Metrica dell'appropriatezza: il punto di vista del clinico

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Disclosures 2020-2021

- **Advisory Board**: MSD, Shionogi, GSK, Menarini, Roche
- **Speaker/chairman**: Angelini, MSD, Pfizer, Menarini
- **Events Sponsorshi**p: Gilead, Pfizer, MSD, Menarini, Angelini, Shionogi, ViiV, Biomerieux, Advanz Pharma, Janssen, Nordic Pharma, Thermo Fisher

Appropriateness measures

- Appropriateness could be considered a process measure,
- Most process measures in ASP relate to the various factors that should lead to better prescribing.
- Indication for the antimicrobial, filling in an antimicrobial order form, or mandating an infectious diseases consult
- **They do not truly reflect the quality of antimicrobial prescribing, or the effect of the prescribing on important outcomes.**

Qualità prescrittiva, audit e ASP

- Nell'audit clinico si analizza il PDT del singolo paziente, per rilevare eventuali problematiche e correggerle
- Nell'ASP si necessita di indicatori aggregabili (metrics) utili a misurare l'impatto del programma
- **La "qualità prescrittiva" rappresenta elemento fondamentale in ambedue i processi**

Appropriatezza della terapia antimicrobica

1. **Congruità della prescrizione**
2. **Scelta dell'antibiotico** (LG, raccomandazioni locali, Sanford Guide, altro)
3. **Dosaggio congruo** (età, peso, funzione renale, etc.)
4. **Via di somministrazione** (parenterale, orale, altro)
5. **Modalità di somministrazione** (bolo, infusione estesa, infusione continua)
6. **Durata della terapia** (predefinita, variabile)
7. **Outcome del paziente** (sopravvivenza, cura, recidiva)

1. Congruità della prescrizione

Livello di evidenza diagnostica:

- Febbre
- SIRS
- Sede dell'infezione identificata (polmonite, cellulite, meningite, etc.)
- Isolamento ed identificazione del patogeno, antibiogramma molecolare e/o fenotipo di sensibilità
- Colonizzazione: tampone rettale di sorveglianza, TAS di sorveglianza, altro

1. Congruità della prescrizione

- Prescriz
- Prescriz
- Prescriz
- Profilass
- Altro (cc

Larga prevalenza di terapie empiriche, per febbre……

30% la quota stimata di ATBT inappropriata

2. Scelta dell'antibiotico

- Profilo di **efficacia e tollerabilità**
- Congrua con le indicazioni di Linee-guida validate ed aggiornate (SNLG)
- Ispirata a "raccomandazioni locali", divisate dal gruppo per l'ASP, su base epidemiologica
- Scelta del professionista (Sanford Guide, altro)
- Scelta della molecola a minor costo nell'ambito della stessa classe o delle stesse indicazioni
- **Scelta della molecola che offra la durata più breve del ciclo terapeutico**

3. Dosaggio

- **Dose congrua** per età, peso, funzione renale, insufficienza epatica, sede dell'infezione
- **Età**: dosaggio pediatrico
- **Peso**: dosi "fisse" o mg/Kg
- **Funzione renale**: dose singola ed intervallo delle somministrazioni variabili
- **CAPD, CRRT**
- **Insufficienza epatica**
- **Sede dell'infezione**: meningite, ascesso etc.

4. Via di somministrazione

- Orale
- Parenterale IV, CVC o altra linea IV
- **Parenterale-orale sequenziale**
- Areosolica (device)
- Congrua con caratteristiche del paziente e della sede d’infezione
- Considera la compliance ed i rischi del CVC

5. Modalità di somministrazione

- Congruo con le caratteristiche PK/PD del farmaco (tempo-dipendente, concentrazione-dipendente, misto)
- Dose da carico
- Bolo
- Infusione estesa
- Infusione continua (ICU)

6. Durata

- Uno dei campi più inesplorati dalla ricerca clinica
- LG indicano durate estese e “fisse” (ad es.: per endocarditi, infezioni osteo-articolari, etc)
- Prevale giudizio clinico sul singolo paziente (defervescenza per 3-5 giorni, miglioramento clinico)
- Terapie di più breve durata: meno impatto sulla flora intestinale (microbioma) e degenza più breve
- Iniziali evidenze cliniche (POET & OVIVA trials)

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Table 2. Distribution of the Four Components of the Primary Composite Outcome.*

Component	Intravenous Treatment (N = 199)	Oral Treatment (N = 201)	Difference	Hazard Ratio (95% CI)
	number (percent)		*percentage points (95% CI)*	
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (–1.4 to 7.7)	0.53 (0.21 to 1.32)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (–3.3 to 3.4)	0.99 (0.32 to 3.07)
Embolic event	3 (1.5)	3 (1.5)	0 (–2.4 to 2.4)	0.97 (0.20 to 4.82)
Relapse of the positive blood culture†	5 (2.5)	5 (2.5)	0 (–3.1 to 3.1)	0.97 (0.28 to 3.33)

CONCLUSIONS

In patients with endocarditis on the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment. (Funded by the Danish Heart Foundation and others; POET ClinicalTrials.gov number, NCT01375257.)

Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 2019; 380: 415-24. POET trial

The POET trial: length of hospital stay

- After randomization, pts were treated according to the assigned regimen **for a median of 19 days (interquartile range, 14 to 25) in the IV treated group and 17 days (interquartile range, 14 to 25) in the orally treated group.**
- **In the orally treated group, 160 patients (80%) were partially or completely treated as outpatients.**
- **After randomization, the median length of stay in the hospital (not a prespecified outcome) was 19 days (interquartile range, 14 to 25) in the IV treated group and 3 days (interquartile range, 1 to 10) in the orally treated group (P<0.001).**

Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med 2019; 380: 415-24. POET trial

Oral versus Intravenous Antibiotics for Bone and Joint Infection

Among the 1054 participants, treatment failure occurred in 74 of 506 participants (14.6%) in the intravenous group and 67 of 509 participants (13.2%) in the oral group.
The intention-to-treat analysis showed a difference in the risk of definitive treatment failure (oral group vs. intravenous group) of −1.4 percentage points (90% confidence interval [CI], −4.9 to 2.2; 95% CI, −5.6 to 2.9), indicating noninferiority.
Complete-case, per-protocol, and sensitivity analyses supported this result.

CONCLUSIONS

Oral antibiotic therapy was noninferior to intravenous antibiotic therapy when used during the first 6 weeks for complex orthopedic infection, as assessed by treatment failure at 1 year.

Ho-Kwong Li et al. N Engl J Med 2019; 380:425-436

The OVIVA trial: length of hospital stay

- We found that appropriately selected oral antibiotic therapy was noninferior to intravenous therapy when used during the first 6 weeks in the management of bone and joint infection, as assessed by treatment failure within 1 year.
- **Oral antibiotic therapy was associated with a shorter length of hospital stay and with fewer complications than intravenous therapy.**

N Engl J Med 2019;380:425-36

Partial Oral Therapy for Osteomyelitis and Endocarditis — Is It Time?

Helen W. Boucher, M.D.

- Surveillance and stewardship through the use of narrow-spectrum therapy, **shorter durations of therapy, and oral rather than parenteral therapy,** as well as the development of new medicines and diagnostics and improvements in infection prevention through a “One Health” approach — with connections among human patients, animals, and the environment taken into account — **are key strategies for combating antimicrobial resistance**

Length of hospital stay

- Outcome measure
- Easy to obtain metric
- Suffers from many of the same problems as mortality (secular trends in developed countries where an emphasis has been placed on early discharges)
- **Attempts to discontinue or transition to oral antimicrobial therapy from parenteral therapy has, perhaps, the strongest relationship to length of stay**

Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score–Matched Cohort

Darunee Chotiprasitsakul,[1] Jennifer H. Han,[2] Sara E. Cosgrove,[3] Anthony D. Harris,[4] Ebbing Lautenbach,[2] Anna T. Conley,[5] Pam Tolomeo,[2] Jacqueleen Wise,[2] and Pranita D. Tamma[6]; for the Antibacterial Resistance Leadership Group

Table 2. Enterobacteriaceae Isolated in the Bloodstream of Hospitalized Adult Patients Between 2008 and 2014

		Duration of Therapy in Matched Cohort	
Enterobacteriaceae	Entire Cohort (N = 1769)	6–10 d (n = 385)	11–16 d (n = 385)
Escherichia coli	841 (47.5)	177 (46.0)	184 (47.8)
Klebsiella species	557 (31.5)	137 (35.6)	114 (29.6)
Enterobacter species	200 (11.3)	36 (9.4)	54 (14.0)
Serratia species	58 (3.3)	13 (3.4)	9 (2.3)
Proteus species	81 (4.6)	13 (3.4)	14 (3.6)
Citrobacter species	32 (1.8)	9 (2.3)	10 (2.6)

Data are presented as No. (%).

