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THERAPEUTICS

Newer insulins in type 2 diabetes

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com.

A 68 year old woman with a body mass index (weight (kg)/(height (m))^2) of 31 has a five year history of type 2 diabetes. She is reasonably active but takes treatment for hypertension, hyperlipidaemia, and angina. She has signs of early diabetic background retinopathy. Her current treatment for diabetes is with metformin 850 mg twice daily and gliclazide 160 mg daily. Her haemoglobin A_{1c} (HbA_{1c}) concentration has risen from 0.076 to 0.085 over the past year, and she is keen to improve her glucose control.

After review of her diabetes management, she opts for insulin as the next step in treatment. She mentions that a friend has just started a special new insulin and wonders if that is what she will be taking too. After discussion of the evidence for insulin analogues, she agrees to start taking isophane insulin rather than an analogue.

What are the insulin analogues?

In health, glucose control is achieved by feedback regulation, such that food intake is matched by sharp spikes of insulin, and the glucose concentration remains stable between meals because of regulated basal insulin secretion. By contrast, injected insulin has no feedback regulation, enters the systemic rather than the portal circulation, is delivered into subcutaneous tissue rather than the bloodstream, and diffuses variably into the circulation. Standard, short acting insulins reach the circulation more slowly than food, so blood glucose tends to swing too high after each meal and to drop too low before the next. Longer acting human insulins reach peak absorption 4-16 hours after injection, which means that insulin injected before the evening meal tends to produce a glucose dip in the middle of the night, followed by a rebound as insulin fades before breakfast. Injection therapy thus tends to produce unwanted oscillations in glucose control, with an increased risk of hypoglycaemia before meals and during the night.

Genetically engineered human insulin, introduced in the 1980s, opened the way to subsequent modifications in the molecule designed to produce faster short acting insulins and smoother long acting insulins. Faster absorption is obtained by minor changes in the amino acid sequence. Smoother absorption was traditionally obtained by addition of a retarding agent, such as protamine—as in isophane insulin (also known as human NPH insulin (neutral protamine Hagedorn insulin)). By contrast, insulin glargine forms an amorphous precipitate when exposed to tissue pH at the injection site, whereas insulin detemir has a fatty acid tail, which allows it to bind to albumin, thus creating a reservoir, which buffers release of insulin into the tissues. The insulin analogues are designed to modify the delivery of insulin to its target tissues, but not its action, and controversy revolves around the clinical utility of such pharmacokinetic differences.[1] The table lists commonly used insulins.

Commonly used insulins with their relative costs

Name and insulin class	Manufacturer	Cost per vial (10 mL) (£)*	Cost per pack of 5 cartridges (15 mL) (£)*
Short acting			
Human:			
Actrapid (soluble insulin)	Novo Nordisk	7.48	Not available
Humulin S (soluble insulin)	Eli Lilly	15.68	19.08
Insuman Rapid (soluble insulin)	Sanofi-Aventis	Not available	17.50
Analogue:			
NovoRapid (insulin aspart)	Novo Nordisk	16.28	28.31
Apidra (insulin glulisine)	Sanofi-Aventis	16.00	28.30
Humalog (insulin lispro)	Eli Lilly	16.61	28.31
Premixed preparations			
Human:			
Humulin M3 (soluble + isophane insulin)	Eli Lilly	15.68	19.08
Insuman Comb 15, 25, or 50 (soluble + isophane insulin)	Sanofi-Aventis	Not available	17.50
Analogue:			
NovoMix 30 (biphasic insulin aspart)	Novo Nordisk	Not available	28.84
Humalog Mix 25 or 50 (biphasic insulin lispro)	Eli Lilly	16.61	29.46
Intermediate or long acting			
Human:			
Insulatard (isophane insulin) (intermediate)	Novo Nordisk	7.48	22.90
Humulin I (isophane insulin) (intermediate)	Eli Lilly	15.68	19.08
Insuman (isophane insulin) (intermediate)	Sanofi-Aventis	Not available	17.50
Analogue:			
Lantus (insulin glargine) (long)	Sanofi-Aventis	30.68	41.50
Levemir (insulin detemir) (long)	Novo Nordisk	Not available	42.00

*£1=€1.3; $1.6.

