# Urinary tract infection in primary care

## How doctors deliver care is as influential as the treatment itself

MAX TACTIC/FOTOLIA

RESEARCH, pp 405, 406, 407, 408

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On the face of it, urinary tract infection seems to be a straightforward clinical presentation with an equally straightforward therapeutic response. Unlike other symptom constellations for which antibiotics are prescribed in primary care, bacterial infection is more likely to be present than not and empirical treatment is cost effective.[1 2] The problem with empirical treatment is that 10% of the healthy adult female population would receive antibiotics each year. The use of antibiotics to this extent in the population has implications for antibiotic resistance. Three linked studies assess the management of urinary tract infection in primary care,[3-5] and one assesses the cost effectiveness of different management strategies.[6]

Research in this area focuses on strategies for reducing the use of antibiotics. This highlights the tension between maximising the benefit for individuals and minimising antibiotic resistance at a population level. In studies of treatment, diagnosis and cure were traditionally defined in bacteriological rather than symptomatic terms, on the assumption that people with detectable infection would benefit whereas those without infection would not. However, evidence indicates that many women with bacteriological urinary tract infection will recover without antibiotics.[7] In addition, around a third of women who present with clinically identical symptoms of urinary tract infection do not have detectable bacteriological infection[8] but do have a symptomatic response to empirical antibiotics.[9 10] This effect persists even when low count bacteriuria is accounted for.[11]

The two linked studies by Little and colleagues[3 4] are useful in this respect, because they look beyond microbiological definitions of diagnosis and cure to tease out both the natural course of the illness and the value of different therapeutic approaches in terms of what matters to patients—symptoms.

Strategies to reduce antibiotic use have included clinical diagnostic algorithms and urine dipsticks to predict who has bacteriological urinary tract infection more precisely, as well as delayed prescription strategies. The first linked study is a randomised controlled trial that compares four permutations of these treatment approaches with empirical prescription—delayed prescription to use after 48 hours if necessary, treatment based on a clinical algorithm, treatment based on a dipstick test algorithm, and in the fourth group, treatment based on urine culture results.[3] The last three options also provided delayed prescriptions for those not receiving immediate antibiotics.

In terms of discriminating between them, the treatment approaches made little difference to the severity of symptoms or to treatment costs to the funder but both symptom duration and antibiotic use differed.[3 6] Use of the clinical algorithm based on a symptom score did not significantly reduce antibiotic use. A modest reduction in antibiotic use was seen in the other three arms, but this was offset by an increase in symptom duration when antibiotics were delayed by 48 hours or more, particularly in the urine culture arm. This is important—any potential population benefits from reducing antibiotic use must be balanced not only against the distress caused by the prolongation of symptoms for the individual but also in lost productivity, which is a substantial cost.[12]

The second study confirms previous findings that in vitro resistance is associated with an increase in symptom duration, in this case severe symptoms.[4 13 14] Women with previous cystitis and more severe initial symptoms also had a longer illness. The proportion of symptomatic women with no identifiable bacteriological infection (36%) was similar to that found in previous studies and 9% took no antibiotics.

The most interesting finding from this study is the reminder of what is often forgotten—that it is not just what is done that matters but how care is provided. Symptoms were less severe and of shorter duration when the doctor took a positive approach to diagnosis and prognosis, whereas, intriguingly, using what seemed to be a patient centred approach when communicating had no effect.[4]

What should clinicians do on the basis of these findings? Sending midstream urine samples for testing is clearly unhelpful and expensive. The approach beyond that is not clear. For funders the approach taken makes little difference to the cost.[6] Empirical prescription, delayed empirical prescription, and prescription based on dipstick results (with back up delayed prescription) are all rational options for different reasons. The patient's situation and preferences determine which approach will probably be most helpful, as shown in the third linked qualitative study by Leydon and colleagues.[5] Delayed empirical prescription or dipstick guided delayed options will reduce the likelihood of the patient having to take antibiotics at all, but delaying antibiotics by two or more days increases the risk for the patient that more severe symptoms will be prolonged. Women can also be warned that if their initial symptoms are severe or if they have had cystitis before, they are likely to have severe symptoms for at least three days.