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Variable	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value
Short-course therapy (6–10 d)	1.12 (.70–1.80)	.64	1.00 (.62–1.63)	.97
Urinary source	0.36 (.19–.67)	.001	0.49 (.26–.94)	.03
Pneumonia	3.06 (1.73–5.42)	<.001	1.60 (.85–3.02)	.15
Pitt bacteremia score	1.31 (1.21–1.42)	<.001	1.29 (1.17–1.43)	<.001
ICU on day 1 of bacteremia	2.38 (1.48–3.81)	<.001	0.99 (.56–1.76)	.98
End-stage liver disease	3.58 (2.05–6.06)	<.001	4.12 (2.30–7.39)	<.001
Immunocompromised status	1.03 (.63–1.70)	.89	1.40 (.83–2.36)	.21

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

[a]Adjusted for immunocompromised status and variables with $P < .10$ in univariable analysis.

Results. There were 385 well-balanced matched pairs. The median duration of therapy in the short-course group and prolonged-course group was 8 days (interquartile range [IQR], 7–9 days) and 15 days (IQR, 13–15 days), respectively. No difference in mortality between the treatment groups was observed (adjusted hazard ratio [aHR], 1.00; 95% confidence interval [CI], .62–1.63). The odds of recurrent bloodstream infections and CDI were also similar. There was a trend toward a protective effect of short-course antibiotic therapy on the emergence of MDRGN bacteria (odds ratio, 0.59; 95% CI, .32–1.09; $P = .09$).

Conclusions. Short courses of antibiotic therapy yield similar clinical outcomes as prolonged courses of antibiotic therapy for Enterobacteriaceae bacteremia, and may protect against subsequent MDRGN bacteria.

Early discontinuation of antibiotics for febrile neutropenia versus continuation until neutropenia resolution (Protocol)

Stern A, Carrara E, Yahav D, Leibovici L, Paul M

MAIN RESULTS:

- 8 RCTs, a total of 662 febrile neutropenia episodes with FUO
- No significant difference between the short-antibiotic therapy arm and the long-antibiotic therapy arm for all-cause mortality.
- **Total antibiotic days were fewer in the intervention arm by three to seven days compared to the long antibiotic therapy**.
- No significant differences in the rates of clinical failure
- No difference in the incidence of bacteraemia occurring after randomisation
- No significant difference in the incidence of invasive fungal infection and development of antibiotic resistance

Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD012184.
DOI: 10.1002/14651858.CD012184

7. Outcome

- Indicatore di esito (il piu’ importante)
- Cura
- Miglioramento
- Modifiche ATBT
- LOS
- Sopravvivenza
- Mortalità (generale, attribuibile)

Clinical outcomes

- A biased belief that “better” antimicrobial use must be better for the patient
- Clinical outcomes are useful balancing measures, **to help ensure that patients are not harmed through efforts to better rationalize antimicrobial prescribing.**

Cure

- There are various ways to measure cure of an infectious disease.
- There is **clinical cure** (whereby the patient is believed to be clinically well after effective treatment of their infection)
- **Microbiological cure** (whereby microbiological cultures or other tests demonstrate that the pathogen is no longer present in a manner capable of causing disease)
- Other forms (e.g., **radiographic cure**).
- These are potentially useful metrics, but are very difficult for programs to reliably measure on a consistent basis.

Mortality

- Most objective clinical outcome for ASPs is mortality.
- Problems with using mortality as an outcome, **especially when ASP evaluate their interventions as before–after studies, rather than randomized controlled interventions**
- Secular trends in healthcare mortality may result in lower “after” mortality (because of concurrent quality improvement initiatives) or higher “after” mortality (because of a trend to limit hospitalization to sicker and/or older patients).
- Accordingly, mortality results should be interpreted with caution

