIs[12-16].

For this reason, rules to limit the reimbursement of these drugs which are paid for by the Italian National Health Service were introduced by the Italian Drug Agency twenty years ago. These were draw up according to the conditions of proven effectiveness and following major international guidelines. Table 1 describes the eligibility requirements for reimbursement of PPI prescriptions according to the Italian Drug Agency rules.

The aim of the study was to retrospectively evaluate, using the patient files provided by a large group of General Practitioners (GPs), the characteristics of PPI prescription and their adherence to the indications of the guidelines regulating the reimbursement limitations set forth by the Italian Drug Agency.

MATERIALS AND METHODS

Forty of the 400 GPs of the Health Agency of Bologna (Northern Italy) were requested to participate in the study. GPs were asked to submit a file containing anonymous data of all adult patients at 1 June 2015. This was obtained using an automated procedure available in the software which is used to manage clinical data. Demographic variables, presence of clinical diseases and drug use were reported in the file. A single database to obtain general population data was then created. The population was divided into non occasional users of PPI drugs (PPI users) and non-users (PPI non-users) based on evidence of a prescription of at least 3 packs of PPIs in the last 90 d before analysis (1 pack = 14 tablets). The data provided allowed an assessment of compliance with the requirements of eligibility for PPI reimbursement according to the Italian Drug Agency rules, in order to obtain subpopulations which complied or not with the rules. Table 1 describes the eligibility requirements for reimbursement of PPI prescriptions according to the Italian Drug Agency rules.

Differences between populations were evaluated using analysis of variance and the chi-squared test. $P < 0.05$ values were selected as the statistical significance limit. The statistical review of the study was performed by a biomedical statistician. The study did not need to be submitted to the Ethics Committee as retrospectively conducted on anonymous database.

RESULTS

Thirty GPs participated in the project and provided anonymous data files for 42548 patients. The study population was made up of 19632 males (46.1%) and 22916 females (53.9%) with a mean age 53 years (28.4% over 64 years old). This study population did not differ from the whole population on record at Health Agency of Bologna, which comprehends about 750000 adults (44% male and 56% female), of whom about 210000 (28%) are over 64 years old.

Six thousand three hundred and twenty-two patients were found to be PPI users, accounting for 14.9% of the patient population. Table 2 summarizes the characteristics of PPI users compared to non-PPI users.

Table 1 Rules of the Italian Drug Agency for the refund of proton pump inhibitor drugs

The prescription of PPI refundable by the National Health Service is limited to
The prevention of serious complications of the upper gastrointestinal tract in patients in chronic treatment with NSAIDS or in antiaggregant therapy with low doses of ASA, provided there is one of the following conditions of risk: (1) history of past digestive hemorrhage or peptic ulcer not healed with *Helicobacter pylori* treatment; (2) concomitant therapy with anticoagulants or cortisone; and (3) advanced age
Duration of treatment 4 wk (occasionally 6 wk): Duodenal or gastric ulcer, in association with drugs eradicating the infection; GERD with or without esophagitis (first episode)
Duration of treatment extended to reevaluate after one year: Zollinger-Ellison syndrome; relapsing duodenal or gastric ulcer; GERD with and without esophagitis (relapsing)

PPI: Proton pump inhibitor; GERD: Gastroesophageal reflux disease; ASA: Acetylsalicylic acid; NSAIDS: Non-steroidal ant-inflammatory drugs.

Table 2 Characteristics of proton pump inhibitor-users (at least 3 packs in 90 d) and non-proton pump inhibitor-users *n* (%)

	All	PPI-users	Non PPI users
Patients	42548	6322	36226
Males	19632 (46.1)	2520 (39.9)	17112 (47.2)
Aged over 64 yr	12084 (28.4)	3902 (61.7)	8182 (22.6)
GERD	5769 (13.6)	2980 (47.1)	2789 (7.7)
Peptic ulcer	689 (1.6)	375 (5.9)	314 (0.9)
Arthropathy	15661 (36.8)	3786 (59.9)	11875 (32.8)
Heart disease	3932 (9.2)	1674 (26.5)	2258 (6.2)
Neoplasms	3384 (8.0)	1076 (17.0)	2308 (6.4)
Use of NSAIDS	1131 (2.7)	416 (4.6)	715 (2)
Use of ASA	4522 (10.6)	2017 (31.7)	2505 (6.9)
Use of OAT	1127 (2.6)	500 (7.9)	627 (1.7)
Use of systemic steroids	547 (1.3)	306 (4.8)	241 (0.7)
EGD scopy	5772 (13.6)	2626 (41.5)	3146 (8.7)
Test per *H. pylori*	4761 (11.2)	1641 (26.0)	3120 (8.6)
PPI refundable for prevention of gastric damage by NSAIDS	4105 (9.6)	1896 (30.0)	2209 (6.1)
PPI refundable for peptic ulcer or GERD	6340 (14.9)	3265 (51.6)	3075 (8.5)
PPI refundable for prevention of gastric damage by NSAIDS or peptic ulcer or GERD	9368 (22.0)	4383 (69.3)	4985 (13.8)