Most importantly, in an age of protocols and targets, Little and colleagues' studies show that the way a doctor provides care can enhance the effectiveness of treatments. The preoccupation with diagnosis and therapeutic goals can obscure the wider aspects of therapeutic influence. This influence is above and beyond that created by the perception of being given a treatment, the traditional notion of the placebo effect.[15] Research is needed into this interface of care

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Trish Groves talks to Paul Little about this group of papers, which compare management approaches for urinary tract infections, look at their cost effectiveness, and analyse patients' reactions. Listen at podcasts.bmj.com/bmj


and science in medicine, as well as into identifying which patients are most likely to benefit from treatments and, more importantly, those who will not benefit.

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# The prognosis for research

## Improve research through training, and begin with editors

**RESEARCH METHODS AND REPORTING, p 410**


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The costs of mistakes in biomedical research include the opportunity cost of misallocated resources and direct harm that leads to suboptimal prevention and treatment. Some scientists have recently questioned the quality of clinical and epidemiological research[1-3]; in the linked article, Hemingway and colleagues highlight "the tide of low quality, low impact, prognosis research."[4] They outline 10 steps to improving such research, and they include in their recommendations the advance registration of study protocols and new guidelines for reporting the results of prognosis research.

The main areas of clinical research encompass studies of diagnosis, prognosis, and treatment. Why should prognosis research be singled out? If the overall aim of clinical research is to improve prognosis, the path towards that end involves accurate diagnosis and effective treatment. With improving diagnostic techniques and evolving treatments, prognosis research may always be in flux and out of date. Indeed, if prognosis research for a disease is current and accurate, it might imply that prevention and treatment for that disease are stagnant.

No doubt the quality of much prognosis research could be improved, but we wonder why this area merits special mention. Problems affecting the quality of research are not restricted to studies of prognosis. Among the many factors that influence research quality throughout the spectrum of biomedical studies are the consistency and quality of training, the vagaries of research funding, the independence of investigators, and the adequacy of peer review. Also pervasive is a system of academic promotion influenced more by the number of publications than by quality, which increases the demand for output of whatever quality.

Thus we suggest that the factors affecting the quality of prognosis research are facets of more general concerns confronting biomedical researchers. We doubt, however, that easy general solutions can be found. Consider the suggestion by Hemingway and colleagues that all human studies should be driven by protocol, and that these protocols should be registered in advance. Their idea is to emulate the registration of clinical trials, which is intended to reduce selective publication and resulting publication bias. Trial registration is now required by law,[5] the Declaration of Helsinki,[6] and the International Committee of Medical Journal Editors.[7] But should it be extended to other types of research? We suspect that historians and philosophers of science would recoil at the notion that advance registration of all scientific studies in a publically accessible database would produce better science. How much room would this policy leave for exploration, serendipity, or pursuit of unpopular theories? Following the lead of Cole's "hypothesis generating machine,"[8] researchers might be well advised to write a programme that would register every study idea imaginable within their purview, just to be on the safe side. If the rules precluded easy registration, that might create an undesirable drag on the end of the research spectrum that constitutes the quirky, brilliant work that is not enterprise driven. Moreover, registration would not prevent publication bias among the many studies conducted with secondary data, because researchers could still selectively register study ideas after the data have been explored.

Another suggestion offered by Hemingway and colleagues is to formulate guidelines for reporting prognosis research. Reporting guidelines do have advantages, but the disadvantages are generally overlooked. On the positive side, guidelines increase uniformity and can improve the average quality of reporting. But guidelines also promote rigidity and can enshrine misconceptions, because they are merely compiled from the consensus of a few opinion leaders and form a common denominator of current beliefs. If all science throughout human history had been filtered through reporting guidelines,

we suspect we would live in a very different world, one in which the science had lagged far behind what actually has been achieved. Philosophers still disagree over the rules for how science is conducted. One of them eschewed the existence of any method in science, "[G]iven any rule, however 'fundamental' or 'necessary' for science, there are always circumstances when it is advisable not only to ignore the rule, but to adopt its opposite."[9] This view may be extreme. But who would suggest that any set of guidelines for a process as complicated as the scientific method would offer perfect guidance? At the very least, guidelines need frequent updating to keep pace with the evolution of research methods.[10]

As Hemingway and colleagues note, good quality data are important for valid research. They acknowledge, however, that it might be more fruitful to use secondary data sources, such as registries, than to incur the costs of collecting expensive primary data and following the cohort over a long time. But should all study protocols that are or could be conducted within such secondary sources be registered, along with guidelines for reporting the results from such studies? We hope not.

