The importance of diagnostics & stewardship in the context of COVID-19

bioSTAR bioMerieux event
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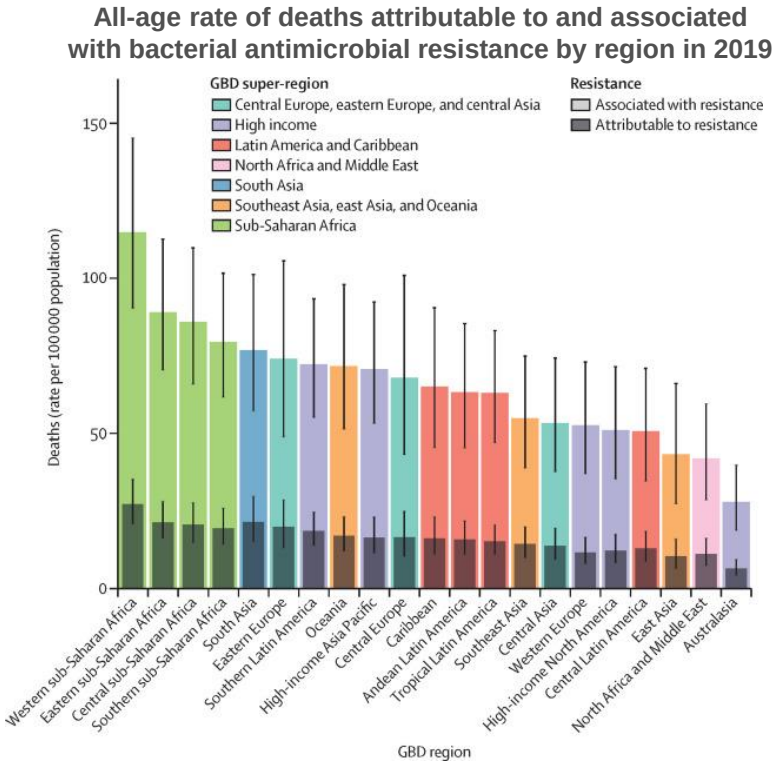
Dr Timothy Miles Rawson BSc (hons), MBBS, MRCP (UK), PDME, DTM&H, PhD
NIHR Academic Clinical Fellow in Infectious Diseases and Medical Microbiology
Health Protection Research Unit for Healthcare Associated Infections and Antimicrobial Resistance

Outline

1. What is the impact of COVID-19 on management of bacterial infection?
2. Decision making process during infection management.
3. How can diagnostics & stewardship may help us optimise antimicrobial use?
4. How has management of bacterial infection evolved during the COVID-19 pandemic?

Current and future impact of AMR



- Antimicrobial Resistance (AMR) is a global challenge.
- In 2019 drug-resistant bacterial infection:
  - Contributed to 4.95 million deaths.
  - Directly caused **1.27 million deaths**.
- Unchecked, by 2050 direct mortality is estimated to increase to **10 million deaths** per year.
- Significant cost to the global economy.

Murray, et al. Lancet 2022; O'Neill. AMR Report 2016

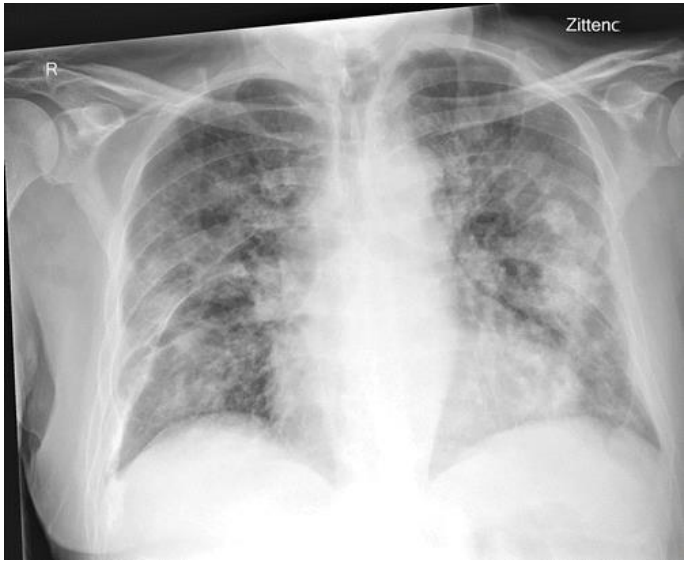
March 2020: Patient 1

Four day history of:

70 years old male
Fever
Cough
Malaise
Low oxygen saturations

Medical history:

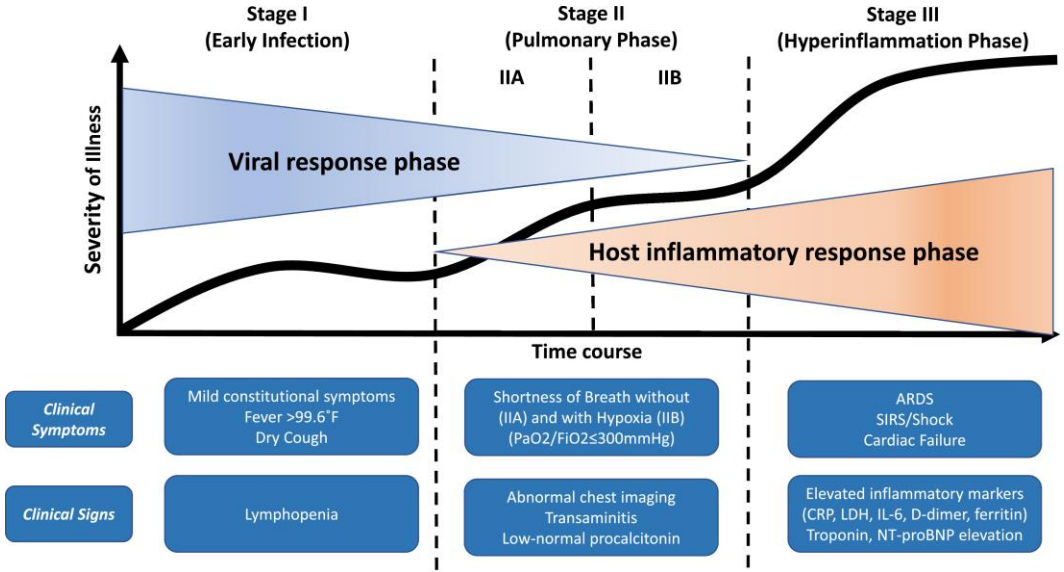
Diabetes (type 2)
Hypertension
Good baseline



Differentials:

COVID-19
&/or
Bacterial infection

Bacterial infection in COVID-19 a challenge for antimicrobial stewardship?



Concerns in early 2020:

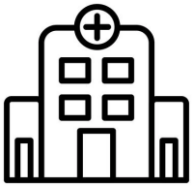
- Signs and symptoms that could be consistent with bacterial infection.
- Limited data on rates of bacterial infection associated with COVID-19.
- Perceived risk based on knowledge of influenza.

Chen et al. Lancet 2020; Siddiqi et al. JHLT 2020

Antimicrobial use, drug-resistance, and the impact of infection on COVID-19.

Reduced antimicrobial use.
Reduced notifiable infections.

Introduction of new therapies.
Potential bacterial infection risk.



High empiric antimicrobial use.
Low rates of reported infections.

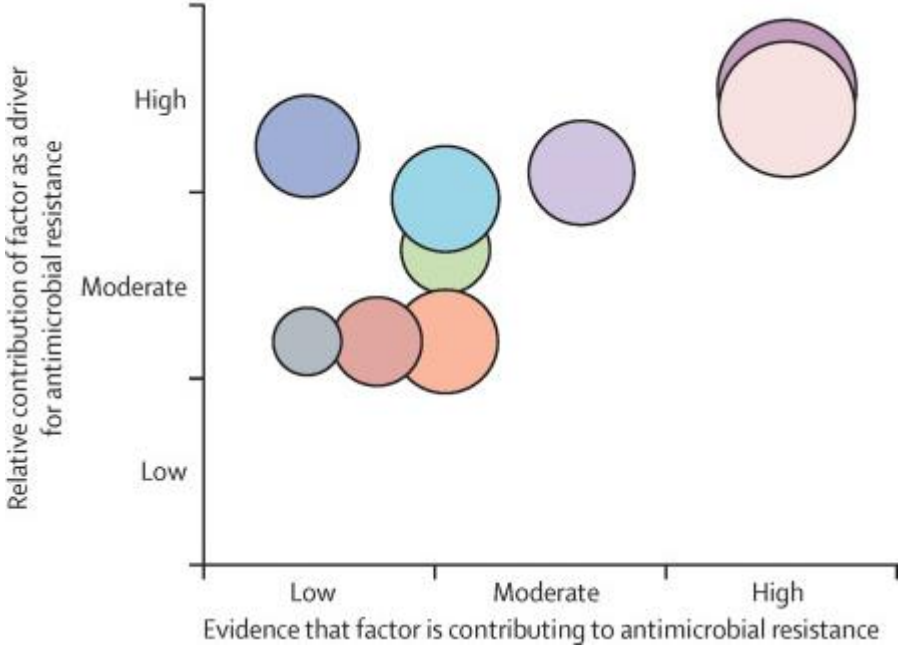
Variable pressures on healthcare.
Variation geographically.
Variation over time.

