The Logic of Causality

Dr Ruth Savage

With acknowledgements to Professor Ralph Edwards

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The logic of causality

The need to think about causal relationships logically, ie apply reasoning.

Not always straightforward.

Did the boy who threw the stone break the window?

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The logic of causality

In our case -

Did the drug do it?

The logic of causality

Did the drug do it?

Some of the answers may be

- Yes
- Yes, but only in certain circumstances (risk factors)
- Yes because it interacted with another medicine
- No, it was another drug prescribed with it
- No, it was due to the patient's disease
- No, that drug could not cause that reaction

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Causality assessment of individual case safety reports

- We have logical methods for assessing single case reports
- the WHO_UMC system for *standardised* case causality assessment is widely used
- http://www.who-umc.org/Graphics/26649.pdf

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The WHO_UMC system for standardised case causality assessment

Categories

Certain

Probable

Possible

Unlikely

Unclassifiable

Unclassified

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Bradford Hill Criteria for Causality

Helps to develop judgement when applying the WHO-UMC system

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Bradford Hill Criteria for Causality

- Strength of Association
  - Disproportionality measures, relative risks etc
- Temporal relationship
  - Commenced after drug started. Reasonable time to onset
- Consistency
  - From a range of reporters or countries
- Theoretical plausibility
  - Not essential but important evidence if exists

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Bradford Hill Criteria for Causality

- Temporal relationship
  - Commenced after drug started. Reasonable time to onset
- Theoretical plausibility
  - Not essential but important evidence if exists

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Theoretical Plausibility

- Theoretical plausibility
  - Eg an anticholinergic medicine may cause urinary retention because the bladder outlet sphincter can't relax. This is most likely to occur if the bladder outlet is already compromised, eg by an enlarged prostate.
  - If a new drug is reported to cause urinary retention then it would be "theoretically plausible" if it has some anticholinergic acitivity.

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Time to onset

- Data from VigiBase – single suspect drug, all dates available:
  - agranulocytosis 5484 reports
  - angioedema 20,930
  - hepatitis 8961
  - serum sickness 1908
  - SJS 6531
  - TEN 2067
    - Khodabakhshi, G. MSc thesis.