How well do the insulin analogues work?

Discussion of the role of the insulin analogues in type 2 diabetes inevitably reflects a wider discussion on the role of insulin itself. The past two decades have seen a drive towards earlier and more aggressive insulin therapy, but the benefits of this strategy are still open to debate. One reason is that attention has focused on the pursuit of lower thresholds for HbA_{1c} concentrations rather than on the global benefits and disadvantages of different treatment strategies. Recent major outcome trials have therefore related their endpoints to glucose control, and have permitted considerable flexibility in the means used to achieve this. The main exception to this was the United Kingdom Prospective Diabetes Study, which subdivided participants randomised to intensified control according to treatment modality; it found no long term benefit from early randomisation to insulin,[2] although the complex study design might leave this conclusion open to some doubt.

Be cautious about making treatment decisions on the basis of HbA_{1c} concentration alone as there are many reasons for suboptimal control, including poor compliance with diet and other aspects of treatment. Furthermore,

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- Antimuscarinic drugs to treat overactive bladder (*BMJ* 2012;344:e2130)
- Hormone replacement therapy (*BMJ* 2012;344:e763)

the undoubted benefits of intensified glucose control are greatest in relatively young individuals with newly diagnosed type 2 diabetes—the group targeted by the United Kingdom Prospective Diabetes Study—but recent analysis and a systematic review suggest that intensified glucose control does not in itself reduce cardiovascular mortality in type 2 diabetes and is associated with diminishing microvascular benefit in older people.[3 4] These recent findings do not provide an argument for poor glucose control but may allow for some relaxation of treatment goals in terms of HbA_{1c} concentration, with more emphasis on blood pressure and lipid lowering, whose cardiovascular benefits are more securely established.[3]

Type 2 diabetes is a heterogeneous condition, typically characterised by high levels of circulating insulin in its earlier stages, later followed by progressive insulin secretory failure. As the relative importance of insulin secretory capacity and insulin sensitivity varies from person to person, as does the rate of β cell failure, each case requires individual consideration and discussion with the patient, and "one size fits all" guidelines based only on the HbA_{1c} concentration should be interpreted in this light.

The use of analogue versus human insulin in type 2 diabetes should be considered against this background. Systematic reviews agree that substitution of an analogue for human insulin does not improve overall glucose control.[5-9] The rationale for using the short acting analogues is thus based on convenience as they can be injected closer to meal times without deterioration of post-prandial glucose control. No outcome data, however, underpin this advantage. Compared with human insulin, the longer acting analogues confer a modest reduction of the risk of nocturnal hypoglycaemia, but this benefit has been exaggerated by "treat to target" studies, which encourage investigators to aim for very low fasting glucose concentrations, thus increasing the likelihood of hypoglycaemia during the night. In most studies the analogues do not affect the rate of severe hypoglycaemia.[7]

How safe are the insulin analogues?

The analogues are designed for improved pharmacokinetics and are almost (but not quite) identical with human insulin in other respects. Their adverse effects are therefore closely similar. Reactions at injection site have been reported in about 1% of those using insulin glargine and in about 0.3% of those using other long acting insulins.[8] Theoretical concerns have arisen because of altered binding of the newer insulins to their receptors. In vitro insulin glargine shows greater affinity for the insulin-like growth factor 1 receptor than for human insulin,[10] although the molecule rapidly loses this property after injection.[11] Some pharmacoepidemiological studies have reported an increased risk of breast cancer with insulin glargine, but the ORIGIN trial reported no excess risk of cancer.[12]

How cost effective are the insulin analogues?