The strongest argument for imposing guidelines is to help researchers reduce both systematic and random error. To accomplish this end, guidelines would require keen understanding of research methods and a development of basic concepts. Such development is lagging behind in the area of prognosis research. For example, few attempts have been made to conceptualise overall determinants of disease outcomes. Five groups of determinants have previously been suggested: the illness, diagnostic tests, potential treatments, clinical performance, and patient compliance.[11] Unfortunately, neither these nor the suggested 10 steps from Hemingway and colleagues include comorbidity, often a powerful determinant of prognosis.[12] The formulation of guidelines might be best deferred until their conceptual basis is further developed.

Surprisingly, improved training of researchers was not on the list of suggested solutions. We think improved training would ultimately bring greater benefits than any measure on the list, although these benefits would be deferred. Meanwhile, consider the crucial role of the gatekeepers of published research. Any published research, including the low quality work that Hemingway and colleagues bemoan, has survived the scrutiny of peer reviewers and of the ultimate gatekeepers, journal editors. Perhaps the priority should be continuing education efforts focused on journal editors. We believe that step would improve the quality of published research faster than any other intervention.

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# Registration of observational studies

## The next step towards research transparency

**EDITORIAL, p 374**
**RESEARCH METHODS AND REPORTING, p 410**

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Observational studies, such as cohort and case-control studies, are an important form of medical research, but they are also vulnerable to bias and selective reporting.[1] They often produce large datasets that can be subjected to multiple analyses. Researchers may then craft a paper that selectively emphasises certain results, often those that are statistically significant or provocative. These decisions may reflect strong financial or academic interests and prior beliefs. At present, consumers of observational research cannot easily distinguish hypothesis driven studies from exploratory, post hoc data analyses. Researchers do not routinely disclose the number of additional analyses performed. Nor is there any satisfactory way to know whether the research questions or methods of statistical analysis diverged from those initially planned. It has been observed that there is "little or no penalty" for data dredging and selective reporting. Rather than attracting censure it can "get you into the *BMJ* and the Friday papers."[2]

In the linked article, Hemingway and colleagues reinforce many of these arguments, particularly with respect to studies of prognosis, because these can be important clinically but are often flawed.[3] This group, which includes two of the *BMJ*'s statistics editors, Doug Altman and Richard Riley, recommends that "all research on humans should have a protocol." Such calls for registries of observational research are gathering pace, and indeed an international meeting held in London last September was devoted entirely to the discussion of such registries and other efforts to improve the credibility of observational research.[4 5]

The *BMJ* publishes a large amount of observational research and has an important stake in its quality. We are now actively supporting the registration of observational

study protocols and results in publicly accessible registries. Although the *BMJ* does not advocate one particular registry, we note that around 14 000 observational studies are already registered with clinicaltrials.gov, and that the results of such studies can be posted there too, as is already the case for clinical trials.[6] The development of registries for randomised trials was driven by several ethical and scientific concerns, not just by the desire to prevent suppression of unfavourable results (box).[7] We feel strongly that most of these points also apply to observational studies.

We recognise the lack of consensus on this proposal. In a linked editorial, Sørensen and Rothman express concerns that the insistence of journals on protocols and registration would be too restrictive, and they argue that peer reviewers and editors are as much to blame as researchers for the publication of low quality work.[8] There are legitimate worries, too, that prioritising protocol driven studies might discourage publication of genuinely important results that emerge from data mining or that it might have other unintended negative effects because "subgroups and multiple analyses are a necessary part of observational research: otherwise, one cannot make new discoveries, nor quickly check discoveries by others."[9] We agree that exploratory observational research is important. Many new ideas arise from unexpected findings in observational research, and many researchers learn their skills from examining available datasets. However, that is not the sort of research the *BMJ* usually aims to publish; rather, we give highest priority to studies that provide strong support for inferences applicable to clinical practice. We think the case against data driven observational studies is particularly compelling under these circumstances.