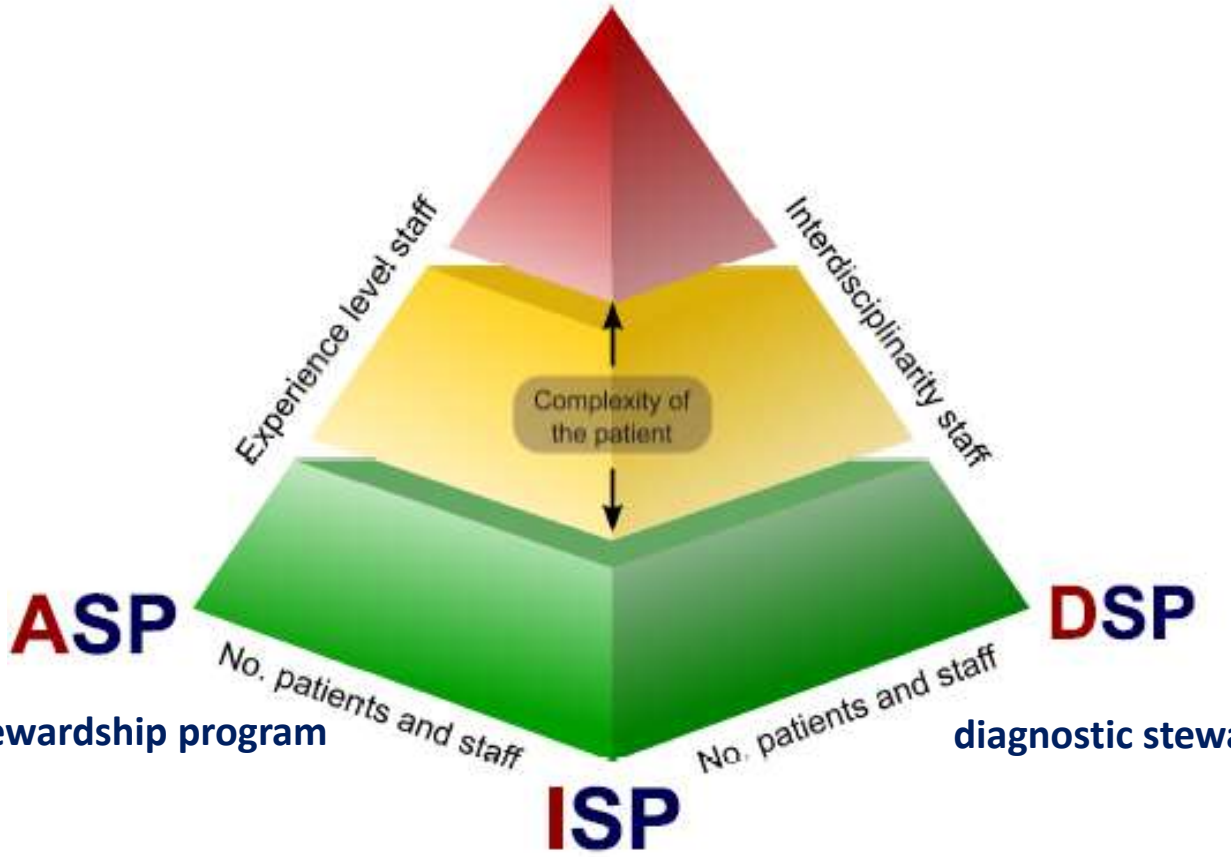
Mortality

- Used as a balancing measure, assuring stakeholders that an ASP intervention does not lead to increased harm
- **Limited studies have shown that increasing appropriate antimicrobial therapy can reduce mortality**
- **A sizable number of studies show that efforts to reduce excessive prescribing do not result in excess mortality**
- To focus the relationship between antimicrobial use and mortality, **organism-specific or syndrome-specific mortality can be used**

Beneficial effects of antimicrobial stewardship on antimicrobial resistance

- There is increasing evidence that antimicrobial stewardship interventions can influence antimicrobial resistance.
- Interventions intended to decrease excessive prescribing were associated with a reduction in *C. difficile* infections and colonization or infection with aminoglycoside- or cephalosporin-resistant Gram-negative bacteria, MRSA, and vancomycin-resistant *Enterococcus faecalis*
- The problem in looking at resistance in a single or few species is the potential for “squeezing the balloon”
- **ASPs may assess their impact by reporting on the reduction of resistance to a certain measured class of antimicrobial when resistance to another antimicrobial or class of antimicrobials increases because of shifted prescribing patterns.**

Multistakeholder platform of antimicrobial stewardship model



antimicrobial stewardship program

diagnostic stewardship program

infection prevention stewardship program

Dik JH, J Clin Microbiol. 2017;55:3306-3307

Conclusioni

- Qualità prescrittiva: di non facile valutazione
- ASP e qualità prescrittiva: necessità di aggregare molteplici informazioni
- Cicli brevi di ATBT ↓ durata del ricovero
- Ambedue sembrano avere un ruolo rilevante nel contenere l'AMR (↓pressione selettiva e ↓ esposizione alla colonizzazione)
- Necessità di studi dedicati con metodologia prospettica e randomizzata