All the features differ significantly ($P < 0.01$) between the two groups. PPI: Proton pump inhibitors; GERD: Gastroesophageal reflux disease; Heart disease: Heart failure, coronary ischemic disease, major heart valves disease; NSAIDS: Non steroid inflammatory drugs; ASA: Acetylsalicylic acid; OAT: Oral anticoagulant therapy; EGDscopy: Esophageal-gastro-duodenal endoscopy; *H. pylori*: *Helicobacter pylori*.

The two groups were statistically different when all the evaluated conditions were compared. PPI users were more frequently female, older and more frequently diagnosed with gastroesophageal reflux disease, gastric or duodenal ulcers, arthropathy, heart disease and cancer than the rest of the population. PPI users had more frequently received prescriptions for NSAIDS, ASA, oral anticoagulant therapy (OAT) and systemic steroids. In addition, PPI users had been more frequently prescribed an esophagogastroduodenoscopy (EGDscopy) and tests for the diagnosis of *H. pylori* infection.

Based on the clinical characteristics of the patients, it was possible to determine the prevalence of patients in the two groups who satisfy requirements set forth by Italian Drug Agency rules and who may be eligible for PPI reimbursement. Based on the data available, PPI reimbursement for the protection of gastric damage caused by NSAIDs is applicable to 30% of PPI users, for ulcers or GERD disease it is applicable to 51.6%, for at least one of the two cases it is applicable to 69.3% of the group. One thousand nine hundred and thirty-nine out of 6322 (30.7%) patients do therefore not comply with PPI prescription suitability according to the Italian Drug Agency.

However potential conditions which are eligible for PPI reimbursement are identifiable for peptic or GERD disease in 8.5% of the non-PPI users (equal to 3075 out of 36226 patients) and for the protection of gastric damage caused by NSAIDS in 6.1% of patients (in 2209 out of 36226 patients).

Figure 1 shows, relative to the total study population, the PPI users who comply with PPI prescription suitability for the protection of gastric damage caused by NSAIDS (1896), the PPI users who are not suitable for prescription (1939) and the non-PPI users who are suitable for prescription for the protection of the gastric damage from NSAIDS (2209), relative to the total study population.

Table 3 shows the characteristics of PPI users who do or do not comply with reimbursement eligibility conditions. The two groups were statistically different in relation to some characteristics. Patients who were potentially eligible for reimbursement were older, were more frequently diagnosed with arthropathy and heart disease and more frequently received NSAID and ASA prescriptions compared with PPI users who do not satisfy eligibility requirements. Also PPI users who comply with reimbursement characteristics were most frequently associated with prescriptions of NSAIDS and ASA. Patients in whom it was not possible to identify conditions related to prescription suitability were more frequently associated with OAT prescriptions.

PPI users considered suitable for prescription were more frequently subjected to EGDscopy and tests for the diagnosis of *H. pylori* infection. No differences were found between the two groups with regard to gender, frequency of malignancies or prescription of systemic steroids.

DISCUSSION

The results of this survey describe the actual prescribing behaviour of a large group of GPs related to the use of

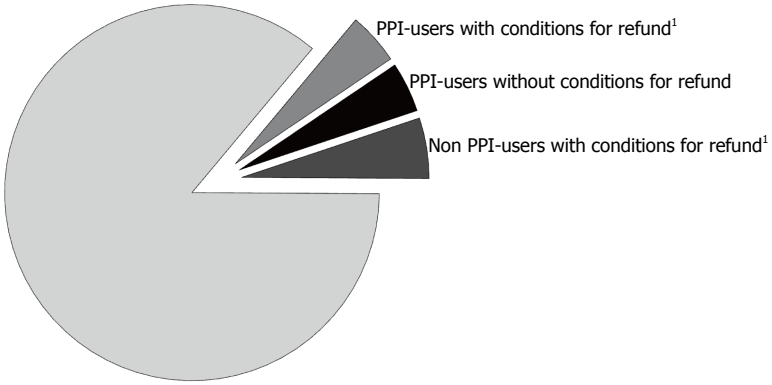

Figure 1 Subgroups of the population of the study divided according the use of proton pump inhibitors and the conditions for refund established by the Italian Drug Agency. [1]For the prevention of gastric damage of NSAIDS. Grey: PPI-users with refundable drug according the Italian Drug Agency because of protection of gastric damage by NSAIDS (4.5%); Black: PPI-users without identifiable refundable drug (4.6%); Dark Grey: Non PPI-users with identifiable need of the protection of gastric damage by NSAIDS (5.2%); White: The remaining population (85.7%); PPI: Proton pump inhibitors; NSAIDS: Non steroid inflammatory drugs.