We understand concerns that extending these rules to observational studies might encourage editors—particularly of general journals—to be overzealous or clumsy in their application. The STROBE statement has improved reporting of observational studies by asking authors to spell out in their papers exactly what they did during their studies.[10] It asks authors to "explain the scientific background and rationale for the investigation being reported" and "state specific objectives, including any prespecified hypotheses." As journal editors, we have probably not paid enough attention to emphasising these points, but we aim to do so from now on. However, like most reporting statements, STROBE is aimed at improving the clarity of study reporting and comes too late to influence study design.

For these reasons, we will now ask authors of papers reporting observational studies submitted to the *BMJ* to tell us more about the origins, motivations, and data interrogation methods of that work. This may not be appropriate for all observational studies, and we aim to apply the policy in a flexible and thoughtful manner. We would not reject an observational study just because it did not have a prespecified hypothesis, but we would want the exploratory nature of its research question, and its design, to be fully reported.

Among other things, we will be asking authors to report in their papers a clear statement of whether the study hypothesis arose before or after inspection of the data (and, if afterwards, we will need an explanation of steps taken to minimise bias); we will ask to see study protocols if they exist; and we will add to the papers' abstracts their registration details, if they have been registered. If the study is registered we will ask whether the protocol was registered before data acquisition or analysis began.

Registration of observational studies is just one of many changes needed to increase confidence in observational research, but we believe it is the crucial next step. The aim is to facilitate the design and reporting of observational research, not to hinder it. Trial registration has had a substantial and important positive effect on the design, conduct, and reporting of randomised clinical trials, and we believe it is time to extend those benefits to observational research.

**Rationale for registration of clinical trials**[7]

**Ethical**

Respect the investigator-participant covenant to contribute to biomedical knowledge by making trial methods and results public
Provide global open access to information
Reduce unnecessary duplication of invested research resources through awareness of existing trials
Assure accountability with regard to global standards for ethical research
Enable monitoring of adherence to ethical principles and processes

**Scientific**

Increase the reliability and availability of evidence on which healthcare decisions are based
Improve trial participation
Increase opportunities for collaboration
Ensure transparency of trial design and methods
Provide open review of protocols to improve trial quality and refine methods
Provide means for identification and prevention of biased under-reporting or over-reporting of research
Accelerate knowledge creation

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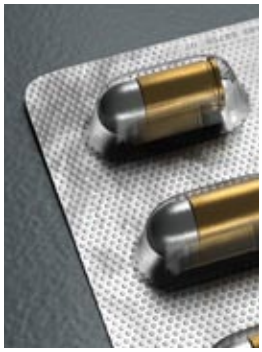
# Withdrawal of sibutramine in Europe

## Another sign that there is no magic bullet to treat obesity



DAVID PARKER/SPL

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**Competing interests:** GW previously (up to 2003) had support for preclinical and clinical research, accepted honorariums to speak at meetings, and acted as a paid scientific and medical adviser to various drug companies, including the manufacturers of sibutramine.

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The therapeutic cupboard containing antiobesity drugs has never been well stocked. The European Medicines Agency (EMA) recently decided that sibutramine must follow the example of rimonabant, withdrawn last year because of safety concerns.[1] This leaves just one drug—orlistat—to face the rising tide of obesity across the continent. The demise of sibutramine carries both irony and wider messages for the management of obesity.