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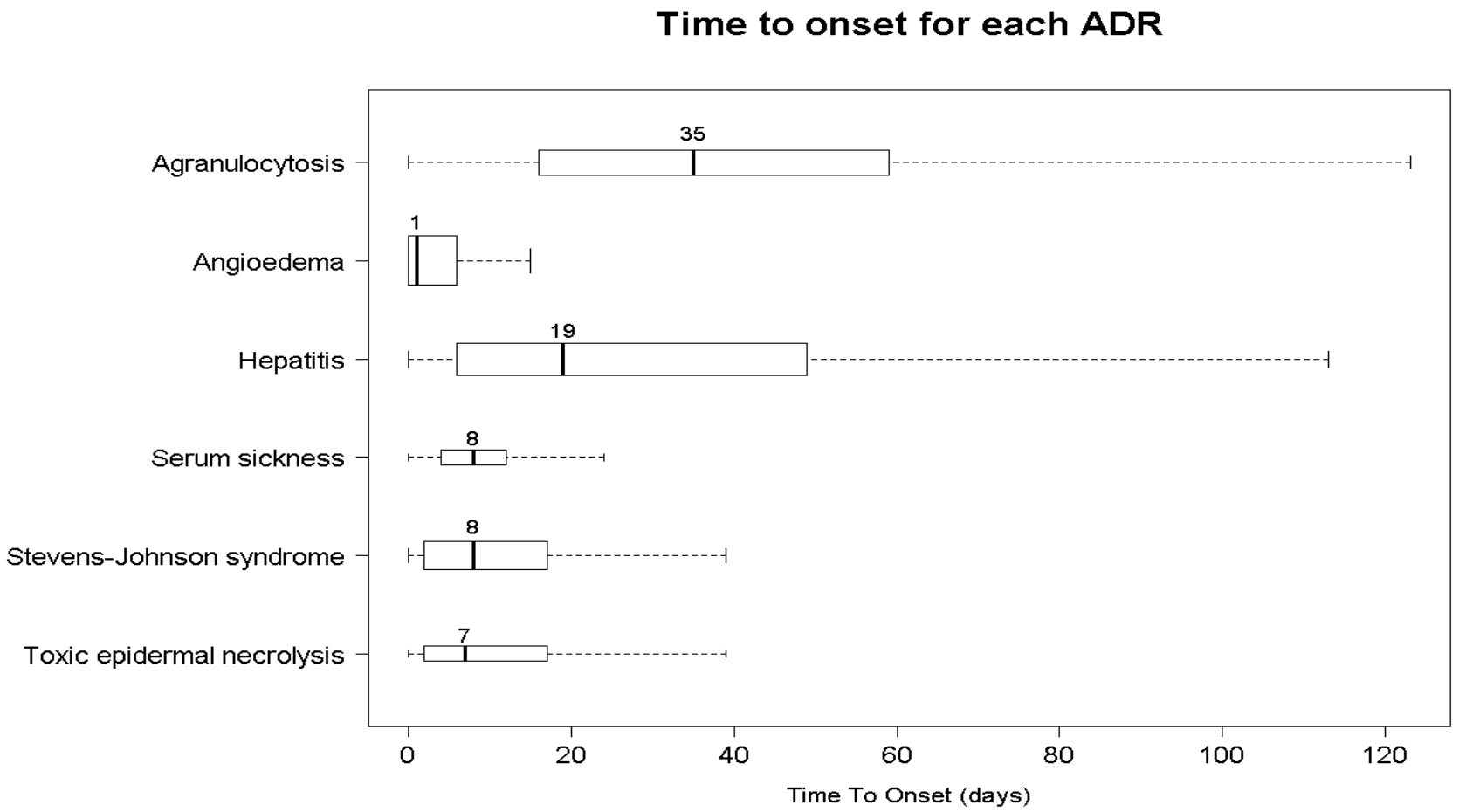
Time to onset



Time to onset

But we don't always know what is a reasonable time to onset!

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Bradford Hill Criteria for Causality

- Coherence
  - Fits with existing knowledge, eg frusemide will not cause hyperkalaemia.
- Specificity
  - Many ADRs have multiple causes eg acute renal failure
  - Generally drugs cause ADRs through specific mechanisms eg interstitial nephritis causing acute renal failure
  - Are a number of medicines suspect?
- Dose-response relationship
- Experimental evidence
- Analogy
  - Similar reactions observed with other members of ATC group

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Sweden

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base

RESTRICTED

WHO Collaborating Centre for International Drug Monitoring

SIGNAL

Analyses of Adverse Reaction Reports in the WHO Database · February 2005

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Signals in this issue

- Proton Pump Inhibitors and pancreatitis
- Thiazolidinediones and lowered High Density Lipoprotein Cholesterol
- Tramadol and hepatic disorders
- Cimicifuga racemosa (L.) Nutt. - Anaphylactic reaction, face and oral oedema
- Gefitinib giving rise to cardiac failure?
- Similasan and glomerulonephritis
- Bosentan - Reports of serious pulmonary, cardiac or hepatic events and of ineffectiveness or paradoxical worsening of pulmonary hypertension: Signal or confounding?

Follow-up

- Follow-up on previous signals
  Signals from 2002

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All correspondence regarding signals presented in this document should go through the Uppsala Monitoring Centre

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Pamidronic acid and synovitis/arthritis

Assessment of individual case reports

Pamidronic acid and synovitis/arthritis -Individual reports

- Female 76 years
- Rx Pamidronic acid iv
  - 23.08.2006
- Other medicines
  - Letrozole. simvastatin
- Synovitis, influenza-like symptoms, skeletal pain
  - 23.08.06
- Dechallenge, reaction abated
  - letrozole and simvastatin continued

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Pamidronic acid and synovitis/arthritis - Individual reports

- Female 68 years.
- Rx. Pamidronate 30 mg iv
  - 15.01.1997
- ADR terms. Arthrosis, arthritis aggravated, ESR increased
  - 18.01.1997
- Outcome - not recovered, no dechallenge data
- When was report sent? Was it too soon to assess outcome?