Table 3 Characteristics of proton pump inhibitors-users with or without refundable conditions according to the Italian Drug Agency *n* (%)

	PPI refundable	PPI not refundable	*P* value
Patients	4383	1939	
Males	1762 (40.2)	758 (39.1)	ns
Aged over 64 yr	2967 (67.7)	935 (48.4)	0.01
Arthropathy	2717 (62.0)	1069 (55.1)	0.01
Heart disease	1263 (28.8)	411 (21.9)	0.01
Neoplasms	764 (17.4)	312 (16.1)	ns
Use of NSAIDS	333 (7.6)	83 (4.3)	0.01
Use of ASA	1857 (42.4)	150 (7.7)	0.01
Use of OAT	255 (5.8)	245 (12.6)	0.01
Use of systemic steroids	201 (4.6)	105 (5.4)	ns
EGDscopy	1984 (45.3)	642 (33.1)	0.01
H. pylori test	1232 (28.1)	409 (21.1)	0.01

All the features differ significantly ($P < 0.01$) between the two groups, except for gender, frequency of neoplasms and use of systemic steroids. PPI: Proton pump inhibitors; GERD: Gastroesophageal reflux disease; Heart disease: Heart failure, coronary ischemic disease, major heart valves disease; NSAIDS: Non steroid inflammatory drugs; ASA: Acetylsalicylic acid; OAR: Oral anticoagulant therapy; ns: Not significant; EGDscopy: Esophageal-gastro-duodenal endoscopy; *H. pylori*: *Helicobacter pylori*.

PPI drugs.

Unlike other analyses based purely on the assessment of administrative databases, this study allows a connection to be made between the prescription data and the records of clinical diagnoses. The analysis of a database of over 40000 patients allows us to highlight the fact that long-term prescription of PPI drugs is found in almost 15% of the population. These data are not dissimilar to those available on the whole Italian population[5], and show how PPI users present a number of clinical conditions (heart disease, cancer, arthropathy, use of ASA, OAT, systemic steroids, NSAIDS) which characterises them as a potentially fragile population. Epidemiological data showing an association between PPI and clinically dangerous conditions (*e.g.*, ischemic heart disease, renal failure, pulmonary disease) must therefore be interpreted with caution since PPIs could actually be used as markers of fragility (probably not always properly) in populations with a high prevalence of serious diseases[17-19]. It is very difficult to compare the prevalence of PPI users obtained in our work with that of other studies carried out on selected populations and in Countries with different health system, as highlighted by a recent study conducted in Sweden[20].

In any case, the main interest of this study concerns prescription suitability based on the requirements for reimbursement eligibility drawn up by the Italian Drug Agency. The methodology of the study has allowed the identification of potential reimbursement eligibility for 69% of PPI users. This is therefore a significant proportion of patients in an area of apparently poor suitability.

On the other hand over 2000 patients can be identified in the population of non-users who comply with reimbursement eligibility criteria for the prevention of damage caused by NSAIDs and over 3000 patients diagnosed with GERD or gastric/duodenal ulcers in whom the use of PPIs could be appropriate. There is therefore a need to rebalance PPI prescription patterns by reassessing patient characteristics according to overall suitability criteria[21].

The study data have made it possible to better define the characteristics of PPI users who are not suitable for PPI prescription. This population, as well as being comprised of younger patients and a lower prevalence of joint disease, heart disease and NSAIDS use, shows an extremely interesting higher prevalence of OAT use and no differences in the prevalence of cancer or use of systemic steroids.

This could indicate that the most effort to modify treatment in order to promote proper use of PPIs could be made among younger patients using OAT in the absence of further gastric hemorrhagic risk factors.

It is important to note that the current reimbursement eligibility criteria were drafted more than 10 years ago. Without an updated version it is difficult and disadvantageous to use PPIs in clinical conditions which are known to potentially cause serious gastrointestinal bleeding, such as the use of new strategies in antiplatelet and anticoagulation therapy[22] and the use of reuptake inhibitors of serotonin especially in conjunction with ASA and NSAIDS[23].

It should also be noted that these problems are widespread when used by hospital doctors[24-28], but the prescribing behaviour of GPs greatly influences PPI use since they are the main prescribers of the drug[29].