Sibutramine fell at the crucial hurdle of cardiovascular risk. Arterial disease—which leads ultimately to myocardial ischaemia, heart failure, and stroke—affects most obese people to some degree and is their major cause of death.[2] Much evidence suggests that weight loss decreases morbidity and mortality associated with cardiovascular disease,[3] and this is an important justification for all antiobesity measures, including drugs. Unfortunately for sibutramine, an interim analysis of the SCOUT (Sibutramine Cardiovascular Outcome Trial) study found that the drug increased morbidity from cardiovascular disease.[1]

The odds were always stacked against sibutramine, because cardiovascular risk is embedded in its mechanism of action. Sibutramine acts centrally to reduce food intake; it inhibits the presynaptic reuptake and degradation of serotonin and noradrenaline, thus enhancing the appetite suppressing actions of both neurotransmitters. Noradrenergic stimulation spills out beyond the circuits that regulate appetite and increases sympathetic drive to the cardiovascular system.[4] The resulting "fight or flight" responses of raised blood pressure and pulse rate are mostly mild, but some patients—who cannot be predicted—show increments of more than 20 mm Hg in systolic or diastolic blood pressure and more than 20 beats/min in pulse rate.[5] Moreover, even small rises in blood pressure and pulse rate (which is an independent predictor of myocardial infarction)[6] are associated with increased cardiovascular risk.

Given this background, the SCOUT study was an act of faith. It exposed older obese patients (≥55 years), deliberately selected for high cardiovascular risk, to sibutramine for five years—five times the maximum licensed duration of treatment.[7] Providence was tempted and duly rose to the bait. In line with the 2% annual event rate expected in this population, 10% of controls had a fatal or non-fatal cardiovascular complication. The rate among participants treated with sibutramine was 11.4%, 16% higher than in controls. The balance was essentially tipped by non-fatal myocardial infarction or stroke in 70 patients out of a total study population of about 10000, but the P value was small enough (0.023) to end the drug's life in Europe. In the United States, the Food and Drugs Administration (FDA) is suspending judgment until the definitive results of SCOUT are published later this spring.

SCOUT was a vast and costly study, suggesting that its manufacturer considered this a risk worth taking—perhaps in an all or nothing attempt to clear sibutramine of its cardiovascular taint. None of the other manufacturers of antiobesity drugs signed up for such a long term study of efficacy and safety; with its patent now expired, orlistat, the last man standing, will never be put to this crucial test.

The FDA has stated that SCOUT was "the first study ever to attempt to prove that anti-obesity drugs can reduce cardiovascular risk."[8] Unfortunately, this notion is obviously flawed—because of its inherent cardiovascular side effects, sibutramine cannot be used to test the hypothesis that weight loss can decrease cardiovascular risk. This is a vital question to ask, as some research, including studies from the revered stable of Framingham,[9] has reached the counterintuitive conclusion that weight loss may increase cardiovascular morbidity and mortality.[3] As well as testing sibutramine to destruction, SCOUT has left behind a mess of data that are impossible to interpret. We cannot know whether the increased risk is caused by the specific properties of sibutramine or by the modest degree of weight loss achieved by antiobesity drugs somehow damaging arteries.

Meanwhile, the world moves on. Within a few days of the EMA's decision, the story had disappeared from Abbott's website, to be replaced by the upbeat news that their share price had risen (coincidentally by the same percentage that sibutramine increased cardiovascular risk). And in the best tradition of abandoned antiobesity agents, sibutramine is still readily available on the internet.

The effect on the drug industry will be interesting to follow. Originally developed by Boots as an antidepressant, sibutramine was sold on as an antiobesity drug to Knoll and then Abbott. During its nine year lifespan, it will not have recouped the several hundred million pounds invested in bringing it to market. When sibutramine joins all the other weight-reducing drugs that have been dumped in unmarked graves because they don't work or are dangerous, Abbott will be yet another drug company to be shot in the foot by a sometime magic bullet against obesity. This could well induce terminal pessimism in the drug industry, especially as the past quarter century of frantic drug discovery has yielded just one surviving antiobesity compound that has failed to generate therapeutic or financial excitement.

One of the safest bets in medicine is that obesity is here to stay. The fate of sibutramine reminds us how little antiobesity drugs have had to offer—at best, a reduction of a few per cent in the total burden of excess weight carried until death. With energy homoeostasis so deeply enmeshed in physiology, it has always seemed unlikely that a magic bullet could ever switch off food intake without hitting something vital. Now, that elusive circuitry is even better protected behind the comfortable barrier of sofa, junk food, drink, and screen based entertainment.