High empiric antimicrobial use.
High rates of reported infections.

No clear framework for reporting.
Difficult to compare data.

Rawson et al. CID 2020; Lansbury et al. JI 2020; Langford et al. CMI 2020; Zhu et al. CMI 2021; Rawson et al. CMI 2020; Langford et al. CMI 2021

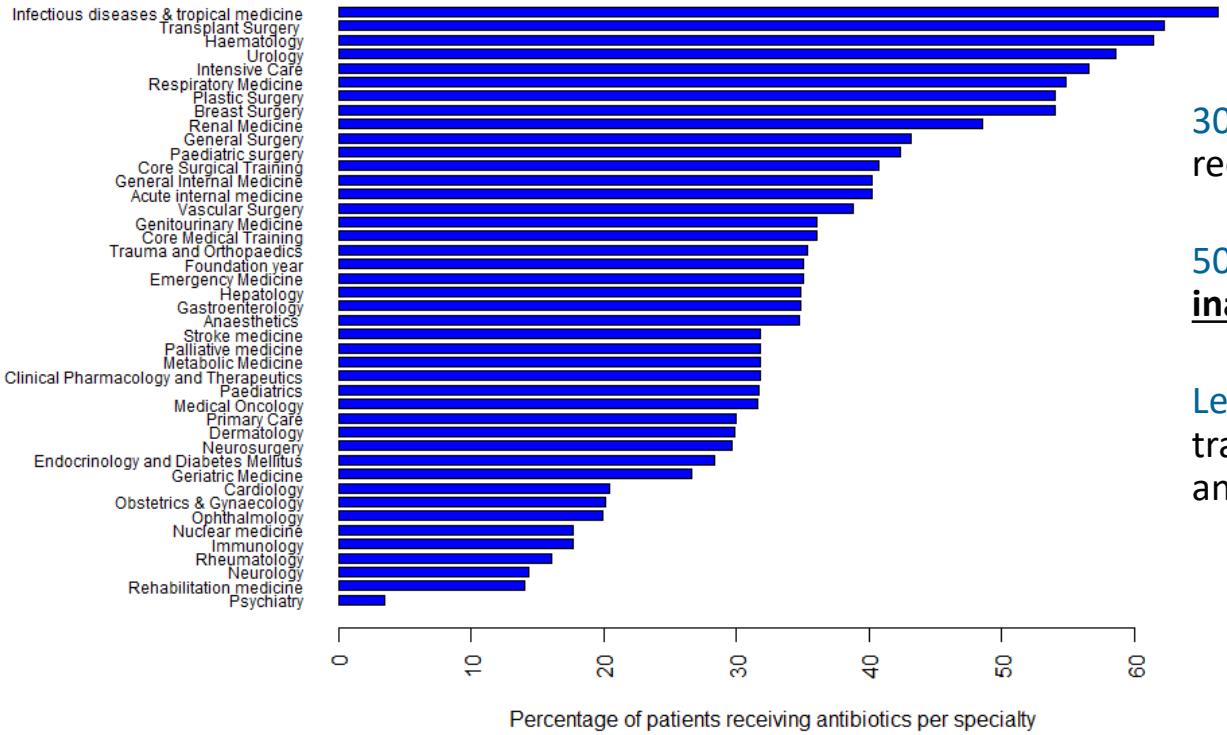
How will COVID-19 impact the modifiable drivers of AMR?



- Antimicrobial resistance is complex.
- Modifiable drivers, many of which have been effected by the COVID-19 pandemic.
- Consider both **positive & negative impact** of the pandemic on these factors.

Holmes, et al. Lancet 2016

Antibiotic prescribing in hospitals



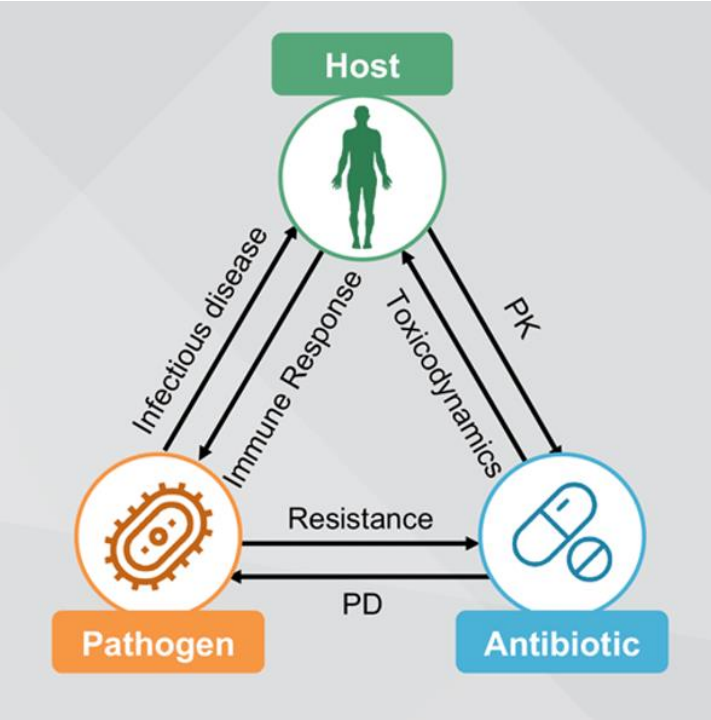
30% of all hospital in-patients will receive antibiotics

50% of prescriptions will be **inappropriate**

Less than 1% of most clinicians training will formally address antibiotic prescribing and AMR

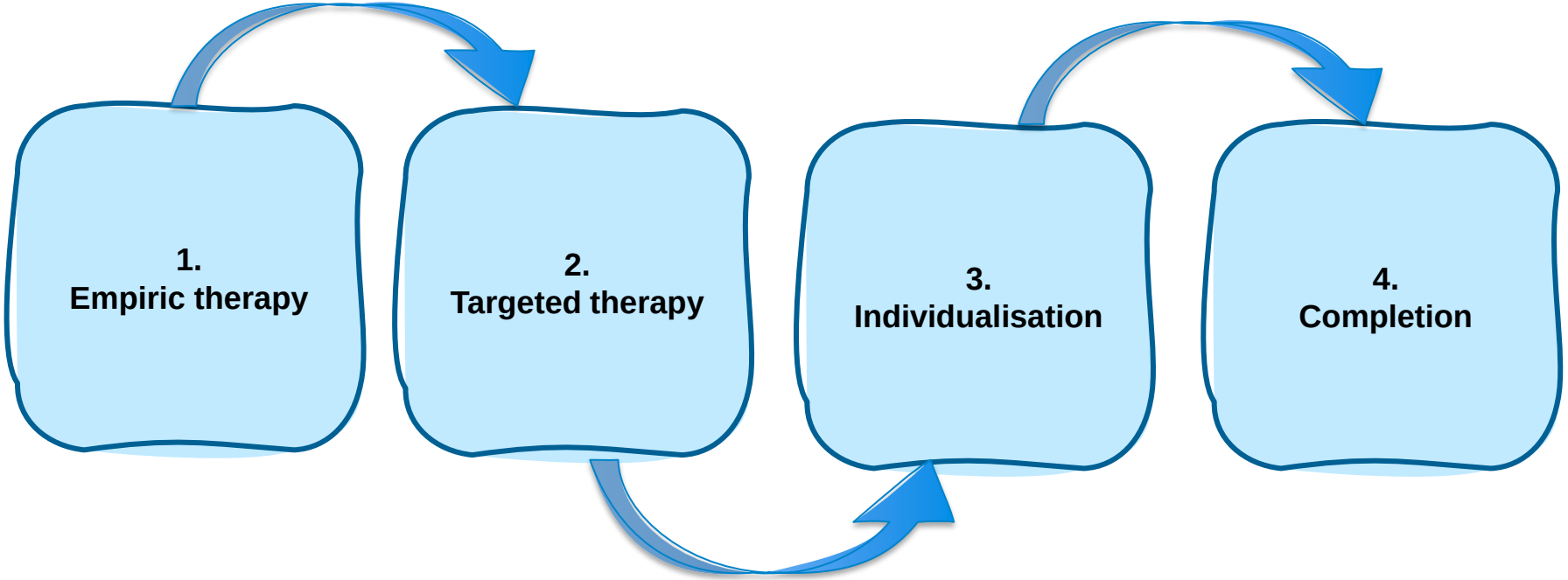
Rawson et al. JAC 2016; ECDC 2016; Hecker MT. et al. Arch Intern Med 2003