A study of the Italian College of General Practitioners showed that almost half of PPIs are suggested or encouraged by specialists, with different degrees of agreement depending on the disease and the type of specialist[30].

This study has limitations due to the retrospective method and due to the potential of poor accuracy of data logging which is typical to databases. In particular, clinical conditions related to prescription suitability such as the diagnosis of GERD or the use of ASA may not be recorded correctly, as due to their very low cost, some patients prefer to buy them without an NHS-paid prescription.

It should be noted that this study takes into account only the use of PPI and does not take account of the use of other drugs such as receptor antagonists H2.

A substantial number of patients who apparently do not meet prescription suitability conditions can be identified, but among non-PPI users on the contrary, it is possible to identify an equal number of patients for whom prescription would be suitable. It is possible that a large proportion of poor suitability can be identified in the population receiving OAT.

Even taking into account that the current rules of reimbursement eligibility in Italy have not undergone an adequate update in response to changes in the use of potentially gastrolesive medications, there is no doubt scope for decreasing inappropriate use of PPI drugs by adhering to certain criteria.

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COMMENTS

Background

Proton pump inhibitors (PPI) are among the most prescribed drugs in the world but it is often difficult to determine the prescription suitability of PPIs. The Italian National Health Service introduced rules to limit the reimbursement of these drugs that were draw up according to the conditions of proven effectiveness and following major international guidelines.

Research frontiers

Most studies showing a wide use of PPIs suspected for an inadequate compliance with the available scientific evidences are based on the analysis of administrative data. These studies cannot fully understand the relationship between clinical characteristics of the patient and the relative drug prescription.

Innovations and breakthroughs

The study clearly shows that most patients who do not meet prescription suitability conditions can be identified in the population receiving anticoagulant treatments. On the contrary, among patients not receiving PPIs, it is possible to identify an equal number of patients for whom prescription would be suitable.

Applications

The findings of this study can help the drug prescribers and the integrated units formed by specialists and general practitioners to identify specific areas of intervention to improve the suitability of the use of this class of drugs.

Terminology

There are five PPIs available in Italy (omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole). This study does not take account of the use of other drugs such as receptor antagonists H2. The population was divided into non occasional users of PPI drugs (PPI users) and non-users (PPI non-users) based on evidence of a prescription of at least 3 packs of PPIs in the last 90 d before analysis (1 pack = 14 tablets).

Peer-review

This is an interesting retrospective analysis of PPI use in Italy assessing adherence to the indications of the guidelines issued by the Italian Drug Agency.

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ORIGINAL ARTICLE

Observational Study

Transition care in inflammatory bowel disease: A needs assessment survey of Quebec gastroenterologists and allied nurses

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Author contributions: Strohl M initially compiled all the data from completed surveys, partook in statistical analysis and interpretation of data; additionally, wrote draft and was the first author of manuscript; Zhang X was responsible for statistical analysis of the manuscript and deriving summary descriptive data; Lévesque D conceived the idea of the survey, took part in designing the survey and assisted in draft revision and editing; Bessissow T was a major contributor to multiple revisions and edits and assisted significantly with fine-tuning the final draft.

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Abstract

AIM

To determine the tools needed and problems encountered during the transition of inflammatory bowel disease (IBD) patients from pediatric to adult gastroenterologists (GIs) in Québec, Canada.

METHODS

We conducted a needs assessment survey of Quebec health care professionals (HCPs). The survey was handed out to 136 Québec HCPs at a local conference in 2013. Additionally, it was emailed to any other HCPs in Quebec involved in caring for IBD patients. The completed surveys were compiled to derive descriptive data. Further specific subgroup analysis was then conducted.

RESULTS

Among the conference attendees and individuals emailed

77 (28.2%) completed the questionnaire. Respondents included adult GIs (61.3%), pediatric GIs (20.8%) and IBD nurses (18.3%). The majority of respondents believed that a standardized structure is important for a successful transition. Adult and pediatric GIs equally felt that patients were inadequately prepared for the transition (P = 0.6). There were significant differences between adult and pediatric GIs when it came to resource availability (55.6% *vs* 90.9%, P = 0.002) and perceived need of a formal transition clinic (21.7% *vs* 68.8%, P = 0.0006). Both transition program and medical summaries were identified as the most valuable tools to improve transition.

CONCLUSION

As described in previous studies, our survey reinforces the importance of a transition program, education for young adult IBD patients and the need to improve communication between adult and pediatric GIs.