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Certain?!

- Female, 42 years.
- Pamidronic acid iv. 16.01.1996
- No other medicines
- Synovitis 20.01.1996.
- Outcome, not recovered
- Dechallenge, unknown
- Rechallenge, reaction recurred

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Pamidronate and synovitis

- Pitfalls in assessing reports
  - Two reports recorded recurrence on rechallenge but with no dates and no evidence of recovery after first infusion.
  - Watch for duplicates
  - And there are more....!

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Pamidronic acid and synovitis/arthritis -Individual reports

- A female patient, age unknown, was given a pamidronic acid infusion. The dose, date of administration and indication are unknown.
- On an unknown date the patient developed arthritis
- No concomitant medicines were reported. No medical history was reported.
- The outcome of the arthritis is unknown.

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Pamidronic acid and synovitis/arthritis -Individual reports

Gabapentin(C)	- - -	-	- -	- / -
Phenytoin(C)	- - -	-	- -	- / -
Ibuprofen(C)	- - -	-	- -	- / -
Paracetamol/Hydrocodone bitart-rate(C)	- - -	-	- -	- / -
Fluticasone propionate/Salmete-rol xinafoate(C)	- - -	-	- -	- / -
Levothyroxine(C)	- - -	-	- -	- / -
Levofloxacin(C)	- - -	-	- -	- / -
Nystatin(C)	- - -	-	5 ml -	- / -
Potassium(C)	- - -	-	- -	- / -
Folic acid(C)	- - -	-	- -	- / -
Potassium(C)	- - -	-	- -	- / -
Pioglitazone(C)	- - -	-	- -	- / -
Pantoprazole(C)	- - -	-	- -	- / -
Furosemide(C)	- - -	-	- -	- / -
Rofecoxib(C)	- - -	-	- -	- / -
Enalapril(C)	- - -	-	- -	- / -
Allopurinol(C)	- - -	-	- -	- / -
Antibiotics(C)	- - -	-	- -	- / -
Lisinopril(C)	- - -	-	- -	- / -
Alendronic acid(C)	- - -	-	- -	- / -
Cyclobenzaprine(C)	- - -	-	- -	- / -
Codeine phosphate/Paracetamol(C)	- - -	-	- -	- / -
Acetylsalicylic acid(C)	- - -	-	- -	- / -
Paracetamol(C)	- - -	-	- -	- / -
Cefalexin(C)	20060302 - 20060525	85 Day(s)	- -	- / -
Diltiazem(C)	- - -	-	- -	- / -
Clonidine(C)	- - -	-	- -	- / -
Diltiazem(C)	- - -	-	- -	- / -
Fluticasone propionate/Salmete-rol xinafoate(C)	- - -	-	- -	- / -
Paracetamol/Hydrocodone bitart-rate(C)	- - -	-	- -	- / -
Naphazoline(C)	- - -	-	- -	- / -
Tocopherol(C)	- - -	-	- -	- / -
Phenoxymethylpenicillin(C)	- - -	-	- -	- / -
Levothyroxine(C)	- - -	-	- -	- / -
Temazepam(C)	- - -	-	- -	- / -
Timolol maleate/Dorzolamide hy-drochloride(C)	- - -	-	- -	- / -
Olmesartan(C)	- - -	-	- -	- / -
Digoxin(C)	- - -	-	- -	- / -
Metronidazole(C)	- - -	-	- -	- / -
Docusate(C)	- - -	-	- -	- / -
Amiodarone(C)	- - -	-	- -	- / -
Chlorhexidine(C)	- - -	-	- -	- / -
Cimetidine(C)	- - -	-	- -	- / -
Omeprazole(C)	- - -	-	- -	- / -
Pantoprazole(C)	- - -	-	- -	- / -
Hydrochlorothiazide(C)	- - -	-	- -	- / -
Travoprost(C)	- - -	-	- -	- / -
Clopidogrel(C)	- - -	-	- -	- / -
Benzylpenicillin(C)	- - -	-	- -	- / -
Clindamycin(C)	- - -	-	- -	- / -
Pamidronic acid(S)	- - -	-	- -	- / -
Zoledronic acid(S)	- - -	-	- -	- / -
Pamidronic acid(S)	- - -	-	- -	- / -