Prescriptions relating to diabetes represent 8.4% of the total cost of prescribing in the UK,[13] and insulin accounts for the highest proportion of the total cost of those prescriptions. The incremental cost to the NHS of prescribing analogue rather than human insulin has been estimated at £625m (€796m; $980m).[14] The table shows the relative costs of commonly used insulins. There is striking variation in the cost effectiveness estimates for the insulin analogues.[5 7 15] The National Institute for Health and Clinical Excellence (NICE) cites a cost effectiveness ratio for glargine of £33 000 (compared with isophane insulin) rising to £43 000 for pen devices. The estimate is based on the assumption of reduced risk of hypoglycaemia and rises to about £10m if the utility gain from hypoglycaemia is discounted. The NICE appraisal concluded that "the face value results all suggested that human insulin regimens were the only cost-effective approach."[5]

What are the precautions?

The insulin analogues are used in the same way as isophane insulin, but their altered pharmacokinetics, such as quicker absorption, should be taken into account. There is, for example, an increased risk of hypoglycaemia with the short acting analogues or premixed preparations if an unexpected delay occurs between the injection and the meal. Weight gain is a common complication of insulin treatment, averaging 5.7 kg (plus a 6 cm gain in waist circumference) over three years in one recent trial; those receiving multiple daily injections gained the most weight.[16] Use metformin in addition to insulin whenever possible and re-emphasise the need for diet and exercise.

How are the insulin analogues taken and monitored?

Choice of insulin

NICE recommends that human insulin should be the first line choice for type 2 diabetes. This advice is based on efficacy as well as cost and is supported by the observation that hypoglycaemia is no more common in the first few years of treatment with insulin for type 2 diabetes than it is with sulfonylureas.[17] The analogues are the second line option for those who need help with injections; those who can achieve adequate control with once daily insulin analogues plus oral agents; and those with troublesome hypoglycaemia. Premixed analogues may be preferred for those who wish to inject shortly before meals.[5]

The type of analogue chosen does not seem to be important, as their prices are closely matched and the short acting analogues seem indistinguishable. Insulin glargine produces more weight gain than insulin detemir but requires a lower dose, which has cost implications; in other respects they are closely similar.[7 18]

Metformin enhances the actions of insulin and restricts weight gain and should therefore be continued alongside insulin. Some physicians continue sulfonylureas when starting insulin, although this strategy may lead to increased weight gain and hypoglycaemia.[5]

Administration

Type 2 diabetes is treated with once or twice daily intermediate or long acting insulin, either taken alone or supplemented by short acting insulin before meals (the short acting insulin may be added before each main meal (basal bolus therapy) or before breakfast and the evening meal only, in which case premixed preparations are often used). Human insulin may be administered as once daily intermediate acting isophane insulin (commonly taken with a bed-

time snack) or as twice daily isophane insulin or premixed preparations. Thrice daily short acting insulin is used without a long acting insulin supplement in some mainland European countries. Intensified treatment is delivered as human short acting insulin given thrice daily before meals with isophane insulin at bedtime.

In a systematic review and meta-analysis that combined data from trials with human and insulin analogues, a twice daily premixed preparation or thrice daily short acting insulin led to significantly better control of HbA_{1c} concentration than long acting insulin alone. Use of short acting insulin was associated with significantly greater weight gain and more frequent minor, but not major, hypoglycaemia.[19] Falls in HbA_{1c} concentration were greater with basal bolus insulin than with long acting insulin alone in the two trials that reported this comparison.[19] The 4T ("Treating To Target in Type 2 diabetes") study found that basal bolus insulin was significantly more likely than premixed preparations to lead to the target HbA_{1c} concentrations, but the differences were relatively small.[16] Note that similar results can be achieved by different strategies of insulin administration, and that none emerges as clearly superior. This allows room for a flexible approach based on a target HbA_{1c} concentration and the patient's preference.

Monitoring

Draft an individualised treatment plan, agree the objectives of treatment with the patient before insulin is started, and monitor the extent to which these have been achieved.