Key words: Inflammatory bowel disease; Transition; Paediatric; Canada; Tools; Health care professionals

Core tip: Transition care and transfer of care from pediatric to adult realms is a major challenge with a paucity of published work in the inflammatory bowel disease (IBD) domain. Transition care varies across different health care systems but from other pediatric entities improved objective outcomes have been demonstrated with more effective transfer of care. This is the first published survey on health care professionals (HCPs) opinion on transition care in IBD in Canada. Barriers related to the patients from the HCPs were identified as were tools that if implemented have potential to improve the effectiveness of transition care. Differences between pediatric and adult gastroenterologists were also identified.

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INTRODUCTION

Inflammatory bowel diseases (IBD), which encompasses both ulcerative colitis and Crohn's disease are common pediatric idiopathic chronic diseases[1,2]. Estimates have shown that approximately 20%-30% of cases of IBD are diagnosed before the age of 18[2,3]. Data also indicate that the incidence and prevalence of IBD have both been increasing over time[4,5] and Canada has been shown to have one of the highest rates worldwide[5]. Hence there exists an inevitable need to manage this growing population and the chronic nature of the disease mandates to establish effective means of coordinating efficient transition care from the pediatric to the adult realm.

There are a number of significant differences between pediatric and adult systems most notably a paradigm shift from a dependent, multidisciplinary and family centered setting in pediatrics to an autonomous and self-reliant framework in the adult system[6-9]. Transition care as defined by the Society for Adolescent Medicine is the "purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health-care systems"[10]. Although lacking convincing objective evidence, there is expert consensus that a coordinated transition between the pediatric and adult realm is essential in the management of IBD[7,11-13]. Transition care provides adolescents the opportunity to acquire the set of skills required to succeed once they are integrated into the adult system. Numerous challenges, both patient and health care system related factors, currently exist making it difficult to consistently achieve successful transition care[9]. Particularly in Canada we face the challenge where patients are expected to become part of the adult system at the age of 18, as they are no longer eligible to be seen in a pediatric setting.

There remains a paucity of published literature on IBD transition. A number of publications have focused on surveying transitioning pediatric patients focusing on their knowledge of their medication, ability to identify associated adverse events, quantifying medication adherence and evaluating their capacity to demonstrate independence[14-16]. Health care providers perception has also been a focus of research to aid in identifying domains to target for transition care amelioration[11-13]. Certain tools guided at improving transition have also been studied such as The MyHealth Passport from the University of Toronto and TR$_x$ANSITION tool out North Carolina[17,18]. To date, no concrete data has been published demonstrating any improvement in a predetermined objective outcome variable with a dedicated standardized transitional care network.

In Quebec, the Transition to Adult care in patients with Crohn's and Colitis (TRACC) program has been established in collaboration between adult and pediatric gastroenterologists with the aim of facilitating and improving transition care in patients with IBD while trying to overcome some of the common obstacles encountered. Currently, in Quebec the age to initiate transition is variable with no standardized age of initiation. On the other hand, the age of transfer of care is fixed at 18 across the province. Previous studies have looked at adult and pediatric gastroenterologists (GIs) perspective of transition care, however no data exists on the perspective of adult and pediatric GIs in the Canadian health care system, more specifically from Quebec. Moreover all of the studies conducted have focused on the perception of transition and barriers to successful transition with none looking at specific tools that may be

of use to yield more successful transition care[11-13]. To our knowledge none of the published conducted studies on surveys focused specifically on needs assessment.

The primary objective of our study was to determine the necessary tools and obstacles encountered during the transition of IBD patients from pediatric to adult care from the perspective of health care professionals (HCPs) in Quebec, Canada. The information obtained *via* the survey will then serve as a basis for establishing methods to achieve more effective transition care. Secondary objectives included comparing pediatric and adult gastroenterologists and identifying any significant differences between the two groups.

MATERIALS AND METHODS

Study design

We performed a cross sectional needs assessment study that was conducted in the province of Quebec between November 2013 and August 2014. We intended to include all HCPs that care for pediatric and adult IBD patients. A total of 136 paper copies of the questionnaires were handed to all HCPs attending the annual association des gastroenterologues du Quebec (AGEQ) meeting in November 2013. In addition, through the contact list provided by the AGEQ, an email was sent to all members of the association (total of 206 individuals) of which included only board certified adult and pediatric gastroenterologists. Within this email it was specified to all members to not fill out and return the survey if they had attended the conference in November (a total of 96/206 members were at the conference). Members were all required to print out the survey and either mail it to our office or bring it by in person.