- Female, age unknown
- 58 medicine entries
- Two suspect medicines- pamidronate, zoledronate.
- No dates!

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Pamidronic acid and synovitis/arthritis -Individual reports

Hypovolaemia	-	Unknown
Cardiac failure	-	Unknown
Gastric ulcer	-	Unknown
GI haemorrhage	-	Unknown
Haemorrhage rectum	-	Unknown
Pneumonia	-	Unknown
Asthma	-	Unknown
Urinary tract infection	-	Unknown
Polyneuropathy	-	Unknown
Insomnia	-	Unknown
Nasal ulcer	-	Unknown
Wound infection	-	Recovered
Infection susceptibility increased	-	Unknown
Arteriosclerosis	-	Unknown
Pulmonary valve disease	-	Unknown
Term not accepted in WHO-ART	-	Unknown
Oedema generalised	-	Unknown
Cellulitis	-	Unknown
Obesity	-	Unknown
Dyspnoea	-	Unknown
Thrombophlebitis deep	-	Unknown
Term not accepted in WHO-ART	-	Unknown
Bradycardia	-	Unknown
Abdominal pain	-	Unknown
Diabetes mellitus	-	Unknown
Glossitis	-	Unknown
Term not accepted in WHO-ART	-	Unknown
Skeletal pain	-	Unknown
Infection	-	Unknown
Pain	-	Unknown

- Female, age unknown
- Total ADR terms 100!
- No outcome data on most
- No dechallenge data

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Pamidronic acid and synovitis/arthritis

Case Series

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Case series

- What guidelines do we have for clinical assessment of a group of reports?

For example, those found through disproportionality analysis in a national or international database.

Pamidronate and synovitis

- New Zealand data base has four reports for pamidronate and synovitis or arthritis.
- Also statistically significant using data mining in NZ database & Vigibase
- Synovitis with alendronate first signalled by UMC. Literature reports for zoledronate and risedronate. Only one for pamidronate and patient had experienced synovitis with zoledronate first.

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Pamidronate and synovitis

- CARM & Vigibase – search principles
  - Ensure find all reports for the drug/s of interest. View ATC group.
  - Ensure find all reports of diagnosis eg synovitis, arthritis, arthritis aggravated, rheumatoid arthritis, arthritis aggravated. View SOC (musculoskeletal) to be sure.
  - Be precise. Not arthralgia or arthropathy without mention of arthritis or synovitis

Signal detection
Clinical Assessment

- Consider

  Patient Characteristics

  Drug Characteristics

  ADR Characteristics

  Outcome (including dechallenge/rechallenge)

  (Seriousness)

& Bradford Hill!

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Pamidronate and synovitis
NZ and international reports

- Total assessed reports 19

Pamidronate and synovitis
NZ and international reports

- Patient Characteristics
- Males/females (17 patients) 4/13
- Age (yrs) (15 patients)
  - Range 42-84
  - Mean 69.6
  - Median 70.5
- Indication (11 patients)
  - Osteoporosis 2
  - Prophylaxis 1
  - Bone metastases
  - Paget's Disease
- Co-morbidities (other illnesses) None relevant

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Pamidronate and synovitis
NZ and international reports

- Medicine Characteristics
- Sole suspect medicine (reports) 19
- Dose (mg) (14 patients)
  - Range 15-300
  - Mean 57.9
  - Median 30.0

- Days from infusion to onset of ADR (13 patients)
  - Range 1-7
  - Mean 3.1
  - Median 2.0

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Pamidronate and synovitis
NZ and international reports

Medicine Characteristics

Concomitant medicines.