TIPS FOR PATIENTS

- People with type 2 diabetes often lose the ability to produce their own insulin over the course of time, and 40-50% are likely to end up having to use insulin (this is just because of the natural course of the disease—there is not much you can do to avoid that)
- The pros and cons of early insulin treatment are still debated by doctors, and you will have some choice in your treatment. But it can harm your health to delay insulin treatment when this is what your body really needs
- The insulin analogues are widely advertised and are popular for type 2 diabetes. So if you receive advice favouring an older and cheaper type of insulin ("human insulin") you might assume the advice has been driven by economy rather than benefit. However, it has become increasingly clear, that most people with type 2 diabetes respond equally well to analogue or human insulin. For those with special problems—such as hypoglycaemia (low levels of blood glucose)—and those who are unable to inject more than once a day, the analogues remain useful alternatives
- Some people prefer to start insulin treatment with a single overnight injection of human NPH insulin, adding injections of quick acting insulin before meals, according to need (this strategy is known as basal bolus therapy). Basal bolus therapy has advantages for those seeking really tight control and/or a more flexible lifestyle. Others begin with two daily injections of human NPH insulin (isophane insulin) or a premixed preparation, which has the advantages of simplicity and convenience
- Many people find that they need to increase their insulin dose over time to maintain good glucose control and thereby stay on top of their diabetes

HOW DO INSULIN ANALOGUES COMPARE WITH HUMAN INSULINS?

The insulin analogues are "designer molecules" altered to improve the pharmacokinetics of injected insulin (more rapid or more sustained delivery to its target tissues) without changing its biological properties. These advantages are best seen when very tight control is attempted in insulin deficient (type 1) diabetes, but are less apparent when insulin injections are superimposed on endogenous hyperinsulinaemia in type 2 diabetes. Systematic reviews show that:

- Analogues do not lead to better glucose control in type 2 diabetes
- There is no difference in major hypoglycaemia (in most studies)
- Analogues may result in fewer episodes of minor and nocturnal hypoglycaemia
- Short acting analogues can be injected closer to meals
- Analogues cost two to four times as much.

NICE accordingly recommends human insulin as first line therapy in type 2 diabetes and analogues as second line therapy for those with special needs or problems.

Ideally, offer treatment in the context of "insulin start" groups which offer education plus group support and interaction.

Encourage patients to adjust their own insulin and to make use of the feedback provided by glucose monitoring. Monitor weight as well as hypoglycaemia, as some individuals gain as much as 10 kg without any improvement in glucose control. Such weight gain is most likely to occur in those who eat too much and may indeed have been the underlying reason for the unsatisfactory control that resulted in insulin treatment. Dietary evaluation and support, combined with metformin and avoidance of sulfonylureas or pioglitazone, will minimise the risk of excessive weight gain.

Individuals omitting to administer their treatment is one of the leading reasons for poor glucose control among individuals being treated with insulin, as in those taking oral agents for their diabetes; only about 70% of the insulin dispensed for type 2 diabetes is actually used within the intended time frame.[20]

Beware harm

Although insulin can and should be a life enhancing treatment, injudicious use can easily do more harm than good. Insulin is one treatment option among several in the earlier stages of type 2 diabetes and should be used accordingly. It is not unreasonable to offer the patient a trial of insulin and to be prepared to try another treatment if this does not bring the expected benefit. On the other hand, when other treatments fail, the introduction of insulin in those who really need it must not be delayed.