Survey/questionnaire

The questionnaire was intended to elicit the opinion of health care professionals on various aspects pertaining to transition care in pediatric patients with IBD. The questionnaire was developed by the TRACC committee, which is made up of adult and pediatric IBD specialists and expert IBD nurses. The questionnaire has not been previously validated but was developed to have a better understanding of the reality of transition care in Quebec. There is no validated questionnaire in existence geared at assessing health care provider perception of transition care in IBD. Certain components that were included in the two surveys previously published prior to our survey's inception[8-9] were also incorporated into our questionnaire. Basic demographic data was collected. With respect to age of transition care initiation and completion respondents were able to choose between different age choices (Initiation: 12, 13, 15, 16, 18; Completion: 16, 17, 19, 20). In addition respondents were asked to rank the degree of importance of different statements describing certain factors related to transition on a Linkert scale from 1 to 5, in which 1 represents "not important" and 5 represents "very important and essential". Additional questions were to investigate the current efficacy of transition through transmission of summary letters from the referring pediatricians what components should be included within the transfer note. The latter section of the questionnaire inquired about what tools, if implemented, would be perceived as beneficial in improving the quality of transition in Quebec.

Statistical analysis

All the completed surveys were compiled and entered into an Excel document, which was then used to derive summary descriptive data. Included in the summary descriptive data was subgroup breakdown. The response rate of every question varies as not all respondents answered all the questions. A respondent was included in the analysis if > 50% of the questions were answered (only 1 survey was excluded ultimately). Differences between subgroups on specific questions was explored using χ^2 analysis with the threshold for significance set at a $P < 0.05$. A two-tailed *T*-test analysis with the assumption of unequal variance was used when comparing means of two different groups for the two age-related questions.

RESULTS

Demographics of respondents

A total of 273 surveys were handed and 77 were filled out yielding a response rate of 28.2% (77/273). Respondents included adult gastroenterologists (GIs) (*n* = 47/77, 61%), pediatric GIs (*n* = 16/77, 20.8%), IBD nurses (*n* = 14/77, 18.3%). 41.6% of individuals (*n* = 32/77) worked in non-academic hospital setting while 57.1% (*n* = 44/77) work in academic centers while only 1 individual worked uniquely in an outpatient clinical setting. Looking at response rates of demographic subgroup based on total number of professionals in Québec 25.5% (*n* = 47/184) of adult GIs and 72.7% (*n* = 16/22) of pediatric GIs responded. With respect to experience 52.6% (*n* = 40/77) had greater than 10 years of experience, 23.7% (*n* = 18/77) had 5-10 years of experience and 23.7% had less than 5 years of experience (*n* = 18/77) (Table 1).

Importance and age of transition

Almost all respondents felt that a standardized structure for transitioning patients with IBD was important (97.4%, *n* = 75/77). Out of these 62.3% (*n* = 48/77) felt this was very important while 35.1% (*n* = 27/77) felt it was moderately important yet important enough to merit a standardized structure (Table S1). There was no significant difference on subgroup analysis comparing pediatric and adult GIs (*P* = 0.388). In terms of age to initiate transition and complete transfer of care from the pediatric to the adult domain the mean age was 16.2 ± 1.46 years and 18.2 ± 1.16 respectively amongst all respondents (Table S2). On subgroup analysis, pediatric GI believed transition should start earlier than adult GI

Table 1 Demographics of respondents

	# Of respondents (total *n* = 77)	Percentage
Profession		
Adult Gastroenterologist	47	61.0%
Peds Gastroenterologist	16	20.8%
Inflammatory bowel disease nurse	14	18.3%
Practice setting		
Academic center	44	57.1%
Hospital setting	32	41.6%
Outpatient	1	1.3%
Experience		
< 5 yr	18	23.7%
5-10 yr	18	23.7%
> 10 yr	40	52.6%

with mean ages of 15.4 ± 1.41 *vs* 16.7 ± 1.27 years (P = 0.003). Age of transfer completion was similar between adult and pediatric GIs with mean ages of 18.2 ± 1.25 and 18 ± 1.1 respectively (P = 0.47).

Adequate preparation for transition

The majority of respondents (58%, n = 45) felt that patients were inadequately prepared prior to being transferred from the pediatric to the adult system. This held true with stratification as pediatric (n = 11/16, 68.8%) and adult GIs (n = 25/44, 56.8%) equally felt that patients were inadequately prepared for (P = 0.4). Amongst all respondent's lack of maturity (n = 46, 60%) and independence of the patient to advocate for their needs (n = 40, 51.9%) were the 2 general domains attributed to the perceived inadequate preparation. In terms of specific factors the following were rated as the most important on the Linkert scale (mean score > 4.5): Patient's knowledge of IBD in general (mean = 4.6) and their particular disease (site affected, medication history, treatment side effects *etc.*) (mean = 4.6), patient responsibility in taking their medication (mean = 4.7), partaking in discussions during doctor visits (mean = 4.7), being able to recognize when their disease may be active and who to contact (mean = 4.8) and understanding the impact of tobacco and drugs on their condition (mean = 4.6) (Table S3)

Tools to improve transition

A significant amount of adult GIs (37%, n = 17/46) stated they do not receive enough information regarding new incoming IBD patients from the referring pediatric GIs.