Antimicrobial prescribing

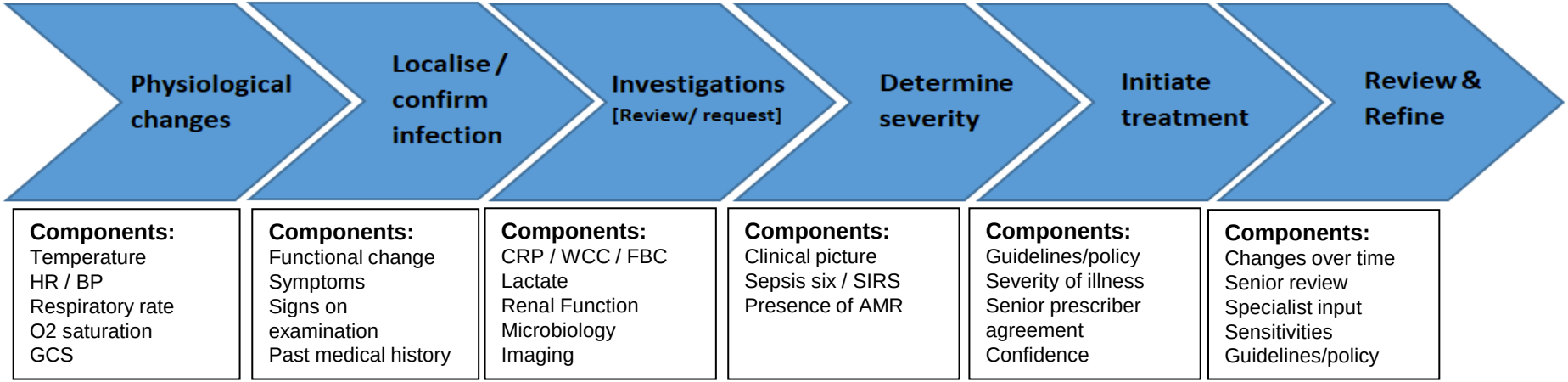


Asin-Prieto, et al. IJC 2015

The four moments of antimicrobial therapy



Antimicrobial decision making

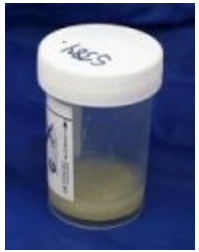


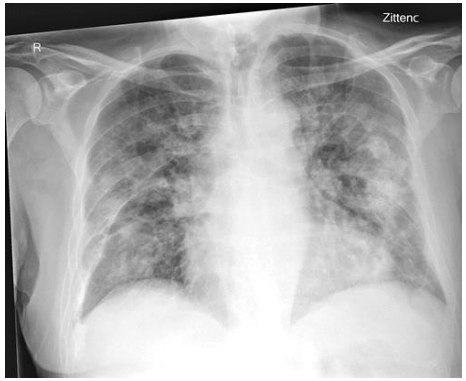
Rawson, et al. BMC Med; 2016

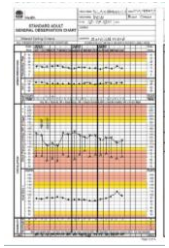
March 2020: Patient 1

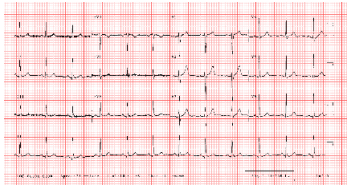
Differentials:

COVID-19
&/or
Bacterial infection









The process of infection management

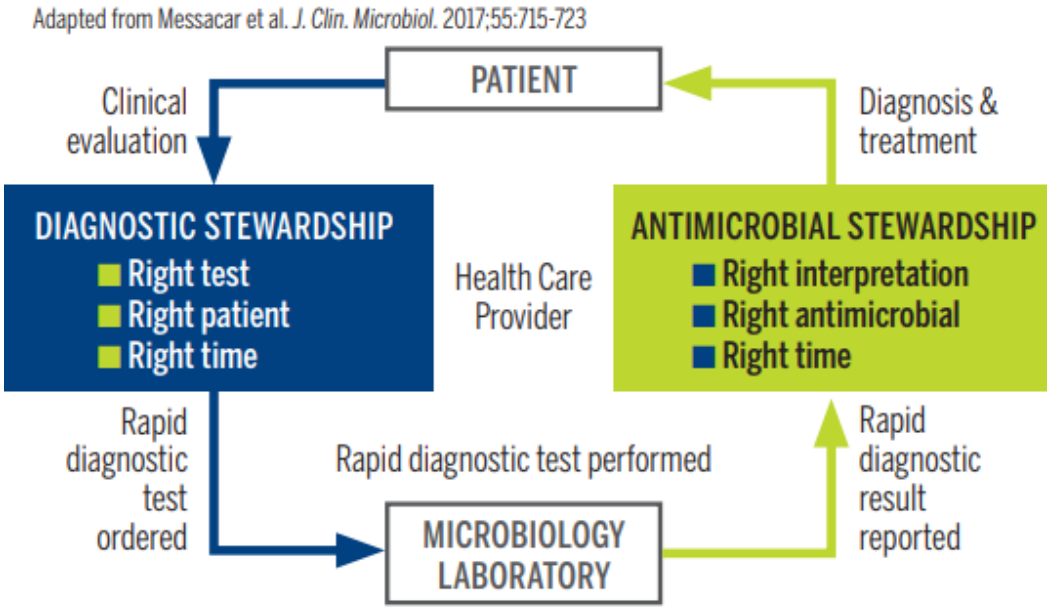
Decision's Day 1:
Is this an infection?
Bacterial / viral / both?
Where is the source?
Further investigations?
Treatment? And how quickly?

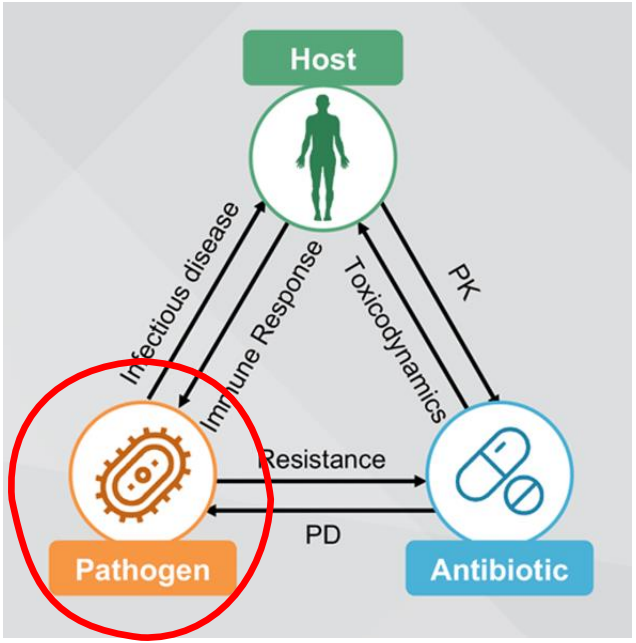
Immediate results:
Observations
Examination findings
Bedside tests
Imaging
Blood tests (WCC / CRP)

Intermediate results:
Blood tests
(hours to days)

Delayed results:
Culture-based microbiology:
Organism identified (24-120 hours)
Antimicrobial susceptibility (48+ hours)