No consistent pattern suggesting an interaction

Three medicines that can cause synovitis

prescribed for two patients – simvastatin, letrozole and atorvastatin

Both patients improved while these medicines were continued

No concomitant medicines suggested patients had arthritic diseases

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Pamidronate and Synovitis
NZ and international reports

- ADR Characteristics
  - Additional ADRs reported more than once
    - C-reactive protein increased 2
    - Headache 2
    - Influenza-like symptoms 2
    - Myalgia 2
    - Oedema 2
    - Skeletal pain 2

Pamidronate and synovitis
NZ and International Reports

- Outcomes
  - Recovered 6
  - Improved 3
  - Not yet recovered 7
  - Unknown 3

Duration of synovitis to improvement/recovery

- 2 days (one patient)

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Pamidronate and synovitis
NZ and International Reports

- Summary of evidence
  - Synovitis/arthritis reported following pamidronate infusion occurred within one week of the infusion in all patients – consistent time to onset
  - No concomitant medicines indicated alternative conditions, medicines or interactions that suggested an alternative explanation - specific
  - Over half of the patients had recovered or improved at the time of reporting – reasonable time to recovery
  - The synovitis was often associated with the influenza-like and pain reactions that occur soon after bisphosphonates are administered - plausibility
  - Other bisphophonates have been shown to cause synovitis –
  - analogy

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Is this a signal?

- 2010 q2.
- Diltiazem/rhabdomyolysis. $IC_{025} > 0$ in Vigibase.
- Number of reports – 55
- *Did the drug do it?*

Some reports of rhabdomyolysis with diltiazem in Vigibase

Country	Concomitant medicines
Australia	Simvastatin, gemfibrozil
Spain	Simvastatin
Netherlands	Simvastatin Metoprolol Paroxetine
New Zealand	Simvastatin Azathioprine Nitro- furantoin
Australia	Simvastatin Ciclosporin Colchicine

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Some Reports of rhabdomyolysis with diltiazem in Vigibase

- Rhabdomyolysis is a severe myopathy often with renal failure due to muscle breakdown and therefore myoglobin in the urine. It is often fatal.
- It is dose-related but occurs very rarely at standard simvastatin doses eg 10 and 20 mg daily.
- The risk is increased if interacting medicines increase exposure to simvastatin through inhibition of CYP 3A4 enzymes
- The reports suggest that simvastatin was the cause of the rhabdomyolysis
- Diltiazem is a weak CYP 3A4 inhibitor and is not thought to interact to a clinically important extent at standard daily doses of simvastatin

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Some reports of rhabdomyolysis with diltiazem in Vigibase

Country	Concomitant medicines	Simvastatin daily dose (mg)
Australia	Simvastatin, gemfibrozil	40
Spain	Simvastatin	80
Netherlands	Simvastatin Metoprolol Paroxetine	60
New Zealand	Simvastatin Azathioprine Nitro-furantoin	40
Australia	Simvastatin Ciclosporin Colchicine	5

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Some reports of rhabdomyolysis with diltiazem in Vigibase

- The additional information in the last slide shows that all but one patient were taking greater than 20 mg simvastatin daily. At these doses the interaction with diltiazem is clinically important.
- One patient was also taking a fibrate, gemfibrizol, which also increases the risk of rhabdomyolysis
- One patient was only taking 5 mg simvastatin daily but was taking a strong CYP 3A4 inhibitor, cyclosporin.

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Conclusion

- Assessing a case series may supply additional information that is missing in individual case reports
- A logical analysis should be applied but this will differ from individual case assessment
- Statistical disproportionality methods highlight case series for clinical assessment. They do not replace clinical causality assessment.

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