Perhaps the time has come for us to face reality and admit defeat. Like climate change, nuclear waste, and other side effects of our current version of civilisation, we shall just have to learn to live with obesity and its hazards.

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- Editorial. Orlistat over the counter (2007;335:1163-4)
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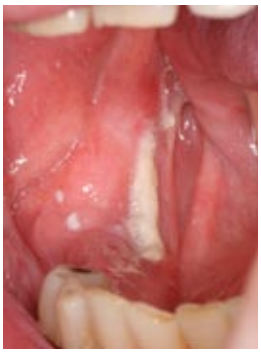
# Osteonecrosis of the jaw and bisphosphonates

## Low doses for osteoporosis seem to be safe



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Bisphosphonate associated osteonecrosis of the jaw is defined as exposed bone in the maxillofacial region for more than eight weeks in the absence of radiotherapy but the presence of bisphosphonate use. The condition is diagnosed clinically with exclusion of local malignancy. Other conditions may present in a similar manner, and these include spontaneous sequestration or lingual mandibular sequestration and ulceration, which is characterised by exposed necrotic bone at the level of the mylohyoid ridge of the lingual mandible. This condition is self limiting and heals spontaneously within three days to 12 weeks.[1]

Other important risk factors for the development of osteonecrosis include local infection, chemotherapy, steroid use, trauma, and periodontal disease.[2] Bisphosphonates are commonly used in the management of skeletal complications of malignancy, and treatment with high dose bisphosphonates has been associated with an increased risk of osteonecrosis of the jaw in patients with cancer.[3-7] In this population, the estimated incidence of osteonecrosis is between 1% and 15%, and it seems to be related to the dose and duration of bisphosphonate treatment.

In patients with osteoporosis, much lower doses of bisphosphonates are used, and a causal link has not been established between low dose oral or intravenous bisphosphonates and osteonecrosis of the jaw.[8] The incidence seems to be between 1 in 10 000 and less than 1 in 100 000 person years of exposure,[9 10] which may be similar to the incidence seen in the general population.[11]

With increased awareness of bisphosphonate associated osteonecrosis of the jaw, cases of spontaneous ulceration are possibly being misclassified as this condition. Further prospective data are needed to quantify the incidence of osteonecrosis of the jaw in the general population and in those receiving high and low dose bisphosphonates.

Multiple factors have been implicated in the development of osteonecrosis of the jaw. The exact mechanism by which high doses of bisphosphonates increase the risk is not fully understood. Local trauma caused by a tooth extraction in the presence of impaired osteoclast function (which can be the result of several factors) may cause inadequate clearance of necrotic debris. Secondary infection may also facilitate the development of local osteonecrosis. Bisphosphonates may have toxic effects on local soft tissue and impair the function of epithelial and vascular cells, which may prevent soft tissue healing and closure after dental surgery and contribute to the development of local osteonecrosis.[12] Osteonecrosis of the jaw can present with local pain, soft tissue swelling, and inflammation, which can progress to fistulas and pathological fractures.

International strategies on prevention and treatment exist, but they are based on expert opinion and anecdotal evidence because of the lack of prospective data. Recommendations emphasise the importance of an oral examination with radiographic visualisation of the mandible and maxilla before starting high dose bisphosphonates in patients with cancer. Treatment may need to be interrupted in the presence of a dental emergency, and this situation should be managed by the medical, dental, and oncology team.

Regarding prevention, it is important to emphasise good oral hygiene and semiannual dental assessment in all patients taking bisphosphonates. Patients should also be encouraged to stop smoking and limit alcohol intake. If possible, any necessary dental work should be completed before starting treatment with bisphosphonates. If a dental procedure is necessary, bisphosphonates should ideally be discontinued three months before the procedure and resumed after the surgical site has healed. Bisphosphonates should be stopped immediately before an emergency dental procedure and resumed once the surgical site has healed.[8]

Treatment of osteonecrosis of the jaw focuses on treating secondary infections, providing suitable analgesia, and ensuring appropriate nutritional intake—tube feeding should be considered if the oral lesions prevent food intake. Surgery is reserved for removal of necrotic debris with limited debridement. Further prospective studies are needed to provide evidence based guidelines on the prevention and management of this uncommon condition.

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