Diagnostics and stewardship

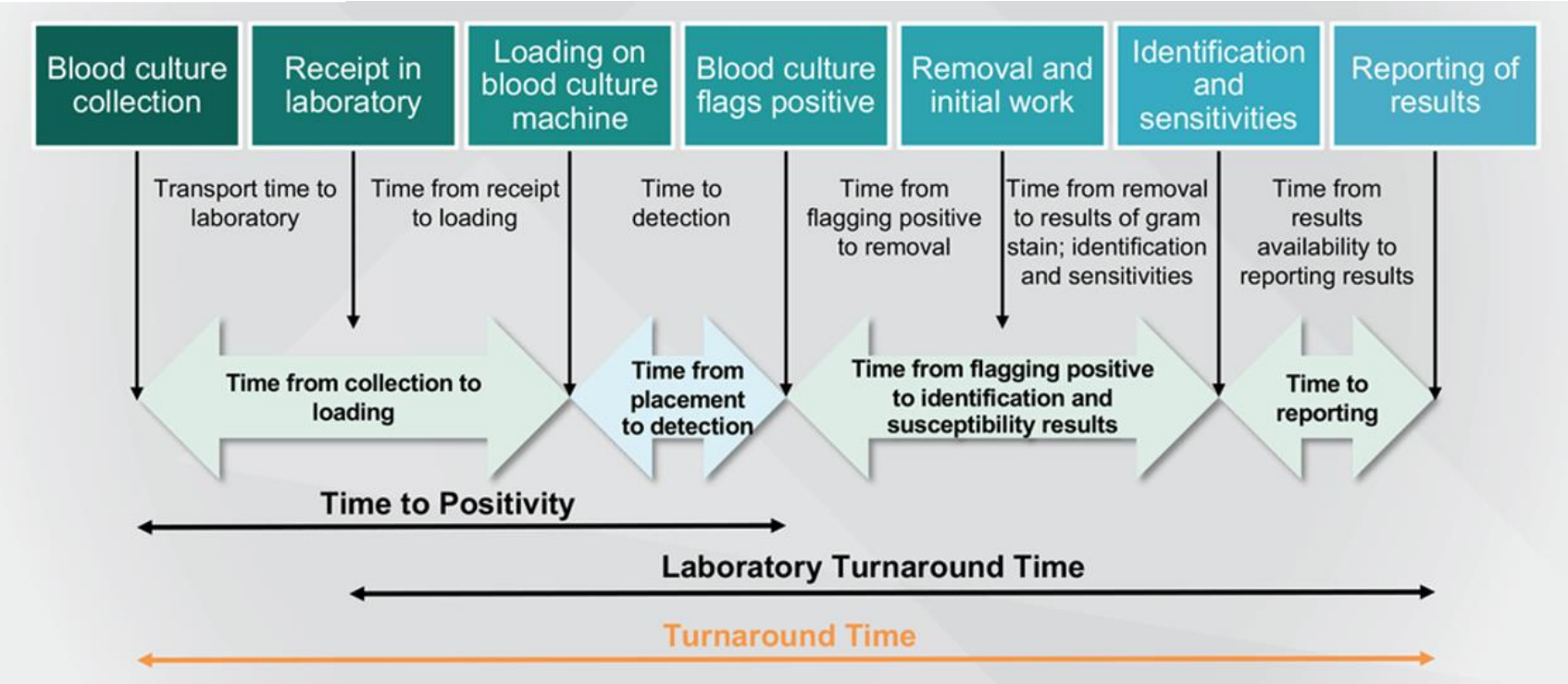




Pathogen identification is crucial in supporting antimicrobial optimisation

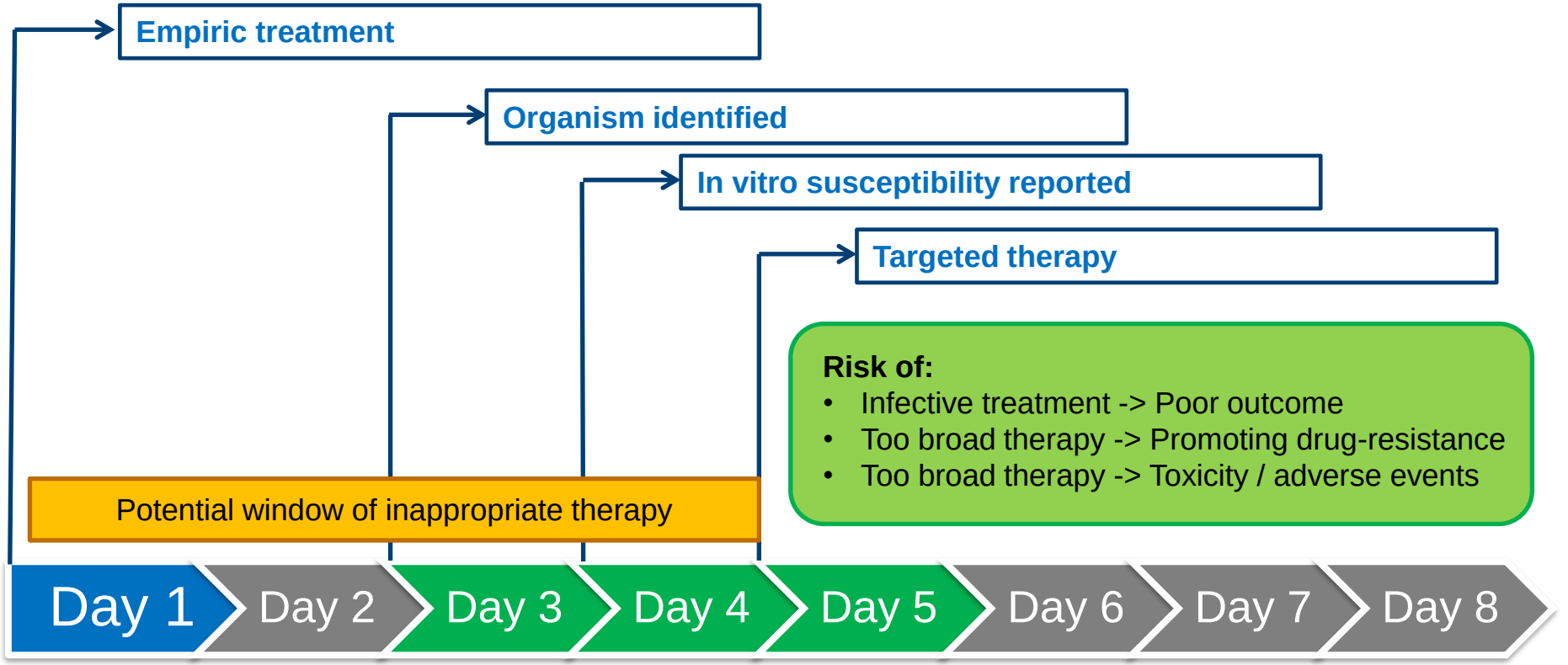
Asin-Prieto, et al. IJC 2015

Turn-around time – blood cultures



Modified from the UK SMI

Culture-based diagnostics



March 2020: Patient 1

Working Diagnosis:

COVID-19 with bacterial respiratory co-infection.

Guideline recommendation:

Co-amoxiclav 1.2g IV TDS & clarithromycin 500mg PO BD

Penicillin allergy: Levofloxacin 500mg BD PO/IV

1.
Empiric therapy

However, in COVID-19 bacterial co-infection is uncommon in acute care

Author	Description	Community bacterial infection	Hospital acquired bacterial infection	Antibiotic prescribing
Hughes et al. June 2020	836 patients United Kingdom	3%	6% Throughout	Not reported
Garcia Vidal et al. July 2020	989 patients Spain	3%	4% (57% VAP)	Not reported
Townsend et al. August 2020	117 patients Ireland	-	6% respiratory	73%
Ripa et al. October 2020	731 patients Italy	Not reported	9%	Not reported
Chawla et al. August 2020	16,780 patients USA	3.6%	Not reported	61%
Zhou et al. March 2020	191 patients China	-	15%	95%
Karami et al. October 2020	925 patients Netherlands	1.6%	-	60%

Bacterial infection in acute care
Current evidence

~8% bacterial infection in COVID-19.

- 3% present with respiratory bacterial infection.
- Up to 15% hospital acquired bacterial infection.