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1 Holleman F, Gale EAM. Nice insulins, pity about the evidence. *Diabetologia* 2007;50:1783-90.
2 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998;352:837-53.
3 Yudkin JS, Richter B, Gale EAM. Intensified glucose lowering in type 2 diabetes: time for a reappraisal. *Diabetologia* 2010;53:2079-85.
4 Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2011;6:CD008143.
5 National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care. Royal College of Physicians, 2008.
6 Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *CMAJ* 2009;180:385-97.
7 Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010;14:1-248.
8 Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2007;2:CD005613.
9 Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, et al. Short-acting insulin analogues versus human insulin for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2006;2:CD003287.
10 Sciacca L, Cassarino MF, Genua M, Pandini G, Le Moli R, et al. Insulin analogues differently activate insulin receptor isoforms and post-receptor signalling. *Diabetologia* 2010;53:1743-53.
11 Sommerfeld MR, Müller G, Tschank G, Seipke G, Habermann P, et al. In vitro metabolic and mitogenic signalling of insulin glargine and its metabolites. *PLoS One* 2010;5(3):e9540.
12 ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *New Engl J Med* 2012;367:319-28.
13 NHS Information Centre for Health and Social Care. Prescribing for diabetes in England 2005/06 to 2010/11. 2011. www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescribing-for-diabetes-in-england-2005-06-to-2010-11.
14 Holden SE, Poole CD, Morgan CL, Currie CJ. Evaluation of the incremental cost to the National Health Service of prescribing analogue insulins. *BMJ Open* 2011;1(2):e000258.
15 Cameron CG, Bennett HA. Cost effectiveness of insulin analogues for diabetes mellitus. *CMAJ* 2009;180:400-7.
16 Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009;361:1736-47.
17 UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;50:1140-7.
18 Swinnen SG, Simon AC, Holleman F, Hoekstra JB, Devries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2011;7:CD006383.
19 Lasserson DS, Glasziou P, Perera R, Holman RR, Farmer AJ. Optimal insulin regimens in type 2 diabetes mellitus: systematic review and meta-analyses. *Diabetologia* 2009;52:1990-2000.
20 Donnelly LA, Morris AD, Evans JM; DARTS/MEMO Collaboration. Adherence to insulin and its association with glucose control in patients with type 2 diabetes. QJM 2007;100:345-50.

GUIDELINES

Prevention and management of neutropenic sepsis in patients with cancer: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Further information about the guidance, a list of members of the guideline development group, and the supporting evidence statements are in the full version on bmj.com.

Neutropenic sepsis is a potentially fatal complication of treatment for cancer, with mortality rates of 2-21%.[1] An investigation by the National Confidential Enquiry into Patient Outcome and Death and a follow-up report by the National Chemotherapy Advisory Group highlighted problems in the management of neutropenic sepsis in adults receiving chemotherapy.[2 3] The problems included inadequate management of neutropenic sepsis leading to avoidable deaths, and the lack of systems for urgent assessment and of policies at organisation level for dealing with neutropenic sepsis. This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the prevention and management of neutropenic sepsis in patients of any age with cancer.[4]

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Information and support for patients and carers

- Provide patients having anticancer treatment and their carers with written and verbal information, before starting and throughout their cancer treatment, on:
  - Neutropenic sepsis
  - How and when to access 24 hour specialist oncology advice
  - How and when to seek emergency care.

Training for healthcare professionals

- Provide training on the identification and management of neutropenic sepsis to all healthcare professionals likely to be involved in the management of patients having cancer treatment.

Reducing the risk of septic complications of anticancer treatment

- For adult patients (aged ≥18 years) with acute leukaemias, stem cell transplants, or solid tumours in whom clinically significant neutropenia (neutrophil count ≤0.5 x 10^9/L) is an expected consequence of chemotherapy, offer prophylaxis with a fluoroquinolone only during the expected period of neutropenia. The lack of data for children and young people and for patients with lymphomas, makes it impossible currently to recommend the use or avoidance of a fluoroquinolone during periods of neutropenia.
- Centres where patients are receiving fluoroquinolones for antibiotic prophylaxis of neutropenic sepsis should monitor rates of antibiotic resistance.
- Do not routinely offer granulocyte colony stimulating factor to prevent neutropenic sepsis in adults having

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Previous articles in this series

- Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance (*BMJ* 2012;345:e4947)
- Management of lower urinary tract dysfunction in neurological disease: summary of NICE guidance (*BMJ* 2012;345:e5074)
- Risk assessment of fragility fractures: summary of NICE guidance (*BMJ* 2012;345:e3698)
- Risk identification and interventions to prevent type 2 diabetes in adults at high risk: summary of NICE guidance (*BMJ* 2012;345:e4624)
- Management of an acute painful sickle cell episode in hospital: summary of NICE guidance (*BMJ* 2012;344:e4063)

Commonly used, validated risk assessment tools for neutropenic sepsis

Multinational Association for Supportive Care in Cancer (MASSC) score for adults[6]

Calculate the score for each patient at admission, according to the factors and scores listed below. If the total score is 21 or higher, they are at low risk of severe septic complications.