The vast majority (82.6%, n = 38/46) of adults GIs prefer to obtain a chart summary prior to the first visit as opposed to at the moment of the first rendezvous.

Among a variety of tools listed which could potentially be implemented by the transition network in Québec (TRACC), a transition program (77.3%, n = 59/76) and medical summaries (76.2%, n = 58/76) were felt to be the most important. On subgroup analysis 71.7% of adult GIs and 93.8% of pediatric GIs felt that a transition program would be a useful tool (P = 0.07) with 84.7% and 62.5% respectively choosing medical summaries as important tools (P = 0.06). A structured educational day on transition care for patients and their families (47.4%, n = 36/76) was also considered useful. A checklist prior to the first adult visit was also considered important (54%, n = 41/76). Surprisingly a dedicated transition clinic, which was not clearly defined to respondents but rather listed as a response (32.9%, n = 25/76) was not perceived to be as important as some of the other tools amongst all responders (Table S4). However on subgroup analysis it became apparent that this was a more important tool amongst pediatric GIs. Only 21.7% of adult GIs compared to 68.8% of pediatric GIs selected dedicated transition clinics as being important in transition (P = 0.00006) (Table 2).

Training and resources

The majority of respondents (75.3%, n = 52/69) felt that they had adequate training to effectively deal with transitioning patients in IBD. On subgroup analysis it became apparent that IBD nurses felt less prepared compared to both pediatric and adult GIs (P = 0.005, P = 0.02 respectively). When looking at the adult GIs (78.3%, n = 36/46) compared to pediatric GIs (100%, n = 10/10) there was a trend towards significance with the adult GIs tending to feel less adequately trained (P = 0.10). Sixty percent (n = 41/68) of all respondents were interested in more training *via* either workshops (23.5%, n = 16/68) or conferences (44.1%, n = 30/68).

Amongst all respondents 64.1% (43/67) felt that they had sufficient resources to manage transitioning IBD patients. However there was a significant difference on subgroup analysis between pediatric GIs (90.1%, n = 10/11) compared to adults GIs (55.6%, n = 25/45) when it came to the opinion of adequate resources available (P = 0.0016) (Table 3). With respect to adequate resources no specifics were detailed, rather this was a general feeling amongst respondents.

DISCUSSION

Our survey of Quebec HCPs working with IBD patients reinforces the notion that a standardized structure for transition is felt to be important. It revealed specifically what HCPs felt were patient related factors that limit effective transition, emphasized the significance of having a dossier summary and identified that a transition program, medical summaries, and potentially a dedicated educational day for patients if routinely implemented might be able to improve transition care in Quebec.

Similarly to previously conducted studies, our survey revealed similar results with respect to patient related factors that are most important for successful transition, including patient's knowledge of their condition and their independence in managing their disease with

Table 2 Select subgroup analysis between adult and pediatric gastroenterologists

	Adult	Pediatrics	*P* value
Importance of transition (moderately or very important)	95.70%	100%	0.39
Age related questions			
Mean age to initiate transition	16.7	15.4	0.003[1]
Mean age to complete transfer of care	18.2	18	0.47
Are patients well prepared for transition?	56.80%	68.80%	0.4
Transition tools			
Transition programs	71.70%	93.80%	0.07
Medical summaries	84.80%	62.50%	0.06
Transition clinics	21.70%	68.80%	0.0006[1]
Pre rendezvous checklists	47.80%	56.30%	0.56
Training and resources			
Adequate training	78.30%	100%	0.1
Sufficient resources	55.60%	90.90%	0.0016[1]

[1]Variable statistically significant with *P* value < 0.05.

Table 3 Training and resources

	Respondents	Percentage
Adequate training (*n* = 69)	52	75.30
Interested in more training (*n* = 68)	41	60.00
Training *via* workshops (*n* = 68)	16	23.50
Training *via* conferences (*n* = 68)	30	44.10
Sufficient resources (*n* = 67)	43	64.10

adequate self-management skills[11-13]. Currently there is limited evidence in the literature of improved objective clinical outcomes in patients with IBD who partake in a structured transition program[9]. However, there is substantial objective evidence that has shown that transitional care can improved clinical outcomes in other pediatric chronic diseases such as diabetes mellitus type 1 and in liver transplant patients[19-22]. By comparison one can stipulate that *via* transition care in IBD their lies significant potential in improving outcomes such as decreasing rate of hospitalization, improving medical compliance, and even improving other objective outcomes. Further studies focused on IBD related transition care are warranted to demonstrate this.