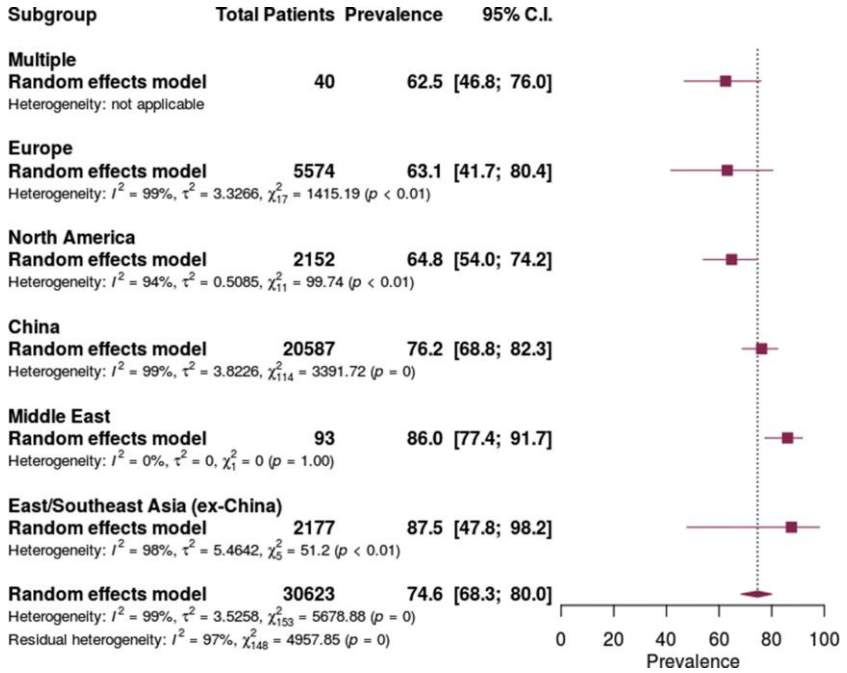
~72% receive antibiotics.

- Often broad spectrum in nature.
- Duration not always clearly defined.

Heterogeneity in studies.

Few data from low resource settings.

Regional rates of antibiotic prescribing in COVID-19.



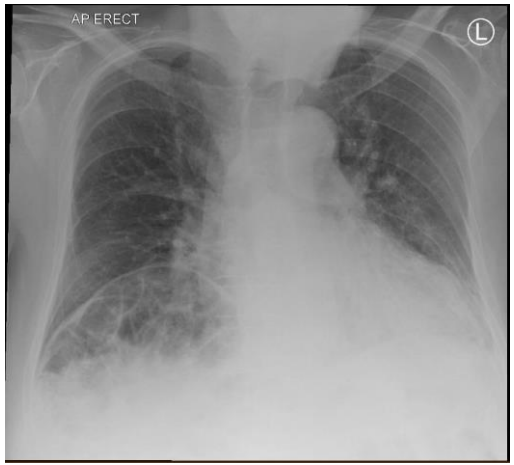
Rawson et al. CID 2020; Lansbury et al. JI 2020; Langford et al. CMI 2020; Langford et al. CMI 2021

December 2020: Patient 2

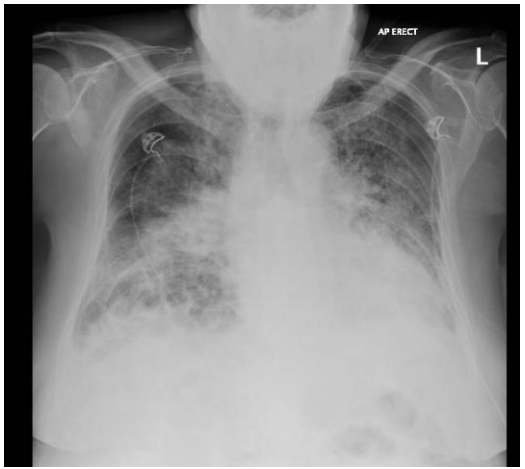
Medical history: Asthma, Hypertension, Hypercholesterolaemia, Stroke, Atrial fibrillation
Social history: Mobile with stick. Walks 1-2 miles.

Recent discharge: COVID +ve - D6 symptoms

Discharge D6



Readmission D8



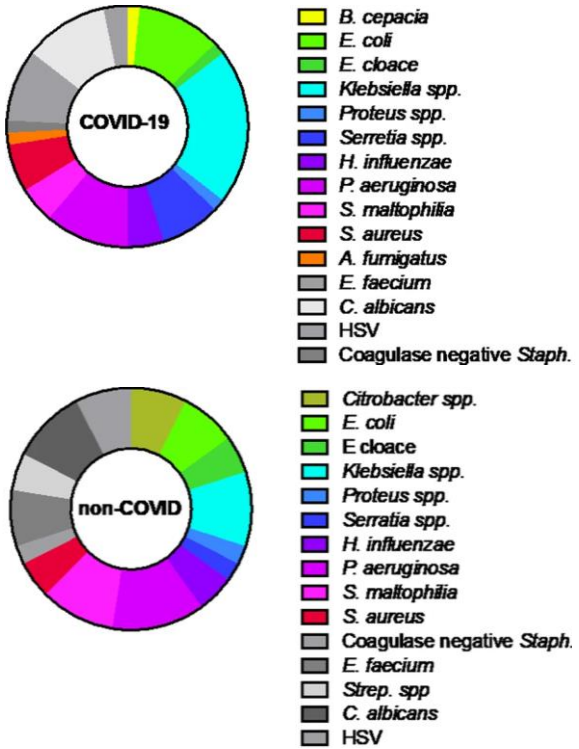
Hospital acquired bacterial infection is observed in COVID-19 patients in critical care

Author	Description	Bacterial infection	Antibiotic prescribing
Yu et al. May 2020	226 patients China	21% (98% HAP)	73%
Dudoignon et al. June 2020	54 patients France	37% VAP/HAP	65%
Contou et al. September 2020	92 patients France	28% on admission to ICU	71%
Buehler et al. October 2020	45 patients Geneva	42% total	89%
Maes et al. January 2021	81 patients United Kingdom	43% VAP	94%
Soriano et al. September 2020	83 patients Spain	51% ICU infections	-
Baskaran et al. October 2020	254 patients United Kingdom	33%	95%

Ventilator associated pneumonia (VAP) in COVID-19

81 COVID-19 vs. 144 non-COVID ventilated patients.

- COVID cohort have more risk factors for VAP:
  - Less immunosuppressed [15% vs. 25%]
  - More had ARDS [78% vs. 15%]
  - More managed prone [49% vs. 0.7%]
  - Longer ICU stays [Med: 15 vs. 9 days]
  - Longer duration of ventilation [Med: 14 vs. 5 days]
- More suspected VAPS [79% vs. 33%]
- More confirmed VAPS [48% vs. 15%]
- Similar causative organisms / microbiomes.

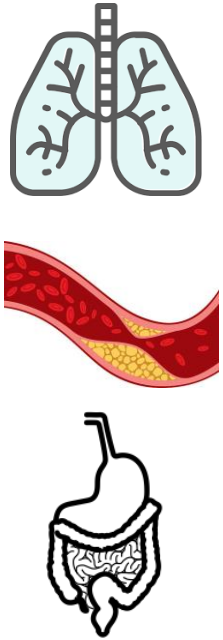


Maes et al. Crit Care 2021

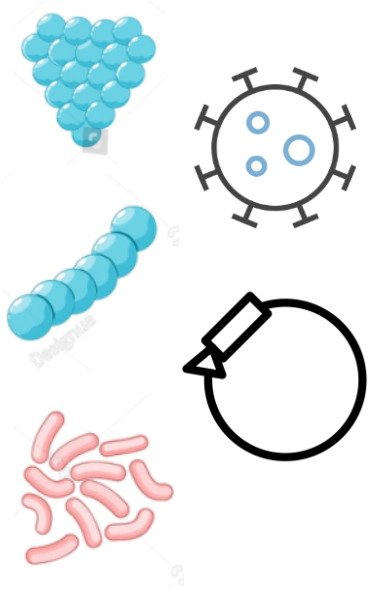
Syndromic testing using molecular diagnostics

Syndromic management involves **making clinical decisions based on a patient's symptoms and signs.**

Patient



Working diagnosis



Target detection

Rule in / rule out

Molecular diagnostics

	Benefits	Limitations
Laboratory	• Minimal hands-on time for staff • **Reduced TAT by over 24 hours** • **High accuracy** compared with conventional MALDI-TOF–based identification systems (>90%) • Can identify presence of markers of drug-resistance	• Remains prone to **contamination** • **Challenge of polymicrobial cultures** • May not cover **all causative organisms** • Does not provide phenotypic susceptibility profiles • **Adjunctive test**
Clinical	• Faster time to result reporting • Reduced time to treatment optimisation/ de-escalation • **When linked with antimicrobial/diagnostic stewardship, interventions can be a powerful tool** to support decision making	• Need clear pathways for appropriate use of the test • No appropriately powered studies to demonstrate impact on mortality/length of stay • **Limited literature** on the direct impact on antimicrobial resistance
Economic	• Potential **long-term cost saving**	• **Relatively high cost** assay • Laboratories need to adapt process to implement

Ramanan et al. CMR 2018; Peker et al. CMI 2018

Real-world potential of syndromic platforms

Potential of syndromic testing in management of lower respiratory tract infections:

- Retrospective study in French ICU's with expert panels selecting antimicrobials.