- Solid tumour or lymphoma with no previous fungal infection = 4
- Outpatient status (at onset of fever) = 3
- Age <60 years = 2
- Burden of illness:
  - No or mild symptoms = 5
  - Moderate symptoms = 3
  - Severe symptoms = 0
- No hypotension (systolic BP >90 mmHg) = 5
- No chronic obstructive pulmonary disease = 4
- No dehydration = 3

Modified Alexander rule for children and young people <18 years old[7]

Patients are at low risk of septic complications if:

- They are not having treatment for acute myeloblastic leukaemia or Burkitt lymphoma, or the induction phase of treatment for acute lymphoblastic leukaemia; do not have a progressive disease; or are not having treatment for relapsed disease with marrow involvement; or
- They do not present with any of the following features: hypotension, tachypnoea or hypoxia <94%, new changes in chest radiography results, altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, other clinical reason(s) for inpatient treatment, neutrophil count <0.1 × 10^9/L.

chemotherapy unless they are receiving this as an integral part of the chemotherapy regimen or to maintain dose intensity.

Outside these indications, the role of granulocyte colony stimulating factor in the treatment of patients with cancer is highly controversial. An economic analysis undertaken specifically for the guideline showed that the use of granulocyte colony stimulating factor when given solely to prevent neutropenic sepsis was highly unlikely to be cost effective.

Referral guidance

- Suspect neutropenic sepsis if patients having cancer treatment become unexpectedly or seriously unwell.
- Refer patients with suspected neutropenic sepsis immediately for assessment at their appropriate local hospital.

Emergency treatment and assessment

Suspected neutropenic sepsis is an acute medical emergency.

- Start immediate empirical antibiotic treatment. The current National Cancer Action Team's guidance and measures for cancer services suggest that treatment should be started within one hour.[5]
- Use monotherapy (the combination piperacillin with tazobactam) as initial empirical antibiotic treatment, and do not prescribe additional aminoglycoside(s), unless there are patient specific or local microbiological indications, such as a high rate of resistance to piperacillin with tazobactam.
- Do a full clinical assessment of patients, including:
  - History and examination
  - Full blood count, and kidney and liver function tests (including albumin)
  - C reactive protein, lactate and blood culture
  - Additional peripheral blood culture, if possible, in patients with a central venous access device to improve the detection rates for bacteraemia
  - Urinalysis in all children aged ≤5 years.
- Do not do chest radiography unless clinically indicated.
- Do not prescribe empiric glycopeptide antibiotics to patients with neutropenic sepsis and a central venous access device.
- Do not remove the central venous access device as empirical management. However, it may require removal if it is suspected to be the focus of uncontrolled infection.

Confirming the diagnosis

- Diagnose neutropenic sepsis in every patient whose temperature is >38°C and neutrophil count <0.5 × 10^9/L.

Assessing the patient's risk of septic complications

- An oncology specialist should assess every patient's risk of septic complications within 24 hours, using a validated risk scoring tool.

No clear evidence describes the superiority of one system over another. The box describes two commonly used systems: the Multinational Association for Supportive Care in Cancer (MASCC) score (for adults) and a modified Alexander rule (for children and young people).[6 7]

Patients at low risk of septic complications

- Consider treating patients at low risk of developing septic complications with outpatient antibiotic treatment, if clinically appropriate and their domestic circumstances will allow them to return to hospital promptly if a problem develops.