In the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPHAGN) position paper one of their key recommendations was that the pediatric GIs provide a medical summary to their adult colleagues prior to the first consultation with them[6]. This study reveals that despite these recommendations a substantial proportion of adult GIs (38.2%) feel that they obtain inadequate information prior to their first encounter. No published or collected data currently exists in Québec about what percentage of adult GIs obtain summaries prior to or at the time of transfer of care. In terms of specific tools identified transition program and medical summaries were the two identified in our survey as important for successful transition care. Examples of such tools exist such as My Health Passport developed at the University of Toronto that serves as succinct summary of a multitude of chronic pediatric disease including IBD that a patient may bring with them to any encounter with health care professionals[23]. This tool was designed to be completed by the patient thereby providing the opportunity of the transitioning adolescent to educate themselves while encouraging independence[17]. The implementation of a tool such as My Health Passport has the dual benefit of acting as a dossier summary for the adult GI and as a method of improving knowledge and inspiring independence.

Respondents also identified a checklist pre 1st adult visit (52.2%) and a "readiness checklist" (39.2%) as other important tools, which provide potential in assisting transition. The TRxANSITION tool created at of the University of North Carolina serves the purpose of being a "readiness" tool with the goals of identifying whether or not a patient is adequately prepared to transition to adult care[18]. This tool also assists in identifying particular aspects that need to be addressed for transition care optimization.

As was the case in Hait *et al*[11] survey ours identified that a proportion of adult gastroenterologists (21.7%) felt they were inadequately trained to manage the population of transitioning IBD patients. Our data also showed that despite a high proportion of respondents felt they were adequately trained (60%) the majority of them were interested in more training *via* conferences or workshops (67.6%) The survey also highlighted an important difference between adult and pediatric GIs when it comes to the availability of resources (55.6% *vs* 90.9%, *P* = 0.002). This finding is consistent with what is seen in the real world practice of many adult GIs in Quebec where additional resources such as Registered Dieticians, IBD nurses, psychologists are more difficult to access in comparison to pediatrics. By implementing a standardized program for transition care there may be potential to facilitate the ability to access additional resources in the adult system.

Our study had a number of limitations. As with any survey study ours was limited by non-response bias given the response rate of 28.2%. This has the

potential of selecting out HCPs who may place less of an importance on transition care. The small sample size of the survey also limits our study's strength. In addition our study may be limited in interpretability in other geographical locations as it was intended on only assessing the current status in Quebec. Our survey was solely focused on the health care provider perception. It would be interesting to use our compiled data in conjunction with a patient based perspective which may offer the best opportunity to more clearly identify exactly where to focus our resources and which tools may be most useful in improving transition care.

As described in previous studies, our survey reinforces the importance of a transition program, education for young adult IBD patients and the need to improve communication between adult and pediatric GIs. A structured and standardized transition network offering appropriate and applicable tools is the cornerstone to optimize adherence to transition tools and ensure a genuine clinical impact for a successful transition. Further studies are warranted which will likely provide additional objective evidence of the importance of effective transition care.

COMMENTS

Background

Inflammatory bowel diseases (IBD) are showing a rising incidence an prevalence in many areas of the world. Therefore, there is an inevitable need to manage this growing population and the chronic nature of the disease mandates to establish effective means of coordinating efficient transition care from the pediatric to the adult health care domains.

Research frontiers

To date there is minimal data on the perception of transition and transfer of care of IBD patients from pediatric to adult care. Improved objective outcomes with amelioration of transition care have been demonstrated in other chronic diseases spanning pediatric life and adulthood.

Innovations and breakthroughs

As with previous survey studies looking at transition care in IBD the authors' study found that there is a lack of communication between pediatric and adult gastroenterologist with suboptimal transfer of information. This study compared pediatric and gastroenterologists and revealed significant differences between the two group's perspective of transition care. Notably it identified a significant discrepancy in terms of resource availability.

Applications

Similar to previous studies the authors' survey reinforces the importance of a transition program, education for young adult IBD patients and the need to improve communication between adult and pediatric gastroenterologists. A structured and standardized transition network offering appropriate and applicable tools has the potential to offer a genuine clinical impact for a successful transition. The idea of focusing more resources on transition of care to improve objective outcomes is applicable to many diseases and spans many different health care systems.

Terminology

Transition is defined as a process that spans before and after the transfer of care. Transfer of care is the formal process of transferring the care of a given patient from one health care professional to another.

Peer-review

The study was conducted by assessment of the survey among 136 health care professionals involved in caring for IBD patients. The findings revealed that the pediatric patients were inadequately prepared for the transition, thus indicating the importance of an educational program for young adults with IBD.

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