- Microbiology identified a significant organism in 60% of cases.
- Syndromic rm-PCR detected an organism in 83%.
- Modification of empirical therapy suggested in 123 (77%) cases.

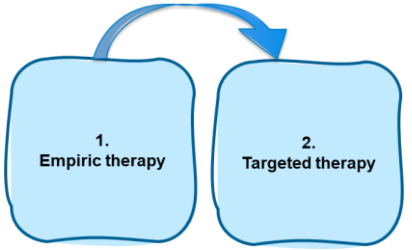
- Increased appropriateness in 83/95 (87%) cases compared to 73/95 (77%) cases with standard of care.

Syndromic testing would have led to:

	Overall, *n* = 159	CAP, *n* = 54	HAP, *n* = 68	VAP, *n* = 37
Antibiotic modification	123 (77)	37 (69)	54 (79)	32 (87)
De-escalation	63 (40)	20 (37)	25 (37)	18 (49)
Escalation	35 (22)	8 (15)	18 (27)	9 (24)
Undetermined	25 (16)	9 (17)	11 (16)	5 (14)
No change	36 (23)	17 (32)	14 (21)	5 (14)

Monard et al. CC 2020

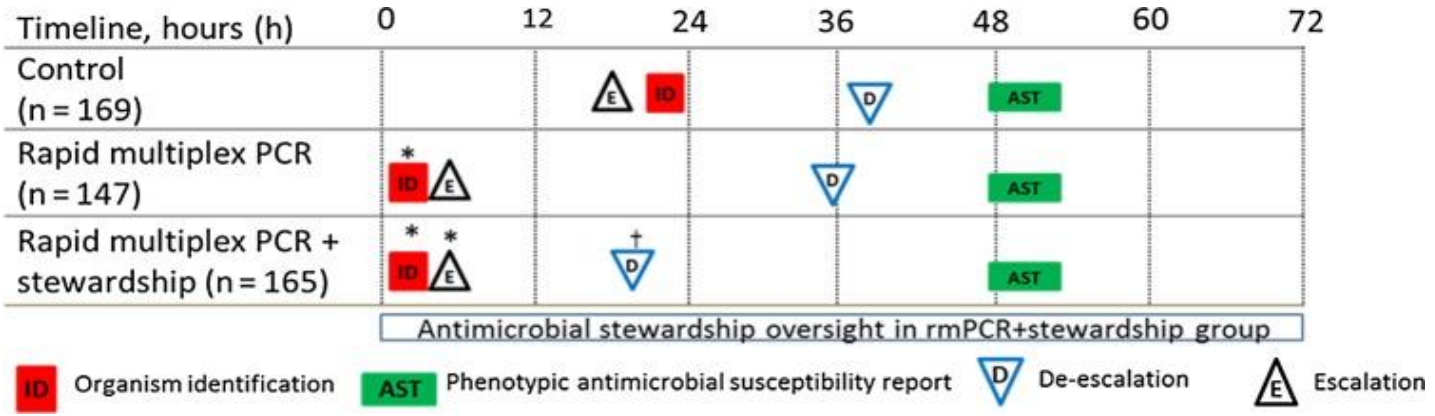
Syndromic testing linked with stewardship



When performed on the correct patient syndromic testing may help determine:

- Prescence / absence of causative organism
- Prescence / absence of resistance markers
- Augment decision making when linked with other interventions (e.g. procalcitonin, audit/feedback)

Example of the impact of multiplex PCR linked with antimicrobial stewardship with positive blood culture



Banerjee et al. CID 2015

Intensivists views on rm-PCR diagnostics

Qualitative interviews of 35 critical care doctors working in 4 UK intensive care units

Perceived benefits of molecular diagnostics	Perceived challenges of molecular diagnostics
Facilitate choosing targeted antibiotics	Unfamiliarity with testing capabilities
Lowers the threshold for starting treatment vs. only influencing choice of agent.	*"They wanted more information about the test, including its sensitivity, specificity, and its place in the diagnostic process"*
Use as a rule-out test	Potential to drive over-treatment
Increase confidence in prescribing decisions	Failing to detect an organism may not over-ride clinical evidence of infection
"*Happier and more confident in decision making*"	Concern of deterioration whilst waiting for a molecular diagnostic result

Pandolfo et al. ARIC 2021

May 2022: Patient 3

PMH: Hypertension, ischaemic heart disease, cancer
SH: Good baseline, independent in activities

Day 0:
Fever
Cough
SARS-CoV-2 +ve

Day 7:
Dexamethasone
Remdesivir
Tocilizumab

Day 13:
Good clinical response.
Discharge planning.

Day 15:
Fever, rising inflammatory markers.

Day 16:
New oxygen requirement

Day 16:
Intensive care review.
For ICU.

Intensive care day 16:
Admission to ICU for respiratory and circulatory support.
New consolidation on chest X-ray.
Indirect bronchoalveolar lavage performed.
Commenced on meropenem empirically.

Respiratory panel run on BAL:
Methicillin Resistant *Staphylococcus aureus*

Vancomycin added.

Why do we perform antimicrobial susceptibility testing?

For the individual patient:

- Ensure that suitable antibiotics are prescribed.
- Monitor for the emergence of resistant pathogens within individuals.
- Support optimised delivery of treatment?

Institutional / regional level:

- Support policy / guidelines for empiric therapy (antibiograms).
- Support infection prevention & control practices.

Epidemiological:

- Monitor incidence / prevalence of resistance.

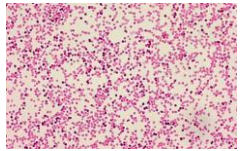
Laboratory diagnostic process

Sample processed

Plated and incubated

Identification

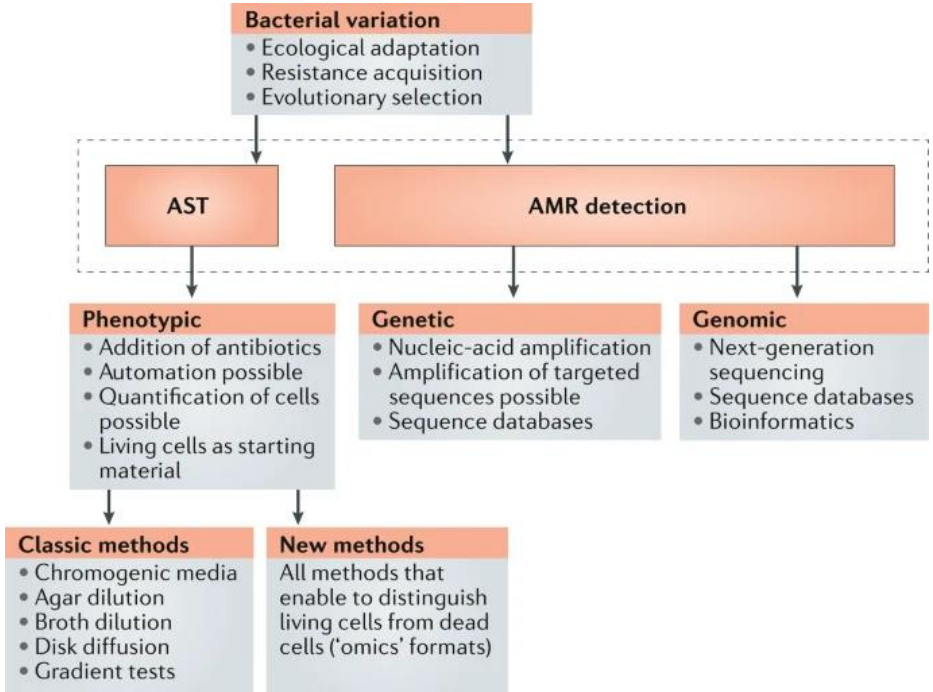
Gram stain
Culture media
Additional tests
Analytical Profile Index (API)
MALDI-TOF