Patients at high risk of septic complications

- Review and repeat the risk assessment daily while the patient is an inpatient, using the validated risk scoring tool.
- Switch from intravenous to oral antibiotic treatment after 48 hours in patients who are reassessed as being at low risk of septic complications, and discharge them home if clinically appropriate and domestic circumstances allow.
- Discontinue empirical antibiotic treatment in patients who have clinically responded to treatment—for example, by defervesence and an absence of signs of infection, irrespective of neutrophil count.
- Continue inpatient empirical antibiotic treatment in patients who have unresponsive fever unless an alternative cause of fever is likely.
- Do not change primary empirical antibiotics in patients with unresponsive fever unless there is clinical deterioration or a specific microbiological indication.

Overcoming barriers

Teenagers and young adults with cancer seem to be twice as likely to die of neutropenic sepsis as other age groups,[4] and the Guideline Development Group urges those who care for these patients to emphasise to them the life threatening nature of this condition. The recommendation not to use granulocyte colony stimulating factor to prevent episodes of neutropenia challenges conventional practice; however, granulocyte colony stimulating factor may be an integral part of the chemotherapy regimen or used to maintain dose intensity in some patients having chemotherapy with proved survival advantage. Clinicians may need to explain clearly their decisions to use granulocyte colony stimulating factor to healthcare commissioners. Effective monitoring and hospital-wide asepsis should mitigate potential problems such as antibiotic resistance patterns and *Clostridium difficile* from the increased use of prophylactic fluoroquinolone antibiotics; the GDG concluded from the available evidence that the potential disadvantage from this was outweighed by the reduction in mortality from neutropenic sepsis. Delivering care outside hospital to patients at low risk of septic complications will need careful implementation of early, risk stratified discharge together with informed community support to enable this to happen safely and improve the experience of patients.

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1 Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 2006;106:2258-66.
2 National Confidential Enquiry into Patient Outcome and Death. Systemic anti-cancer therapy: for better, for worse? NCEPOD, 2008. www.ncepod.org.uk/2008sact.htm.
3 National Chemotherapy Advisory Group. Chemotherapy services in England: ensuring quality and safety. Department of Health, 2010. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/DH_104500.
4 National Institute for Health and Clinical Excellence. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. (Clinical guideline 151.) 2012. http://guidance.nice.org.uk/CG151.
5 National Cancer Action Team. Manual for cancer services: acute oncology—including metatastic spinal cord compression measures. 2011. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_125727.
6 Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000;18:3038-51.
7 Dommett R, Geary J, Freeman S, Hartley J, Sharland M, Davidson A, et al. Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting. *Eur J Cancer* 2009;45:2843-9.

ANSWERS TO ENDGAMES, p 50

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PICTURE QUIZ

An unusual case of pneumonia

1 The radiograph shows bilateral, particularly right sided, peripheral air space consolidation. Consolidation is also seen posteriorly and peripherally in the right lower zone, below the level of the right hilum. The cardiac outline is normal and no pleural effusion or pneumothorax is seen.
2 Given the clinical history, eosinophilia, and radiographical changes, the diagnosis is probably one of the pulmonary eosinophilia syndromes.
3 Further tests include antineutrophil cytoplasmic antibody (ANCA) serology, total IgE values, testing for *A fumigatus* (skin prick tests or specific IgE), and stool microscopy and culture. High resolution computed tomography of the thorax provides more detail than plain radiography, and flexible bronchoscopy with bronchoalveolar lavage can confirm whether the infiltrate is eosinophilic and provide samples for microscopy and culture. Lung function testing may also be useful because several causes of pulmonary eosinophilia are associated with asthma and airflow obstruction.

CASE REPORT

Taught a lesson by taut skin

1 Scleroderma renal crisis, which results in a hypertensive emergency.
2 Fundoscopy, which might show the presence of grade III or IV hypertensive retinopathy.
3 Drugs, especially high dose corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), are predisposing factors. The condition is also more common in certain subgroups of patients, such as those who are positive for anti-RNA polymerase III antibodies.
4 Angiotensin converting enzyme (ACE) inhibitors are the main form of treatment.
5 Prognosis is poor, with progression to end stage renal disease occurring in 20-50% of patients.

STATISTICAL QUESTION

Standardisation of outcome measures (z scores)

Statement *a* is true, whereas *b* and *c* are false.