Susceptibility

Disc diffusion
E-test
MIC

AST versus AMR gene detection



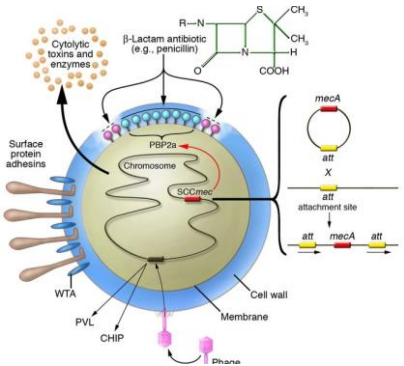
Comparing AST to AMR detection

AST	AMR detection
Universally applicable	Rapid
Mechanism independent	Confirms presence of resistance mechanisms
Phenotypic characterisation	
Therapeutic relevance	
Requires time for growth	Does not necessarily mean susceptibility / phenotype
Gene expression-dependent	Limited to certain antibiotics

Idelevich & Becker. CMI 2019; Belkum et al. Nature Rev Micro 2020

Genotype versus phenotype

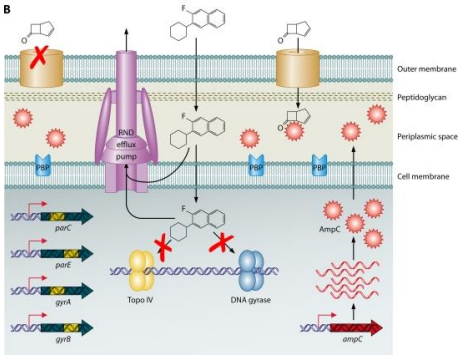
Methicillin Resistance Staphylococcus aureus (MRSA)



Resistance mechanism:

- mecA gene infers PBP-2a mutation
- **Genotype = phenotype**

Pseudomonas aeruginosa

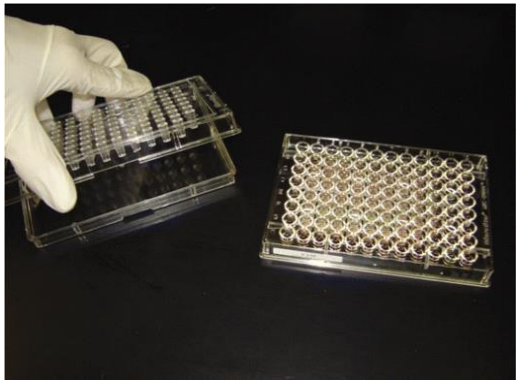


Resistance mechanisms:

- Chromosomal ampC & DNA gyrase
- OprD porin downregulation
- RND efflux pump over-expression
- **Genotype ≠ phenotype**

Lister at al. Clin Microbiol Rev 2009

Phenotypic antimicrobial susceptibility testing



Broth dilution

Two-fold dilution method

MIC determination
Gold standard

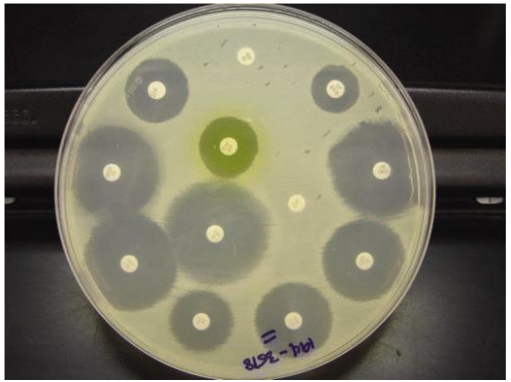
Time consuming
Open to human error

Antimicrobial gradient

E-test method

MIC determination
Quick to set up

Some variation in MIC
compared to broth



Disc diffusion

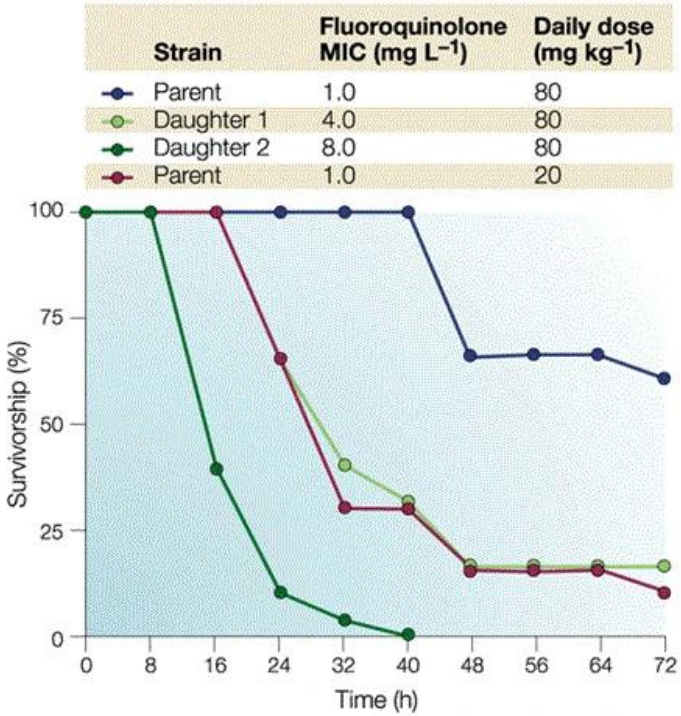
Disc method

Disc diameter
Quick, cheap, ease of use

Qualitative “S/I/R”

Reller et al. CID 2009

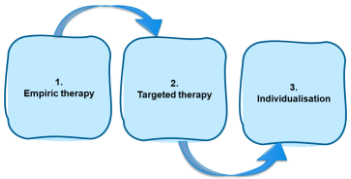
Why is MIC important in practice?



Neutropaenic rat model of Pseudomonas sepsis

Clear relationship between drug-exposure and response:

- Minimum inhibitory concentration (MIC): *Smallest concentration of antimicrobial that inhibits the visible growth of an organism in vitro.*
- A higher MIC will lessen the effect of the drug.
- A lower dose will also lessen the effect.
- Allows us to infer likelihood of treatment success / failure through assignment of clinical breakpoints.



Drusano, Nat Rev Mic 2004; Harris et al, JAMA 2018; Henderson et al. CID 2021

May 2022: Patient 3

Day 18:
MRSA on sputum.
Meropenem stop.
Vancomycin cont.

Day 21:
Extubated.
Clinical improvement.

Day 23:
CRP falling.
PCT < 0.09 ng/mL.
Step down planned.

Question on the ICU AMS round:
What duration of therapy is required for our patient?

Treatment considerations – duration

"What is an appropriate duration of antimicrobial therapy for my patient?"

Where does evidence for duration of therapy come from?

Evidence based on clinical data :
- Mycobacterium tuberculosis
- Staphylococcus aureus
- Syndromic treatment

In vitro data:
- Time-kill analysis

Clinical judgement:
- How the patient responds

Biomarkers:
- C-reactive protein
- Procalcitonin

Short course antibiotic therapy

"Current evidence supports that each day of antibiotic therapy beyond the first confers a decreasing additional benefit to clinical cure while increasing the burden of harm…" (Spellberg, AIM; 2019)

45 RCT's & 2 meta-analyses explored short vs. traditional courses of therapy

- Shorter course therapy has non-inferior clinical outcomes
- Reduced development of resistance and toxicity / side effects

Pneumonia: 8 RCTs

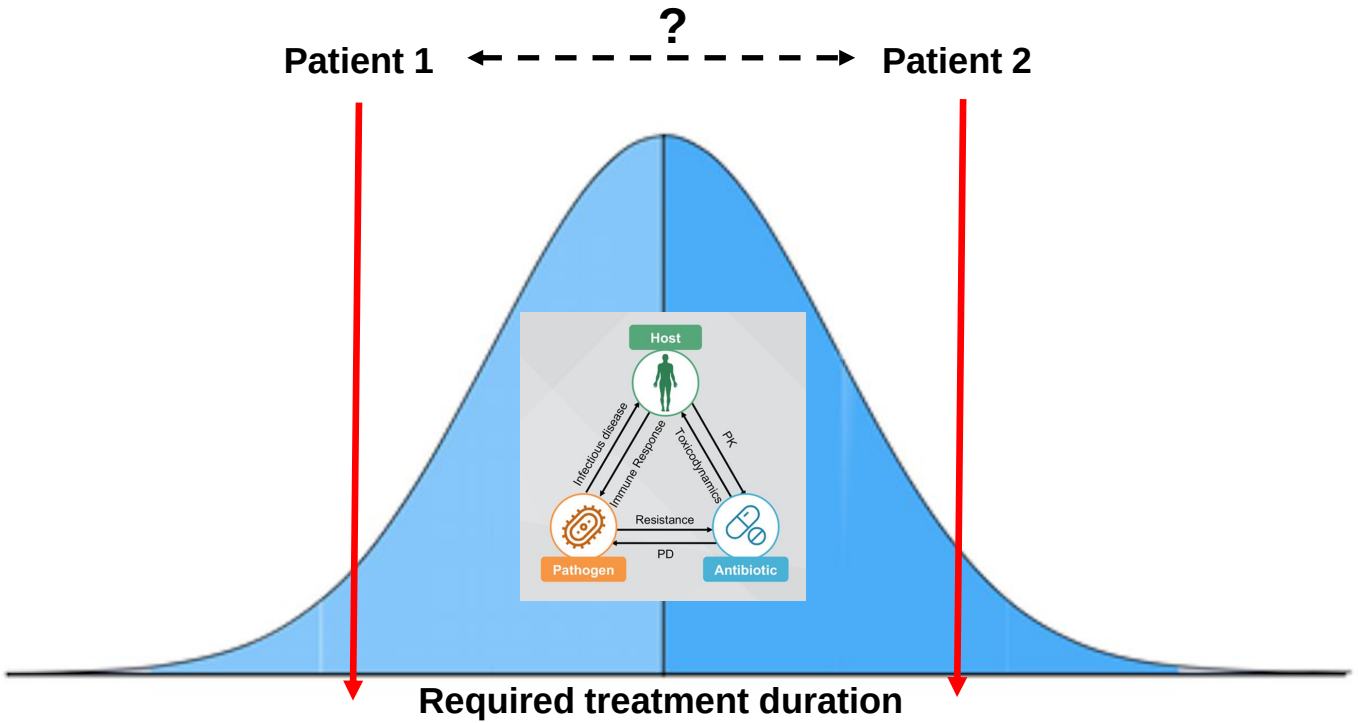
- No difference between 3-5 vs. 7-14 day courses in CAP
- No difference between 8 vs. 15 day courses in HAP
- 1 dose of ceftriaxone effective in some populations (Pertel et al. CID 2008)
- Shorter courses decrease resistance and toxicity / side effects (Vaughn et al. AIM 2019)

Short vs. traditional course antibiotic therapy

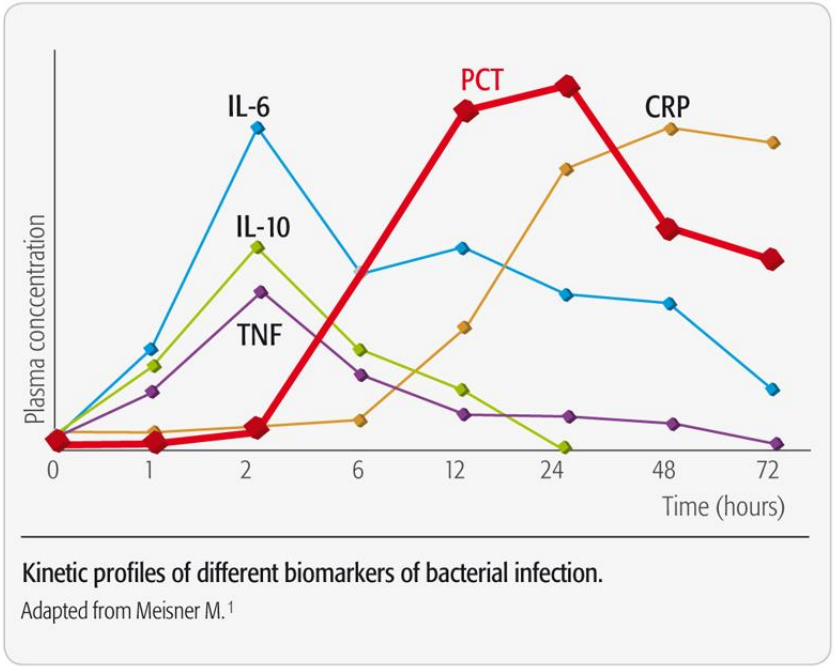
Diagnosis	Short (d)	Long (d)	Result
CAP	3 or 5	7, 8, or 10	Equal
HAP	7	10-15	Equal
VAP	8	15	Equal
Pyelo	7 or 5	14 or 10	Equal
Intra-abd	4	10	Equal
Gram Neg Bacteremia	7	14	Equal
AECB	$\leq$5	$\geq$7	Equal
Cellulitis	5-6	10	Equal
Osteo	42	84	Equal
Septic Arthritis	14	28	Equal
Neutropenic Fever	AF x 72 h	+ANC > 500	Equal

Spellberg; 2019

Treatment cessation decision making



Biomarkers used to support decision making



Kinetic profiles of different biomarkers of bacterial infection.

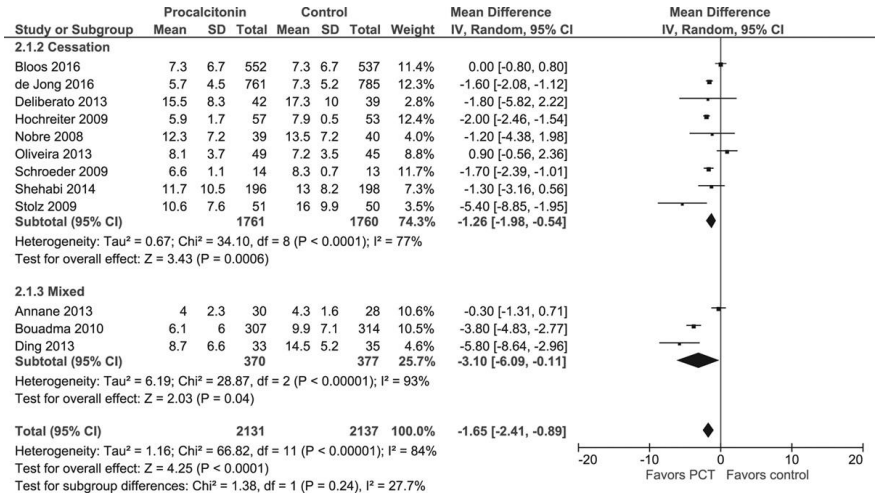
Adapted from Meisner M.[1]

	CRP	PCT
Trigger	Acute phase response	Bacterial endotoxins
Cytokines	IL-6, IL-1B	TNF-a, IL-1B, IL-6, IL-8
Production	Liver (APP)	Extra-thyroidal
Kinetics	Inc: 6hrs Peak: 48hrs T1/2: 19hrs	Inc: 2-3hrs Peak: 12hrs T1/2: 24hrs

Pepys et al. JCI 2003; Charles et al. CC 2009; Christ-grain et al. 2011

Procalcitonin guided cessation of therapy

PCT versus SOC on duration of therapy in critically ill patients



Procalcitonin in COVID-19:

- CRP and PCT will be higher in patients with bacterial co-infection & higher risk of mortality.
- PCT has a good negative predictive value.
- PCT introduction into UK hospitals led to a **short term** reduction in antimicrobial consumption.

Lam et al. Crit Care Med 2019; Williams et al. JoI 2021; Lewellyn et al. JAC 2022

Summary (1)

- As the COVID-19 pandemic and available therapies have evolved, so have the challenges of diagnosing and managing bacterial infections.
- In general, bacterial infection in patients with COVID-19 pneumonitis was uncommon and antimicrobial prescribing was almost universal.
- Bacterial infection in COVID-19 pneumonitis is challenging to define and driven by a multitude of factors.
- Molecular diagnostics have significant potential to enhance diagnostics.
- These require an additional focus on stewardship and links with an understanding of human behaviour, culture, and context.

Summary (2)

- Antimicrobial Susceptibility Testing (AST) and Antimicrobial Resistance (AMR) gene detection provide different information.
- Genotype does not always = phenotype.
- AST can support individualisation of treatment in the septic patient.
- Antimicrobial cessation can be supported by the use of biomarkers, such as procalcitonin.
- In general short course antimicrobial therapy is appropriate and associated with lower rates of adverse events and emergence of drug resistance.
- Individualisation of antimicrobial therapy requires an understanding of prescriber decision making and an ability to support sustained stewardship of diagnostics and antimicrobials.

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